



Practice Opportunities:

***Prevention of Osteoporosis
and Osteoporotic Fracture***

Continuing Pharmacy Education



Creative Educational Concepts, Inc.

116 Dennis Drive, Lexington, Kentucky 40503
859-260-1717, Toll Free 1-866-360-1717
FAX 859-276-6118
www.CEConcepts.net

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Dear Pharmacist:

In our aging society, osteoporosis has become an increasing health care concern with more patients seeking knowledge and assistance regarding this disease. Pharmacists have an essential role in the pharmaceutical care of these patients. For example, pharmacists can be actively involved in patient education, risk factor assessment, peripheral bone density screening, and managing drug therapy for patients with osteoporosis.

It is our pleasure to provide you with this comprehensive, up-to-date continuing education program on the prevention of osteoporosis and osteoporotic fractures. We hope you will be able to utilize this information, including valuable diagrams, tables, and protocols, to enhance your current practice. Our focus on the evaluation, prevention, and treatment of osteoporosis aims to help you develop a greater knowledge base and the ability to provide a higher level of pharmaceutical care to your patients.

Because information about osteoporosis is rapidly changing, pharmacists should be willing to commit to being life-long learners. We encourage you to use this continuing education program as a stepping-stone in your development as an osteoporosis pharmaceutical care provider. Good luck in your endeavor!

Sincerely,

Sheryl Follin, Pharm.D.

Laura Borgelt Hansen, Pharm.D.

Sheryl Follin, PharmD, BCPS
Assistant Professor
University of Colorado School of Pharmacy

Laura Borgelt Hansen, PharmD, BCPS
Assistant Professor
University of Colorado School of Pharmacy

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Procter&Gamble

Health Care

Educational Goal

This continuing education program will provide the pharmacist with education on the prevention of osteoporosis and osteoporotic fractures. The knowledge gained by the pharmacist will enhance his/her ability to provide pharmaceutical care to patients with osteoporosis or those at risk for osteoporosis in an attempt to prevent or limit associated fractures.

Educational Objectives

After reading this monograph, the participant should be able to:

1. Describe normal bone remodeling and the pathophysiology of bone loss in Type-1 (postmenopausal), Type-2 (senile) and Type-3 (secondary) osteoporosis.
2. Discuss the various components of osteoporosis assessment, including risk factors, techniques used to measure bone mineral density and markers of bone turnover, and who should be tested/screened.
3. Recommend appropriate lifestyle modifications and calcium/vitamin D intake for the prevention of osteoporosis.
4. Compare and contrast the safety and efficacy of the four FDA-approved drug therapies for the treatment and prevention of osteoporosis.
5. Discuss the prevention and/or treatment of osteoporosis in special populations including patients receiving glucocorticoids, adolescents, perimenopausal women, men, and frail elderly.
6. Describe the pharmacist's role in the prevention of fracture and osteoporosis.

Disclosure of Affiliations and Significant Relationships

The following faculty members disclosed financial interest/affiliations:

Sheryl L. Follin, PharmD, BCPS:

Speakers' Bureau for Merck and Procter & Gamble

Laura Borgelt-Hansen, PharmD, BCPS:

None

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Prevention of Osteoporosis and Osteoporotic Fracture



Lesson Outline

- I. Introduction
- II. Pathophysiology
- III. Classification and Risk Stratification of Osteoporosis
- IV. Assessment and Diagnosis of Osteoporosis and Fracture Risk
- V. Prevention and Treatment of Osteoporosis
- VI. Special Populations
- VII. Role of the Community Pharmacist

Authors

Sheryl L. Follin, Pharm.D., BCPS

Sheryl L. Follin is a full-time Assistant Professor with the Department of Pharmacy Practice and the Department of Family Medicine at the University of Colorado Health Sciences Center. Her current area of practice is the Inpatient Family Medicine Service at University of Colorado Hospital. Dr. Follin received her B.S. in Pharmacy and Pharm.D. from Wayne State University in Detroit, MI. She completed a postdoctoral Specialty Residency in Adult Internal Medicine with Purdue University at the Indiana University Medical Center. Prior to becoming a full-time faculty member at the University of Colorado, Dr. Follin was an adjunct faculty member at the School of Pharmacy and a Clinical Pharmacy Specialist in Internal Medicine at Exempla Saint Joseph Hospital in Denver. Dr. Follin is a board certified pharmacotherapy specialist and is a member of ASHP, ACCP, AACP, and STFM. Her areas of interest are wide ranging and include women's health, nephrology, geriatrics, and chronic pulmonary disorders.

Laura M. Borgelt-Hansen, Pharm.D., BCPS

Laura Borgelt-Hansen received her BS degree from the University of Iowa and her Doctorate of Pharmacy degree from the University of Colorado. She completed a Primary Care Residency with the University of Colorado and Kaiser Permanente Rocky Mountain Division. Dr. Borgelt-Hansen is a board certified pharmacotherapy specialist and is a member of ASHP, ACCP, AACP, APhA, and STFM. Prior to joining the faculty at the University of Colorado, she was an Assistant Professor at Shenandoah University for two years and actively served as a clinical pharmacist in a private family medicine practice in Winchester, VA. She joined the University of Colorado in July 2000 as an Assistant Professor of Pharmacy and Family Medicine. Her primary interests include women's health, smoking cessation, respiratory disorders, and diabetes.

Prevention of Osteoporosis and Osteoporotic Fracture

I. Introduction

Osteoporosis is a disease that may be considered the "silent thief" because it robs the skeleton bank of its resources. It slowly and quietly causes deterioration of bone as people age and can greatly increase the risk of fracture.

In the United States, an estimated 10 million people have osteoporosis and nearly 19 million have osteopenia or low bone mass.¹ Osteoporosis is more prevalent in the US than cancer, Alzheimer's, or stroke and is almost as prevalent as diabetes. The majority of these populations are postmenopausal women, but men and women of all ages can have osteoporosis or osteopenia.

Osteoporosis accounts for 50-90% of fractures among elderly men and women and 1.5 million fractures in the United States annually.^{2,7} Perhaps the most devastating consequences of fracture are the increase in mortality and morbidity. Mortality rates among the elderly one year after hip fracture are significantly increased and range from 14-36%.⁴

Additionally, morbidity data show that after hip fracture, only

33-40% regain the ability to perform basic activities of daily living, 20% are non-ambulatory, and 10-60% are unable to return home.⁴ Patients' perceptions of the effect of a hip fracture on quality of life are such that 80% of women > 75 years of age stated that they

“Osteoporosis accounts for 50-90% of fractures among elderly men and women and 1.5 million fractures in the United States annually.”

preferred death to a bad hip fracture resulting in nursing home placement.⁵ Half of all Caucasian women have osteoporosis or osteopenia by the end of the first postmenopausal decade, and vertebral fracture incidence is greater than 20% at that time.^{6,7} The lifetime fracture risk of a 50 year-old white woman is 40%, and women who develop a vertebral fracture are 20% more likely to have another vertebral fracture within the subsequent year.⁸

The occurrence of bone loss is more common in Native Americans, Asians, and whites

compared with Hispanics and African Americans and is more common in women than men.⁵

The economic impact of osteoporosis incurs a considerable burden upon the health care system. An estimated \$13.8 billion was spent in the United States for direct medical expenditures in 1995. This included over 400,000 hospital admissions, almost 2.5 million physician visits, and approximately 180,000 nursing home admissions.¹ It is estimated that costs may increase up to \$240 billion during the next 50 years.⁶

One survey of women aged 45-75 indicated that 75% never spoke to their doctors about osteoporosis.⁹ Therefore, pharmacists can have a significant role in assessing, screening, educating, and collaborating with physicians regarding drug therapy management for patients with osteopenia and osteoporosis. The optimal goal of these interventions is to prevent fracture. This monograph aims to discuss current approaches in the detection, prevention, treatment, and monitoring of osteoporosis.

II. Pathophysiology

Normal Bone Physiology and Remodeling

There are two types of bone, cortical and trabecular (cancellous). Cortical bone comprises approxi-

mately 80% of the skeletal mass but only 20% of the surface area.¹⁰ It is found mostly in the peripheral skeleton and forms a compact shell around trabecular bone. Trabecular

bone is found mostly in the axial skeleton. It forms a honeycomb or lattice-like structure in the interior of bones (such as the vertebral bodies and distal radius). While

trabecular bone comprises only 20% of the skeleton, it has a much larger surface area than cortical bone due to its structure. It is also much more metabolically active.¹⁰ Therefore, bone turnover has a greater effect on trabecular bone compared to cortical bone (Figure-1).

Bone is like a well-traveled highway.¹¹ Over time, it becomes worn and cracked and must undergo repair to keep healthy. This repair is called bone remodeling and occurs continuously as a normal process in the body. There are approximately 1 million small sections of bone (basic multicellular units or BMUs) being remodeled at any one given time.¹¹ Bone remodeling is a coupled process of continuous bone resorption and subsequent bone formation. The two primary bone cells involved with remodeling are osteoclasts and osteoblasts. Osteoclasts "breakdown" or resorb old and damaged bone, while osteoblasts "build" new bone.

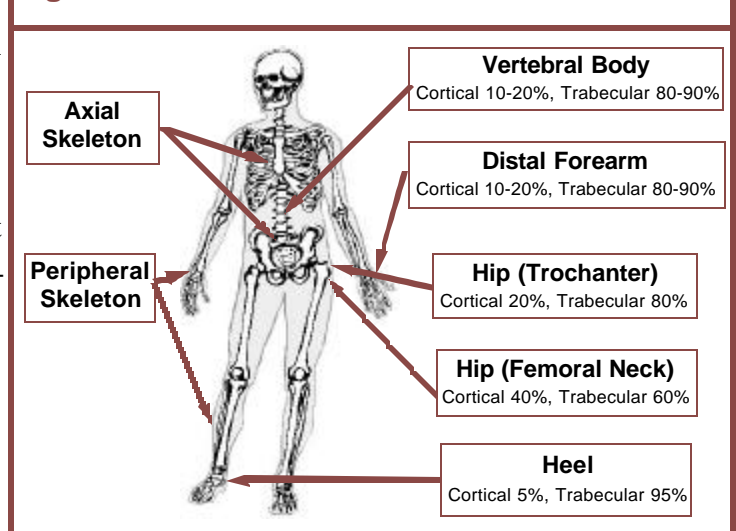
In the remodeling process, osteocytes (immature osteoblasts) sense damage to bone and send signals that stimulate the differentiation and activation of osteoclasts. It takes approximately 3 weeks for osteoclasts to resorb bone to the appropriate depth. Once this depth has been reached, signals are sent to stimulate the differentiation and activation of osteoblasts as the osteoclasts move to another remodeling site or die.

Osteoblasts secrete collagen and other matrix proteins to form osteoid (new bone) and stimulate subsequent bone mineralization. This process takes approximately 3-4 months. Based on the differences in time for osteoclastic bone resorption and osteoblastic bone formation, there is a continuous bone deficit in the body called remodeling space.

Bone Loss and Peak Bone Mass

Bone loss usually results from either an increase in osteoclast activity or a decrease in osteoblast activity. An increase in the function and life-span of osteoclasts may lead to more remodeling sites (high bone turnover) and/or deeper resorption sites. Osteoblasts are unable to adequately fill all the additional resorption sites leading to a continuously increasing remodeling space and bone deficit. Alterations in the function and life-span of osteoblasts can lead to low-turnover bone loss. In this scenario, osteoblasts are unable to ade-

Figure 1: Architecture of Bones That Fracture



quately fill remodeling sites of normal depth and quantity. (Figure-2)

Bone mass begins to decline late in the 4th decade of life in both men and women at a rate of approximately 0.5% per year. During the perimenopausal time period and for 5-7 years post-menopause, women will experience a dramatic increase in the rate of bone loss of up to 3-5% per year. This period of bone loss is directly related to the loss of estrogen. After this time period, the rate of bone loss will slow to a rate of 0.5-1% per year. Bone loss in men remains fairly consistent at a rate

Figure 2: Normal Bone Remodeling and Bone Loss

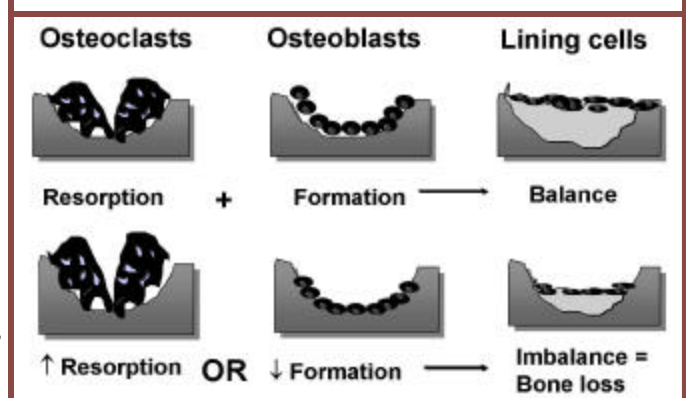
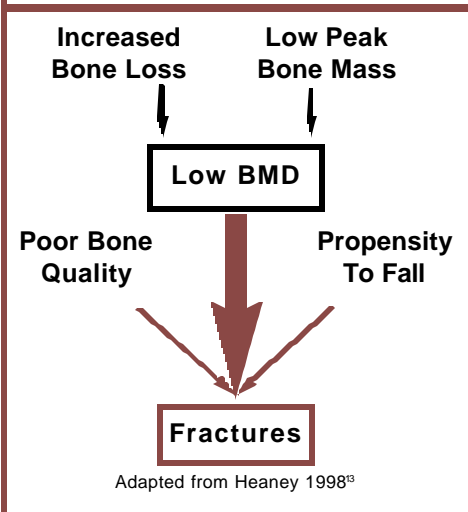


Figure 3: Pathogenesis of Fractures



of 0.5-1.0%. Bone loss is multifactorial. Genetic predisposition, lifestyle, sex hormone deficiency, disease states, and medications can all contribute to bone loss throughout life.

Peak bone mass describes the maximum bone density achieved for any one individual. More than 90% of peak bone mass is reached by age 18 years with the completion of adult mass attained by the age of 35 years.¹² Achieving a high peak bone mass is essential. The higher the peak bone mass, the lower the risk for reaching the "fracture threshold", or that point where fracture will occur.

Genetic predisposition accounts for approximately 75-80% of the inter-individual variation in peak bone mass.¹⁰ Similar to bone loss, inactive lifestyle, sex hormone deficiency, disease states, medications, malnutrition, and diets low in calcium and vitamin D are contributors to peak bone mass. Exercise performed throughout bone development is especially

important as bone deposition is dependent on the "strain" placed on bones.¹³ Lack of exercise during bone growth causes suboptimal loading and decreased bone mass.

Pathogenesis of Fractures

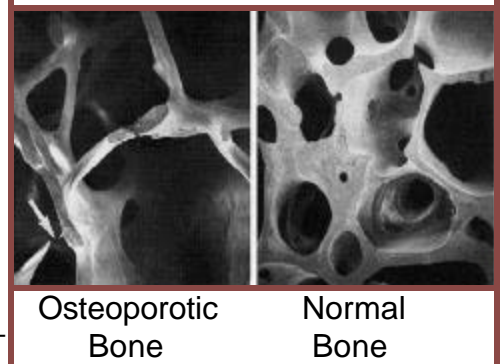
Osteoporosis is a term that encompasses both a risk factor for fragility (low bone density) as well as a condition of fragility (fractures).¹³ Osteoporotic fractures are frequently referred to as "fragility fractures" or "low trauma fractures" and can occur with minimal to no trauma. Several factors contribute to low trauma fractures (Figure-3). Low bone density is by far the greatest predictor of fracture risk.¹⁴ Bone density accounts for 70% of bone strength. For every one standard deviation (SD) decrease in bone density, the risk for fracture at any given site increases 2-3 fold.¹⁵ Low bone density occurs as a result of bone loss or failure to reach an adequate peak bone mass during growth.

Other factors that contribute to fracture risk, such as risk for falls and quality of bone, must also be considered. Almost all osteoporotic fractures result from a low impact injury or fall.¹³ It is estimated that 30% of women 85 years of age will fall at least once per year and 15% will fall two or more times.¹⁶ Approximately 6% of these falls result in fracture.¹⁷ The elderly fall more often due to decreased muscle strength and agility, a higher number of medications, and/or co-morbid disease

states that impair cognition and gait. The elderly tend to fall more often to the side where they are unable to break the force of the fall, therefore landing directly on an unprotected hip.¹⁸ Persons who are thinner or taller are at greater risk for hip fracture with a sideways fall due to less energy absorbing padding and a longer hip axis length.¹⁸

High bone turnover, which is seen most commonly in postmenopausal women, is considered to be an independent risk factor for fracture. High turnover can lead to deeper resorption at remodeling sites and the potential for trabecular perforations (Figure-4). This leads to significant weakening of the bone structure (poor bone quality) and risk for fracture regardless of the bone density. Thinned trabeculae can be strengthened by deposition of new bone through alterations in remodeling, but perforated trabecular bone cannot be strengthened through new bone formation. Therapy aims to strengthen bone prior to perforation.

Figure 4: High Bone Turnover Leading to Trabecular Perforations



III. Classification and Risk Stratification of Osteoporosis

Classification

Osteoporosis is classified as either primary (related to aging and decreased gonadal function) or secondary (due to chronic disease states, drug therapy or lifestyle). Primary osteoporosis can be subdivided into Type-1, which is seen most commonly in postmenopausal women, and Type-2, which occurs in men and women over the age of 75. Type-1 or postmenopausal osteoporosis is due to high bone turnover. The decrease in estrogen that occurs with menopause leads to an increase in the number and lifespan of osteoclasts and an

calcium absorption and activation of vitamin D, impaired osteoblast function, reduced osteoblast lifespan, and decreased sex hormone production all contribute to the bone loss in this population. Cortical and trabecular bones are equally affected leading to an increase in hip fractures in the elderly.

Secondary (Type-3) osteoporosis is a condition that occurs in response to certain medical conditions or treatments. Table 1 lists

diseases and medications that can potentially cause bone loss.

This type of osteoporosis does not discriminate as men and women of all races and ethnic backgrounds can be affected.

Risk Factors

Risk factors alone are not sufficient to detect osteoporosis, but assessment of risk factors can increase awareness of osteoporosis and help identify patients at high risk for fracture. Risk factors for osteoporosis can be characterized as modifiable or potentially non-modifiable (Table 2).¹ The most important risk factors are personal his-

Table 1: Secondary Causes of Osteoporosis

Diseases	Drugs
Acromegaly	Aluminum
Alcoholism	Anticonvulsants
Anorexia nervosa	(phenytoin, phenobarbital)
Calcium deficiency	Cigarette smoking
Chronic liver disease	Cytotoxic drugs
Chronic obstructive pulmonary disease	(tamoxifen)
Diabetes Mellitus, Type 1	Excessive thyroid medication
Hyperadrenocorticism	Glucocorticoids
Hyperprolactemia	Gonadotropin-releasing hormone agents
Hyperparathyroidism	Heparin
Hypogonadism (including Amenorrhea)	Lithium
Hypophosphatasia	
Malabsorption syndromes	
Malnutrition	
Pregnancy	
Porphyria	
Rheumatoid arthritis	
Thyrotoxicosis	
Vitamin D deficiency	

tory of fracture as an adult (40-45 years or older) and low bone mineral density. A low-trauma fracture as an adult is important because it establishes an unusual susceptibility to fractures and strongly predicts future fracture potential.⁶

“Risk factors alone are not sufficient to detect osteoporosis, but assessment of risk factors can increase awareness of osteoporosis and help identify patients at high risk for fracture.”

increase in the number and depth of remodeling sites. As stated previously, women can lose up to 3-5% of their bone mineral density during this time period. Since trabecular bone is more metabolically active and affected by high bone turnover, vertebral and wrist fractures are more common in the early postmenopausal time period. (Refer back to Figure 1.)

Type-2 osteoporosis typically presents in men and women after the age of 75 and is due to several age-related changes. Decreased

Table 2: Risk Factors for Osteoporotic Fracture²⁰

Nonmodifiable	Potentially Modifiable
Personal history of fracture as an adult	Current cigarette smoking
History of fracture in first-degree relative	Low body weight (<127 lbs)
Caucasian or asian race	Estrogen deficiency:
Advanced age	- Early menopause (< age 45) or bilateral ovariectomy
Female sex	- Prolonged premenopausal amenorrhea (>1 year)
Dementia	Low calcium intake (lifelong)
Poor health/frailty	Alcoholism
	Impaired eyesight despite adequate correction
	Recurrent falls
	Inadequate physical activity
	Poor health/frailty

Risk factors that have been shown to increase the risk of hip fracture include family history of fracture in a first-degree relative, current cigarette smoking, and low body weight (<127 lbs). Other risk factors that may impact the incidence of osteoporosis include nulliparity,

immobilization, high caffeine intake, and petite body frame. Since more than 1/3 of women and up to 2/3 of men have secondary causes of bone loss, it is important for the pharmacist to carefully assess risk factors and medication use.

Fracture Risks Associated with Risk of Falls:²⁰

- History of falls
- Low physical function
 - ◆ Slow gait speed
 - ◆ Decreased quadriceps strength
- Impaired cognition
- Impaired vision
- Presence of environmental hazards

IV. Assessment and Diagnosis of Osteoporosis and Fracture Risk

Assessment

The assessment of a patient at risk for osteoporosis includes several important steps. First, a thor-

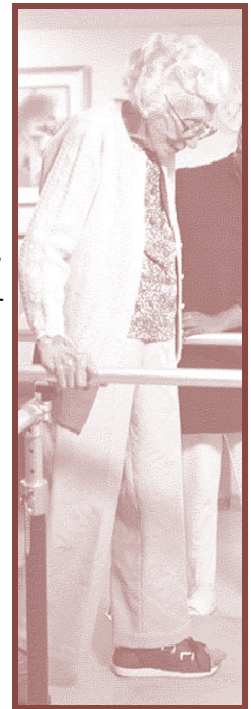
ough medical history should be performed. This includes past medical history, medication history, family history, and social history.

Criteria	Point Value
1. What is your current age?	_____
Less than 65	0
65-69	1
70-74	2
75-79	3
80-84	4
85 or older	5
2. Have you broken any bones after age 50?	_____
Yes	1
No/Don't know	0
3. Has your mother had a hip fracture after age 50?	_____
Yes	1
No/Don't know	0
4. Do you weigh 150 pounds or less?	_____
Yes	1
No	0
5. Are you currently a smoker?	_____
Yes	1
No	0
6. Do you usually need to use your arms to assist yourself in standing up from a chair?	_____
Yes	2
No/Don't know	0
If you have a current bone density (BMD) assessment, then answer next question.	
7. BMD results: Total Hip T-score	_____
T-score > -1	0
T-score between -1 and -2	2
T-score between -2 and -2.5	3
T-score < -2.5	4
Total Score	_____
Recommend that postmenopausal women with a total score of 4 or above without BMD assessment or a total score of 6 or above with BMD assessment, should undergo further evaluation from physician.	

The main purpose of the medical history is to identify risk factors for fracture and low bone density. This is essential for determining the patient's future risk for fracture and whether or not they should go on for bone mineral density testing. See Table 3 for an assessment tool that can be used to help assess a person's risk of hip and other osteo-

porotic fractures.

A physical examination can help identify possible secondary causes of osteoporosis and reveal signs/symptoms of fragility fracture. These include the presence of bone pain, postural changes, loss of height (>1.5 inches from tallest mature height), and a dowager's hump (kyphosis).⁶



Bone mineral density (BMD) testing is the standard method for diagnosing osteoporosis as well as predicting future fracture risk. Guidelines are available to assist in the identification of women at greatest risk for fracture in whom bone density testing would be most valuable. (Table-4)

Once the diagnosis of osteoporosis is made, several simple laboratory tests should be performed to rule out the more common secondary causes of osteo-

Table 4: Who Should Undergo BMD Testing? ^{6,20}

Guidelines	
AACE ^a (Postmenopausal Women)	<ul style="list-style-type: none"> Risk assessment in perimenopausal or postmenopausal women who have risk factors for fracture and are willing to consider therapy Women who have X-ray findings that suggest osteoporosis Women beginning or receiving long-term glucocorticoid therapy or other drugs associated with bone loss All women > 65 years of age In all women 40 years old or older who have sustained a fragility fracture At baseline and for monitoring response to therapy in women receiving treatment for osteoporosis.
NOF ^b (Postmenopausal Women)	<ul style="list-style-type: none"> Postmenopausal women < 65 years of age who have one or more additional risk factors Women who have been on hormone replacement therapy for prolonged periods of time All women > 65 years of age Postmenopausal women who present with fractures (to confirm diagnosis and determine disease severity)

^a ACCE = American Association of Clinical Endocrinologists

^b NOF = National Osteoporosis Foundation

porosis. These would include a complete blood count, serum chemistry (including calcium, phosphate, creatinine, and electrolytes), liver enzymes, and urinary calcium excretion.⁶ If the medical history or physical examination suggests a specific secondary cause, further tests may be necessary. An X-ray should be performed to confirm the presence of any suspected fragility fracture.

Bone Densitometry

Several technologies are available for measuring BMD (Table-5). These techniques vary in the sites they measure (central vs. peripheral) and the methods of measurement (bone absorption of radiation or high-frequency sound waves). Most available bone density techniques are able to predict general fracture risk. However, to best predict fracture risk at a given

site, the BMD at that site should be used (i.e., hip BMD is the best predictor of future hip fracture risk).¹⁴

The three key pieces of information obtained from a bone den-

sitometry report are the actual bone density value, T-score and Z-score. The actual bone density value is reported in grams of calcium hydroxyapatite per square centimeter and is used to monitor response to drug therapy. The T-score is a comparison of the patient's bone density value to the mean value of a young (25-30 years), healthy, sex-matched reference population. The Z-score is similar to the T-score, however it compares the results to a sex- and age-matched population.²⁴ Both the T-score and Z-score are reported as the number of standard deviations away from the mean. One standard deviation is approximately a 10-12% difference in bone density. The T-score is utilized by the World Health Organization (WHO) to describe diagnostic thresholds and by the National Osteoporosis

Table 5: Technologies for Bone Mineral Density Testing

BMD Technique	Site Measured	Comments
Single-energy X-ray Absorptiometry (SXA)	♦ Heel	♦ Rarely used ♦ Water bath needed
Dual-energy X-ray Absorptiometry (DXA)*	♦ Hip (femoral neck, Ward's triangle and greater trochanter) ♦ Spine ♦ Total Body	♦ Gold standard ♦ Takes only ~ 10 mins
Peripheral Dual-energy X-ray Absorptiometry (pDXA)	♦ Forearm ♦ Finger ♦ Heel	
Quantitative Computed Tomography (QCT)	♦ Spine	♦ Measures both trabecular and cortical bone
Peripheral Quantitative Computed Tomography (pQCT)	♦ Forearm	♦ Measures both trabecular and cortical bone
Quantitative Ultrasonography (QUS)	♦ Heel ♦ Shin	♦ Portable ♦ No radiation exposure ♦ No water bath ♦ Takes ~3 mins

* Radiation dose < standard X-ray

Foundation (NOF) in determining treatment thresholds. Deviation from the age-matched reference group (Z-score) is most useful for identifying patients who have secondary causes of osteoporosis but is not used for diagnosis.⁶

Central BMD testing of the hip and/or spine utilizing dual-energy absorptiometry (DXA) is the preferred method for diagnosing osteoporosis and monitoring changes due to drug therapy. Machines that measure peripheral sites utilizing ultrasonography (e.g., heel) are not currently recommended for the diagnosis of osteoporosis or for monitoring response to therapy. They are, however, valuable as screening devices because they are easy to use, safe (no radiation exposure), and portable. Pharmacists are increasingly becoming involved in osteoporosis disease state management programs with peripheral bone screenings.

Bone loss occurs at differing rates depending on the anatomical site. In the early postmenopausal time period, there can be discordance between central and peripheral skeletal sites (i.e., BMD in the heel may be normal, but low in the spine or the hip).²³ Based on this, the rule of thumb is to confirm any normal peripheral BMD test in women considered at risk for osteoporosis. Ideally, bone density at more than one anatomical site should be tested, as there is always a risk of missing a diagnosis when

one skeletal site is measured regardless of a peripheral or central measurement. This helps to explain why it is optimal to obtain both hip and spine measurements for DXA scans.

There is little evidence to show that healthy young women lose bone or those with low bone density have an increased risk of fracture.²⁵ A low BMD does not necessarily represent loss but may indicate a low peak bone mass. Therefore, young women should not routinely have BMD testing performed unless there is a reason to suspect secondary osteoporosis.

Biochemical Markers of Bone Turnover

Bone turnover markers (such as N-telopeptide crosslinks and bone-specific alkaline phosphatase) are either enzymes or proteins secreted by osteoblasts or osteoclasts or substances produced during the formation or breakdown of type-1 collagen.²⁶ Urinary or serum markers of bone turnover provide useful information to sup-

plement bone mineral density measurements. They can help identify patients with high bone turnover and are utilized for early monitoring of drug therapy response. While it takes 1-2 years to see significant changes in bone mineral density with drug therapy, changes in bone turnover markers can be seen as early as 3 months.²⁵ Biochemical markers cannot be used to diagnose osteoporosis due to the high variability in results with currently available tests and the limited data on correlation between levels and fracture risk.

Diagnosis

Central BMD testing is the gold standard method for establishing a diagnosis of osteoporosis in postmenopausal women. It can also be useful as a tool in determining risk for future fracture. WHO has developed definitions and criteria for the diagnosis of osteoporosis (Table 6). Women with osteoporosis who have already experienced one or more

Diagnosis	BMD Criteria
Normal	BMD value within 1 SD of young adult mean (T-score above -1)
Osteopenia	BMD value between -1 SD and -2.5 SD below young adult mean (T-score between -1 and -2.5)
Osteoporosis	BMD value at least -2.5 SD below young adult mean (T-score below -2.5)
Severe Osteoporosis	BMD value at least -2.5 SD below young adult mean and presence of fracture (T-score below -2.5 and presence of fracture)

fractures are considered to have severe or established osteoporosis. It is important to remember that

this diagnostic criterion was based on large cohorts of caucasian postmenopausal women and extrapolation

to other populations has not been validated.

V. Prevention and Treatment of Osteoporosis

Goals

Since osteoporosis is often asymptomatic, it is important to educate patients about the disease process and its long-term sequelae. Outcomes and goals should be discussed so patients better understand why it is important to comply with osteoporosis management strategies. Additionally, pharmacist-initiated programs should establish goals to measure success. The following goals are important in osteoporosis prevention and treatment:

- Prevent fractures
- Optimize skeletal development and maximize peak bone mass at skeletal maturity
- Prevent age-related and secondary causes of bone loss
- Preserve the structural integrity of the skeleton
- Improve quality of life
- Decrease morbidity and mortality

These goals can be attained with patient adherence and appropriate non-pharmacologic and pharmacologic management.

Lifestyle Modification

Pharmacists can have an active role in educating patients about attaining peak bone mass and maximizing their ability to prevent osteoporosis. Lifestyle modifica-

tion measures, such as increasing exercise and decreasing caffeine intake as well as alcohol and tobacco, impact the development of osteoporosis. These interventions are cost-effective and can be recommended to persons of all ages.

Physical activity or exercise is one of the most important non-pharmacologic approaches to preventing fractures in persons at risk for osteoporosis. As mentioned previously, fracture risk involves bone strength, previous fracture history, and mechanical aspects of fractures. Exercise, especially weight-bearing exercise, has the potential to stimulate bone growth

“Since osteoporosis is often asymptomatic, it is important to educate patients about the disease process and its long-term sequelae.”

and improve bone strength, muscular performance, joint flexibility, and balance to decrease the risk of falls and fracture

National guidelines recommend regular weight-bearing and muscle strengthening exercise to reduce the risk of falls and fracture.²⁰ Examples of weight-bearing exercises are walking, jogging, stair climbing, basketball, soccer, hiking, gymnastics, dancing, and

tennis. Weight lifting can also improve muscle mass and bone strength. Swimming is not considered a weight-bearing exercise but can be used in conjunction with other exercises. Exercise programs that include weight-bearing activity performed 3-4 times per week for 45 minutes and/or weight lifting 2-3 times per week for 20-30 minutes have been shown to be beneficial.^{27,28} Caution must be used to make sure that the appropriate exercises are performed using correct techniques.

The pharmacist should be adequately prepared to discuss physical activity with patients. Prior to discussing exercise, the pharmacist should ensure that the patient is medically clear to proceed with activity. An evaluation of current exercise habits should be performed to establish a baseline.

This would include the type, frequency, duration, and intensity of the exercise(s). Considerations for a successful program include site specific exercising, continuation of the exercise program, and application of progressively increasing loads.²⁹ In patients with restricted activity levels, non-weight bearing exercises, such as bicycling or chair exercises, can improve balance and may be sufficient to improve bone density.³⁰ Virtually

all patients should be counseled on proper exercise regimens since this approach can help in preventing osteoporosis.

Cigarette smoking is associated with a lower baseline BMD, decreased sex hormone concentrations, lower body weight, early menopause, increased bone markers, and decreased calcium and vitamin D absorption.³¹⁻³³ Studies have shown up to 80% increased risk of developing fracture in smokers.³⁴⁻³⁶ Since the use of tobacco is harmful to bone and an independent risk factor for osteoporosis, all smokers should be encouraged to quit and the pharmacist can play an active role in helping

with smoking cessation.

Excessive consumption of alcohol and caffeine should also be discouraged. Moderate alcohol and caffeine consumption, at approximately two drinks per day, may be acceptable for bone health.

Alcoholics are at increased risk of osteoporosis due to poor nutrition, impaired calcium and vitamin D metabolism, and risk of falls.

Caffeine consumption has been associated with increased calcium excretion. Patients consuming large amounts of caffeine should have adequate calcium intake.

Pharmacists should encourage patients to limit alcohol and caffeine intake.

Fall Prevention

Falls present significant problems for patients at high risk for fracture. Common causes of falling include frailty and associated deconditioning, poor visual acuity, impaired hearing, and use of medications that impact neuromuscular reflexes.⁶

Pharmacists can play a significant role in this prevention strategy by asking patients about their home environments to ensure safe living. Table 7 provides a checklist and suggestions for preventing common hazards.³⁷ Additionally, the pharmacist can evaluate patient medication lists for agents that may impair cognition and balance. Multiple medications have been associated with increased risk of falls in the elderly. For example, long-acting hypnotics/ anxiolytics, anti-hypertensives, anticonvulsants, antipsychotics, antidepressants, and analgesics.

Calcium and Vitamin D

Adequate calcium and vitamin D intakes are necessary to maintain bone health throughout life. Calcium is valuable to the skeleton because it can decrease bone turnover and decelerate bone loss.³⁸ Vitamin D increases calcium absorption in the gastrointestinal tract and affects bone resorption.³⁹ Calcium and vitamin D have been shown to increase BMD 2-10% and decrease fracture rates 35-50%.⁴⁰⁻⁴³ It should be noted that vitamin D alone does not decrease fracture rate but appears to provide

Problem	Suggestion
Lighting Poor access to switches/lamps Low lighting Lack of night lights	Place switches/lamps at room entrances Provide extra lighting, especially along paths and stairways Use nightlights, 100- to 200-watt bulbs
Floors and hallways Clutter Low-lying objects Waxed or wet floors Sliding throw rugs Curled carpet edges Raised door sills	Keep home environment neat and tidy Remove low-lying or difficult to see objects Provide non-skid rugs and carpet runners Replace throw rugs with non-skid rugs or place pads beneath rugs Tape down all carpet edges prone to curling Remove or place carpet over sills to create smooth transition
Bathrooms problems Low toilet seat Inaccessible tub/shower stall Slippery floor tiles Slippery tub/shower floor	Use elevated toilet seat Install wall-mounted or tub-attached grab bars Apply non-skid strips/decals Place non-skid rubber mat/decals
Stairway problems Lack of handrails Slippery steps	Install cylindrical handrails Apply non-skid treads to steps
Furniture problems Low chair or bed height Armless chairs	Replace low furniture with higher or thicker furniture Provide chairs with armrest support
Storage problems Shelves too low/high Unstable chairs/step stools	Keep frequently used items at waist level Use "reach" device to obtain objects

Table 8: Calcium and Vitamin D Recommendations

Group	National Institutes of Health ⁴⁶	
	Calcium	Vitamin D
Infants Birth to 6 mo 6-12 months	400 600	
Children 1-5 years 6-10 years	800 800-1200	
Adolescents/young adults 11-24 years	1200-1500	600-800
Women 25-50 years >50 years (postmenopausal) On estrogen Not on estrogen Over 65 years Pregnant and nursing	1000 1000 1500 1500 1200-1500	600-800 600-800 600-800 600-800
Men 25-65 years Over 65 years	1000 1500	600-800 600-800

an additive effect to calcium for fracture reduction.⁴⁴ Studies have shown that adequate amounts and high absorption of calcium and vitamin D are important to maximize the benefits of these nutrients.⁴⁵

Several different organizations have established the appropriate intake amounts of calcium and vitamin D. Table 8 lists recommended calcium and vitamin D intake as determined by the National Institutes of Health.⁴⁶ According to this guideline, most patients aiming to reduce the risk of osteoporosis should consume 1000-1500 mg elemental calcium and 400-800 IU vitamin D daily. A more simplified guideline from the National Osteoporosis Foundation suggests a daily calcium intake of 1200 mg for women > 20 years old

and an additional 400-800 mg of vitamin D intake for women > 65 years old. It is important to note that only about 50-60% of adults meet the recommendations.⁵ It is optimal to achieve these calcium requirements through calcium-containing foods. Table 9 lists foods with increased calcium content. Food labels list the calcium content based on consumption of 1000 mg daily. For example, milk containing 30% calcium per serving is equivalent to 300 mg elemental calcium. Beverages fortified with calcium citrate malate (CCM) or FruitCal

(e.g., Sunny Delight with Calcium®, Tropicana Bursters®) provide more absorbable calcium gram for gram than milk. (i.e., 5.3 ounces of CCM-fortified beverage equals same amount of absorbable calcium as 8-ounces of milk.)

If patients are unable to con-

sume adequate amounts of calcium through foods, calcium supplements may be used. Controversy exists regarding the best calcium salt for supplementation. The two primary types of calcium used are calcium carbonate and calcium citrate. Calcium phosphate and calcium gluconate are also available. Calcium carbonate should be taken with food since it requires an acidic environment to maximize its absorption capacity. Calcium carbonate contains 40% elemental calcium, the highest amount available compared to other calcium formulations. This option is cost-effective and may be preferred for most patients.⁴⁶ Calcium citrate may have better absorption than calcium carbonate and can be taken with or without food. However, it is more expensive, contains less elemental calcium (21%), and is available in fewer formulations.⁴⁷ Calcium citrate may be beneficial for patients with

Table 9: Calcium Content of Selected Foods^{6,29}

Foods	Calcium content (mg)	Foods	Calcium Content (mg)
Milk, 1 cup (skim, lowfat, whole)	290-300	Calcium-fortified orange juice, 1 cup	300
Yogurt, 1 cup	240-415	Salmon, canned with bones, 3 oz.	167-210
Frozen yogurt, 1 cup	180-240	Sardines, canned with bones, 3 oz.	372
Swiss cheese, 1 oz.	250-270	Shrimp, canned, 3 oz.	98
Cheddar, mozzarella, or muenster cheese, 1 oz.	205	Collard greens, cooked, 1 cup	357
Ricotta cheese, 4 oz.	335	Broccoli, cooked, 1 cup	100-180
Cottage cheese, 4 oz.	78-100	Soybeans, cooked, 1 cup	131
Vanilla ice cream, 1 cup	176-200	Tofu, 4 oz.	108-155
Soft-serve vanilla ice cream, 1 cup	236	Almonds, 1 oz.	75

achlorhydria or those taking H₂ antagonists or proton pump inhibitors. Calcium phosphate contains 30% elemental calcium for a dibasic formulation and approximately 37.5% elemental calcium for a tribasic formulation. Calcium gluconate has a low elemental calcium content at 9%. CCM is absorbed 35-55% greater than calcium carbonate^{48,49} and is available as a calcium supplement (CalciMate[®]) found in selective nutrition stores. CCM, like calcium citrate, can be taken with or with food and is absorbed in low GI acidity conditions.⁵⁰

The labels of various calcium supplements should be evaluated to determine the amount of elemental calcium per dose. Labels will usually provide a total strength per dose and elemental calcium content. Additionally, the total amount of calcium may vary depending on the formulation. For example, the extra strength or ultra formulations of some products will contain more calcium. Table 10 lists several available over-the-counter calcium supplements. The pharmacist can make a significant impact by assisting patients with appropriate calcium supplement selection since labels can be confusing. Many patients do not take the correct amount of calcium because they base their dosage upon the total strength per dose and not the elemental calcium content.

Calcium absorption can be affected by several medication factors. The absorption is decreased with dietary fiber, fiber laxatives,

“Once a diagnosis has been made and non-pharmacologic measures have been instituted, drug therapy for prevention/treatment of osteoporosis should be initiated.”

and antacids. Conversely, calcium can decrease the absorption of iron, quinolones, and tetracyclines. Patients should take <500 mg elemental calcium per dose to maximize absorption potential.⁵¹ The most common adverse effects of calcium are constipation, bloating, cramps, and gas. Patients can increase fluid intake, eat more fiber, and if necessary, try a different product to reduce these side effects if they occur.

The first step in the activation of vitamin D occurs in the skin

through the conversion of 7-dehydrocholesterol to vitamin D₃ (cholecalciferol) by ultraviolet (UV) light.⁵² Subsequent activation

occurs through the liver and kidneys. Vitamin D deficiency often occurs in the elderly because their ability to convert vitamin D through the skin

decreases with aging. In addition, elderly patients that are institutionalized are not adequately exposed to sunlight. Most patients require 400 IU vitamin D daily. Older and severely osteoporotic patients need 800 IU per day. Exogenous vitamin D can be obtained from milk, green vegetables, vitamin D supplementation, or multivitamins.

Drug Therapy

Once a diagnosis has been made and non-pharmacologic measures have been instituted, drug therapy for prevention/treat

Table 10: Over-the-counter Calcium Supplements

Name	Type of calcium	Strength per tablet (mg)	Elemental calcium (mg)
Alka-Mints [®]	Calcium carbonate	850	340
Caltrate [®]	Calcium carbonate	1500	600
Caltrate + D [®]	Calcium carbonate + vitamin D	1500	600+200 IU Vit D
Oyster shell calcium Oscal [®] and generics	Calcium carbonate	1250	500 (Vit D in some formulations)
Titralac [®]	Calcium carbonate	420	168
Tums [®]	Calcium carbonate	500	200
Tums EX [®]		750	300
Tums ULTRA [®] (Generics available)		1000	500
Viactive [®]	Calcium carbonate	1250	500
Viactive with D [®]		1250	500+100 IU Vit D
Citracal [®]	Calcium citrate	950	200
Citracal + D [®]		1500	315+200 IU Vit D
Posture [®]	Calcium phosphate	1500	600
Posture-D [®]		1500	600+125 IU Vit D

Table 11: FDA Approved Indications and Dosing

Drug	Prevention PMPW	Treatment PMPW	Prevention GIOP	Treatment GIOP	Treatment Men
Estrogen Dose	Yes Depends on Product	No	No	No	No
Risedronate Dose	Yes 5 mg QD 35 mg QWk*	Yes 5 mg QD 35 mg QWk*	Yes 5 mg QD	Yes 5 mg QD	No
Alendronate Dose	Yes 5 mg QD 35 mg QWk	Yes 10 mg QD 70 mg QWk	No	Yes 5/10 mg QD	Yes 10 mg QD 70 mg QWk
Raloxifene Dose	Yes 60 mg QD	Yes 60 mg QD	No	No	No
Calcitonin Dose	No	Yes 200 IU QD	No	No	No

PMPW = Post-menopausal Women GIOP = Glucocorticoid-induced Osteoporosis
*Pending FDA approval at time of writing

ment of osteoporosis should be initiated. The NOF suggests starting drug treatment when the T-score reaches -2.0 standard deviations below the mean in women without risk factors, when the T-score reaches -1.5 standard deviations below the mean in women with risk factors, and those with fragility fracture. The American Association of Clinical Endocrinologists⁶ also suggests drug treatment in women where nonpharmacologic measures are ineffective as evidenced by continued bone loss or occurrence of low-trauma fractures.

There are five agents approved by the U.S. Food and Drug Administration (FDA) for the prevention and/or treatment of osteoporosis: estrogen, risedronate, alendronate, raloxifene, and calcitonin. Table 11 summarizes the FDA-approved indications and recommended dosing for these products. All of these agents

are considered antiresorptive therapies as they decrease bone turnover through various effects on osteoclasts. These therapies do not stimulate new bone formation. They slow the remodeling process and reduce the depth of resorption. Bone formation exceeds bone resorption at these remodeling sites leading to the gains in bone density seen with these agents. The following sections will discuss the evidence supporting the effect of

“...to maximize the effect of prescription drug therapies for osteoporosis, consumption of adequate amounts of calcium and vitamin D are essential.”

these agents on fracture risk and BMD as well as non-bone effects. In almost all the drug studies discussed in this section, both the placebo and treatment group consumed calcium (500-1000 mg) and vitamin D (400-800 IU) throughout the course of the studies.

Therefore, to maximize the effect of prescription drug therapies for osteoporosis, consumption of adequate amounts of calcium and vitamin D are essential.

Hormone Replacement

While these terms are frequently used interchangeably, hormone replacement

(HRT) refers to the use of both estrogen and progesterone and estrogen replacement (ERT) refers to the use of estrogen alone. The progesterone component of HRT is utilized to protect the endometrium in women with an intact uterus. ERT is used in women who have had a hysterectomy and are no longer at risk for endometrial cancer.

Effect on Fractures and BMD

As mentioned previously, the most important goal of osteoporosis therapy is the prevention of fractures. The ability of HRT/ERT to reduce the risk for vertebral and non-vertebral fractures has been demonstrated in several

observational studies.⁵³⁻⁵⁵ Reductions of up to 43% in spinal fractures and 45% in non-spinal fractures have been observed. A recent meta-analysis evaluated the effects of HRT on non-vertebral fractures.⁵⁶ The results demonstrated a significant reduction in hip

and wrist fractures of 40% with HRT. The benefit was greater in women aged 60 years and younger.

Although HRT/ERT has been proven in prospective, randomized studies to increase BMD, and multiple observational studies have suggested positive effects on fracture risk, the fact remains that the anti-fracture efficacy of HRT has not been established in a large, prospective clinical trial. In order to receive a treatment indication, osteoporosis therapies must demonstrate fracture risk reduction. Due to the lack of fracture data, the FDA "quietly" removed the indication for treatment of osteoporosis. Estrogens are only FDA-approved for the prevention of osteoporosis.

The ability of estrogen to increase bone mineral density at the hip and spine is well documented in several controlled trials and observational studies. Increases in BMD of approximately 5% at the spine and 2% at the hip have been observed.⁵⁷ Positive effects on BMD are also evident in older women with low bone density. Low dose conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) in combination with adequate doses of calcium and vitamin D significantly increased spine BMD in late postmenopausal women (age > 65 years).²² HRT also significantly increased BMD in women over the age of 75 years with mild to moderate physical frailty.⁵⁸

While significant increases can

be seen with HRT, they may not be as great as those seen in younger postmenopausal women. Some studies have shown HRT to be most beneficial when initiated early after menopause and when continued for at least 7 years duration.^{59,60}

Transdermal estrogens also significantly increase BMD and can be effectively used in women who have contraindications to or cannot tolerate the oral forms of estrogen.⁶¹

It is important to be aware that some postmenopausal women

“It is important to be aware that some postmenopausal women receiving HRT/ERT will continue to lose bone mass despite adequate therapy.”

receiving HRT/ERT will continue to lose bone mass despite adequate therapy.⁶² The reasons for this continued bone loss is not completely understood. A current smoking history and low body weight have been associated with HRT failure.⁶³ The NOF recommends women who have been on long term estrogen therapy undergo BMD testing to confirm an adequate response to therapy.²⁰

HRT/ERT does not stop the menopausal increase in bone resorption but delays it. Once therapy is stopped, a rapid state of bone loss will ensue.⁶⁴ This phenomenon was supported by data from observational studies which showed that BMD/fracture risk in past users of estrogen was similar to never users.^{54,59} Bone loss may

be prevented by placing high risk women who stop HRT/ERT on a bisphosphonate.⁶⁴

Non-bone Risks/Benefits of HRT

Controversy still exists as to the non-bone benefits and risks of HRT/ERT. An individualized benefit/risk analysis should be done at the time of menopause to determine whether or not HRT/ERT is the best choice for the management of osteoporosis in a particular patient.

In addition to osteoporosis, estrogens have other well-documented benefits. They are the most effective agents for the management of menopausal symptoms such as hot flashes and genitourinary symptoms.⁶⁵⁻⁶⁷ Oral

estrogens have beneficial effects on lipoproteins, decreasing low-density lipoprotein (LDL) levels, and increasing high-density lipoprotein (HDL) levels. These positive effects are not seen with transdermal administration and are blunted by the administration of medroxyprogesterone acetate (MPA).⁶⁸⁻⁷⁰ Data also suggest estrogen use may decrease the risk of developing dementia^{71,72} and colorectal cancer.⁷³

Until the Heart and Estrogen/Progestin Replacement Study (HERS) was published, cardioprotection was considered one of the primary benefits of estrogen therapy.⁷⁴ Numerous cohort studies indicated that patients who received HRT had a lower risk for cardiovascular disease (CVD) events.^{53,75}

The problem with these non-randomized trials was that they were subject to the "healthy-user" bias. It is well described that women who choose to be on HRT tend to be younger, healthier, thinner, more educated and of a higher socioeconomic class.⁷⁶⁻⁷⁸ Therefore, these differences may be due to the type of women receiving HRT rather than the effect of HRT. The HERS trial, the first prospective, randomized study to evaluate the effects of HRT on secondary prevention of CVD, showed no difference between the treatment and placebo groups in the occurrence of CVD events.⁶⁹ There was a significant trend towards an increase in CVD events in the treatment group within the first year and a decrease in years 4-5. Other subsequently published studies have demonstrated similar results.⁷⁹⁻⁸² Results are conflicting whether HRT/ERT is beneficial for the primary prevention of CVD. The results of the Women's Health Initiative, a large, prospective study examining this issue, will be available in 2005.⁸³ Based on HERS and other recent studies, the American Heart Association recommends that HRT not be initiated in patients with known CVD or for the sole purpose of cardiac protection.⁸⁴

One of the main reasons for women to refuse HRT/ERT is their fear of breast cancer. There have been multiple observational studies published evaluating the risk of

breast cancer with HRT/ERT.⁸⁵⁻⁹⁰ The results of these studies have been conflicting. Overall, it appears there may be a small increased risk for breast cancer in women who use HRT/ERT for 5 years or more. However, mortality rates from breast cancer are lower in HRT users.^{88,91} Due to the emotional impact of breast cancer, the risk should be thoroughly discussed prior to committing a patient to long-term HRT/ERT.

Other risks associated with oral estrogen therapy include up to a 3-fold increased risk for venous thromboembolism (VTE), an increased risk for gallbladder disease and hypertriglyceridemia, and a two-fold increased risk for endometrial cancer.^{69,92} Transdermal estrogens bypass the liver; therefore they do not increase triglycerides or the risk for gallbladder disease. Adding progesterone therapy (usually 10 days per month) in women with an intact uterus will decrease the risk for endometrial hyperplasia and cancer back to baseline.

According to the American College of Obstetrics and Gynecology, the following are absolute contraindications to the use of estrogens: pregnancy, active or severe chronic liver disease, unexplained vaginal bleeding, recent vascular thrombosis, and history of breast or endometrial cancer.⁶⁵ Side effects of estrogen therapy include breast tenderness, nausea, headaches, fluid retention,

and vaginal bleeding. Progesterone side effects are minimal but may include fluid retention, vaginal bleeding, and mood swings.

Bisphosphonates

Bisphosphonates are structural analogs of pyrophosphate. They have a strong affinity for the hydroxyapatite crystals in bone and once absorbed into the systemic circulation, rapidly distributed to bone resorption sites. At these sites, the bisphosphonates are potent inhibitors of osteoclastic activity. Once bone resorption at a remodeling site is inhibited, the bisphosphonates are either released back into circulation where they undergo elimination through the kidneys, or they get incorporated into new bone. Bisphosphonates that are incorporated into bone are inactive until they are released back into circulation.

Risedronate (Actonel[®]) and alendronate (Fosamax[®]) are the only bisphosphonates FDA-approved for the prevention and treatment of osteoporosis. (See Table 11.) Alendronate, a nitrogen-containing bisphosphonate, came onto the market in 1995, risedronate, a pyridinyl bisphosphonate, in 2000. No new oral bisphosphonates are scheduled to become available for at least several years.

The strict administration guidelines for bisphosphonates are based upon bioavailability and tolerability issues with these agents. The bioavailability of risedronate in the fasting state is <1% with reduc-

tions in bioavailability of 30-55% if dosed 0.5 or 1.0 hour before breakfast.^{93,94} One study that evaluated the effect of dosing 2 hours after an evening meal demonstrated similar bioavailability to administration 0.5 hour before breakfast. The mean bioavailability of alendronate is also < 1%. It is decreased by approximately 40% when administered either 0.5 or 1 hour before breakfast and 60% when administered with coffee or orange juice. It differs from risedronate in that its bioavailability is negligible if administered up to two hours after breakfast.^{95,96}

Risedronate is well tolerated. Clinical trials have shown similar incidences of GI adverse events when compared to placebo even in patients with a history of upper GI disease, those receiving NSAID or salicylates, or those using acid suppression therapy (i.e., H₂-antagonists, proton pump inhibitors). The most common adverse events reported with risedronate include arthralgia, diarrhea, headache, abdominal pain, and skin rash.⁹⁴ Postmarketing surveillance has also supported risedronate's excellent tolerability. During its first 6 months on the market, approximately 250,000 prescriptions were written with only 29 spontaneous reports of upper GI adverse events, three of which were considered severe.⁹⁷

The most common concern patients and healthcare providers have with alendronate is the poten-

tial for gastrointestinal (GI) upset. Data from randomized clinical studies have shown similar incidences of side effects (abdominal pain, nausea, dyspepsia, and acid regurgitation) with alendronate compared to placebo, even in patients with a history upper GI tract disease or NSAID use.⁹⁵

However, post-marketing surveillance for alendronate revealed a larger than expected number of reports of esophageal adverse events, such as esophagitis and esophageal ulcers and erosions.⁹⁸ Inappropriate administration of the drug was thought to contribute to many of these adverse events. Alendronate is contraindicated in patients with abnormalities of the esophagus that delay esophageal emptying such as stricture or achalasia.⁹⁶

To maximize the absorption of risedronate and alendronate, it is important that patients are instructed that both products must be taken with 6-8 oz. of plain water first thing in the morning on an empty stomach. Patients need to wait a minimum of 30 minutes before eating, drinking, or taking any medications. Dosing directions from other countries state that risedronate can be given at other times of the day provided that administration is separated 2 hours before and after food or drink (except water) and at least 30 minutes before bedtime.⁹⁴

To decrease the risk for GI adverse events, patients must take

these medications (with at least 6-8 oz of plain water) and remain upright for at least 30 minutes and until the first food of the day has been ingested.^{93,96}

Risedronate's Effect on Fractures and BMD

Two large randomized trials compared the effects of risedronate and placebo on vertebral fractures in postmenopausal women with severe osteoporosis (low bone density and existing vertebral fractures).^{99,100} In these trials, risedronate 5 mg/day resulted in a statistically significant 61-65% reduction in the risk for new radiographic vertebral fractures (identified by scheduled X-ray evaluation) at one year and 41-49% reduction after 3 year. Multiple vertebral fractures were reduced by 96% at one year.¹⁰¹ Non-vertebral fractures were reduced by 39% in one trial but not the other. A two-year extension demonstrated a sustained risk reduction of 50% in new vertebral fractures and a statistically significant reduction in non-vertebral fractures of 37% at 5 years.¹⁰² A pooled analysis of these studies has also revealed a statistically significant reduction in clinical vertebral fractures (those identified by the patient or doctor due to symptoms) as early as 6 months.³

The effect of risedronate on the risk for hip fractures was evaluated in a large 3-year prospective trial.¹⁰³ This is the only osteoporosis trial with a primary endpoint of hip fracture reduction. Two groups

of postmenopausal women were evaluated. The first group included women aged 70-79 years with osteoporosis. The second group included women 80 years and older with either one non-skeletal risk factor (i.e., smoking, fall history) for hip fracture or osteoporosis. Patients were not recruited based on a history of a previous fracture. Overall, risedronate 5mg/day reduced the risk of hip fracture by 30% in both groups of women studied. Evaluation of the two groups independently revealed a significant reduction in hip fractures only in the 70-79 age group. The incidence of hip fracture was not significantly reduced in the over 80 group, most of whom only had risk factors for hip fracture. The reduction was most notable in the women with baseline vertebral fractures.

In healthy, early postmenopausal women, risedronate 5 mg/day significantly increases spine and hip BMD by 1-3%.¹⁰⁴ Increases in BMD of approximately 5-6% at the spine and 2-3% at the hip can be seen in postmenopausal women with severe osteoporosis.^{99,100}

Alendronate's Effect on Fracture and BMD

The Fracture Intervention Trial (FIT) was designed to determine the effect of alendronate on the

incidence of vertebral and non-vertebral fractures in postmenopausal women with low bone mass. The trial was divided into two separate arms. The clinical fracture arm evaluated only postmenopausal women with low bone density (osteopenia or osteoporosis). The vertebral fracture arm included postmenopausal women with existing vertebral fractures.

Patients in the clinical fracture arm received alendronate therapy (5 mg for 2 years, then 10 mg for 2 years) or placebo for 4 years.¹⁰⁶ In this arm of the study, alendronate

“Based on their superior fracture efficacy and their ability to reduce the risk of vertebral fractures within the first year of therapy, bisphosphonates are considered first-line therapy for the treatment of osteoporosis, especially in patients with preexisting fractures.”

significantly reduced the risk for clinical fractures by 36% only in women who had osteoporosis. The overall risk of new radiographic vertebral fractures was reduced by 44%. Again, the affect was greatest in the women with osteoporosis.

Patients in the vertebral fracture arm received alendronate therapy (5 mg for 2 years, then 10 mg for 1 year) or placebo for 3 years.¹⁰⁷ In these patients with severe osteoporosis, alendronate therapy reduced the risk for new radiographic vertebral fractures by 47%, multiple radiographic vertebral fractures by 90%, clinical ver-

tebral fractures by 55% and hip fractures by 51%.

To further examine the effect of alendronate on fractures, women enrolled in FIT who had osteoporosis with or without the presence of a baseline vertebral fracture, were included in a pooled analysis.¹⁰⁸ The results of this analysis demonstrated similar fracture risk reductions of 53% at the hip and 45-48% at the spine. In addition, there was a 59% reduction in clinical vertebral fractures which was statistically significant by 12 months.

Alendronate prevents bone loss in early postmenopausal women with osteopenia. At the FDA-approved prevention dose of 5mg/day, studies have shown increases in bone density at the hip and spine of up to 3-

4%.^{109,110} Greater effects on BMD have been demonstrated in women with more severe disease.

Alendronate 10mg/day for 3-4 years in postmenopausal women with osteoporosis resulted in BMD increases of up to 8-9% at the spine and 6-8% at the hip.^{106,111} Seven-year data indicates continued increases in spinal BMD of up to 11% in this population.¹¹²

Risedronate and alendronate have been shown to preserve bone in early postmenopausal women with osteopenia. They have the largest increases in bone density of all the available antiresorptive

therapies. They rapidly decrease the risk for vertebral fractures (risedronate within 6 months) and are the only FDA-approved agents that have demonstrated anti-fracture efficacy at the hip in prospective, randomized, controlled trials. The greatest benefits with these therapies are seen in women with severe osteoporosis who are at the highest risk for fracture. Based on their superior fracture efficacy and their ability to reduce the risk of vertebral fractures within the first year of therapy, bisphosphonates are considered first-line therapy for the treatment of osteoporosis, especially in patients with preexisting fractures.

Once-Weekly Bisphosphonates

Compliance with drug therapy in chronic disease states is a challenge, especially in those that are asymptomatic. Once weekly administration of bisphosphonates may increase patient convenience and compliance.¹¹³ Once weekly administration of alendronate has been shown to result in similar increases in BMD, changes in markers of bone turnover and side effects as once daily.^{114,115} Once weekly alendronate is FDA-approved at a dose of 35 mg/week for prevention and 70mg/week for treatment of postmenopausal osteoporosis. Once weekly risedronate at a dose of 35mg/week is currently being evaluated; FDA-approval is pending at the time of this writing.

Selective Estrogen Receptor Modulators (SERMS)

Selective estrogen receptor modulators (SERMS) have mixed agonist and antagonist effects on various estrogen receptors throughout the body. Raloxifene (Evista[®]) is the only SERM approved for the prevention and treatment of osteoporosis in the U.S. Raloxifene has estrogen-like effects on lipid metabolism and bone and estrogen-antagonist effects on endometrial and breast tissue.

Raloxifene's Effect on Fractures and BMD

Raloxifene significantly increases bone mineral density, but to a lesser degree than estrogen and the bisphosphonates. Two identical, prospective, randomized, controlled trials were conducted which compared raloxifene to placebo in 1145 healthy postmenopausal women with normal BMD or osteopenia. The combined 3-year interim analysis demonstrated that raloxifene 60 mg/day increased BMD by 1-2% from baseline at all body sites.¹¹⁶ Raloxifene has also been shown to significantly increase bone density and reduce the risk for new and recurrent vertebral fractures in osteoporotic women with or without baseline vertebral fractures.¹¹⁷ In the MORE trial (Multiple Outcomes of Raloxifene Evaluation), raloxifene 60 mg/day significantly increased BMD by 2-3% at the hip and spine and significantly reduced the risk for new

vertebral fractures by 30-50%. The risk for multiple vertebral fractures was significantly reduced by 93% only in those patients without pre-existing vertebral fractures.¹¹⁸

Raloxifene did not reduce the risk for nonvertebral fractures. A subsequent evaluation of the MORE data revealed a statistically significant 68% relative risk reduction in the incidence of new clinical vertebral fractures at 1 year.¹¹⁹

Non-bone Risks/Benefits of Raloxifene

Like estrogen, raloxifene has non-bone benefits and risks that must be taken into consideration. Raloxifene has no effect on the endometrium. Therefore, it does not cause vaginal bleeding or increase endometrial cancer risk. Raloxifene has been shown to have some positive effects on surrogate markers of cardiovascular risk including reducing LDL cholesterol, but it has no effect on HDL cholesterol.^{70,116,120} The effect of raloxifene on CVD events is currently being investigated in the RUTH trial (Raloxifene Use for The Heart) which has an anticipated publication date of 2005.

Raloxifene's effect on breast cancer risk may prove beneficial. The overall risk of breast cancer for postmenopausal women who received raloxifene in the MORE trial was 65% lower than the placebo group.¹²¹ The RUTH study will also be further evaluating this benefit. It is hoped that raloxifene may be a viable alternative for

women at high-risk for breast cancer.

Raloxifene is contraindicated in any woman with a history of VTE as it can increase the risk for VTE by 3-fold.^{117,122} The most common side effects associated with raloxifene are leg cramps and hot flashes.¹²² Raloxifene should be used with caution in postmenopausal women suffering from hot flashes as this drug can make the symptoms worse.

Raloxifene is effective at reducing vertebral fracture risk. However, it has not been proven to reduce hip fracture risk. In most circumstances, raloxifene is considered a second- or third-line therapy for postmenopausal women who refuse or cannot tolerate HRT/ERT and have a contraindication to bisphosphonates.²⁰

Calcitonin

Calcitonin (derived from salmon) is a polypeptide hormone that inhibits ongoing bone resorptive processes by decreasing the number and activity of osteoclasts. Calcitonin is available as a subcutaneous or intramuscular injection (Calcimar[®]) or nasal spray (Miacalcin[®]). It is only approved for the treatment of osteoporosis in females greater than 5 years postmenopause. Adverse reactions associated with the injectable form (local reactions, flushing, rash, and rare systemic allergic-type reactions) have limited its use. The recommended dose of Miacalcin[®] is one spray (200 I.U.) per day

administered intranasally, alternating nostrils daily. Side effects are rare and include mostly nasal complaints of dryness, soreness, irritation, itching, and epistaxis.¹²³

Calcitonin Effect on Fractures and BMD

Studies in postmenopausal women with low bone density have demonstrated significant increases in spine BMD over baseline (1-3%) with 200 I.U. calcitonin nasal spray. Significant changes in hip BMD have not been demonstrated.¹²⁴⁻¹²⁶

Intranasal calcitonin (200 IU/day) was shown in a large, prospective trial to significantly reduce the risk for new vertebral fractures by 33-36%. Interestingly, reductions in vertebral fractures were not seen with the 100 IU or 400 IU, and the 200 IU dose did not result in a significant reduction in the risk for multiple new vertebral fractures.

Overall, the effect of calcitonin on non-vertebral fractures has not been well established. Calcitonin is considered third-line therapy for postmenopausal women with osteoporosis who refuse HRT and have a contraindication to bisphosphonates.²⁰

Calcitonin Other Effects

There is some antidotal evidence that calcitonin has an analgesic effect in patients with osteoporotic fracture pain.^{127,128} The mechanism is not well understood, but increases in beta-endorphin levels have been implicated. Some

physicians may use intranasal calcitonin short-term for pain relief in patients with an acute vertebral fracture. It is important to keep in mind that there is only one small study (21 patients) that has demonstrated a benefit with intranasal calcitonin. Physicians should be educated that this proposed effect is not well supported in the literature. If a patient is started on calcitonin for pain relief, it is important to document an objective benefit, otherwise it should be discontinued. In addition, the use of calcitonin should not preclude the use of other first-line osteoporosis therapies (i.e., bisphosphonates) in this high risk patient population.

Combination Therapy

The following drug combinations have been evaluated in small randomized, controlled trials: raloxifene and alendronate, risedronate and HRT, and alendronate and HRT.¹²⁹⁻¹³² Statistically significant increases in bone density can be seen without increases in side effects. None of the combinations studied evaluated the impact on fractures. Until larger and longer trials with fracture data are available, combination antiresorptive therapy should not be recommended. Combination therapy with HRT/ERT and a bisphosphonate may be appropriate for postmenopausal women who are receiving HRT/ERT for its non-skeletal benefits (e.g., menopausal symptoms).

Other Non-FDA Approved Therapies

Etidronate and Pamidronate

Etidronate and pamidronate are bisphosphonates that have been used off-label in the management of osteoporosis. Etidronate is approved for this indication in Europe. Etidronate significantly increases BMD at the spine and hip and reduces the rate of spinal fractures.^{133,134} It is given in an intermittent cyclic regimen of 400mg daily for 14 days, repeated every 3 months. Concerns regarding etidronate's potential to inhibit mineralization of new bone leading to osteomalacia and the FDA-approval of newer bisphosphonates (e.g., risedronate, alendronate) has decreased its role in osteoporosis. Pamidronate is administered by intravenous infusion. A loading dose of 90 mg is typically given followed by 30 mg every 3 months. It can be tried in patients who are unable to absorb or cannot tolerate oral bisphosphonates.

Parathyroid Hormone (PTH)

As mentioned previously, all current FDA-approved agents for osteoporosis reduce bone resorption and have only a modest effect on increasing BMD. PTH is the first agent nearing approval that affects bone formation (although its full mechanism of action is not fully understood). Continuous exposure to PTH has been shown to cause an increased differentiation of osteoclasts and increased bone resorption. Intermittent expo-

sure appears to increase osteoblast numbers and activity leading to increased bone formation. In postmenopausal women with prior vertebral fracture, daily subcutaneous injections of 20-40mcg recombinant human PTH (1-34) for 18 months significantly reduced the risk of one or more new vertebral fractures by 65-69%, two or more by 77-86%, and non-vertebral fractures by 53-54%.¹³⁵ Bone density increases of up to 14% at the spine and 5% at the hip were observed. Side effects associated with PTH included nausea, headaches, leg cramps, and dizziness. Similar effects have been seen in studies evaluating the addition of PTH to HRT.^{136,137} July 2001, the Endocrinologic and Metabolic Drugs Advisory Committee recommended that the FDA approve Fortéo[®] (recombinant human parathyroid hormone) as a second-line agent for the treatment of osteoporosis in postmenopausal women and men. This committee also stated that more studies need to be done to determine the optimal duration of therapy and safety of combination therapy, and they recommended risk management steps to help assure the safe use of this agent.¹³⁸ Those steps include:

- ♦ A monitoring protocol for osteosarcoma and cardiovascular response
- ♦ Limiting the use to patients who are at significant risk for osteoporotic fractures
- ♦ Use as second line therapy in combination with an antire-

sorptive agent or in patients unresponsive or unable to take antiresorptive agents

- ♦ Limit the use of this agent to 2 years

Thiazide Diuretics

Thiazide diuretics may be beneficial as adjunct therapy for the prevention of osteoporosis due to their ability to decrease urinary excretion of calcium.

Observational studies have suggested that patients who receive thiazide diuretics have a greater bone mass, lower rates of bone loss, and fewer fractures. Two recent prospective, controlled trials demonstrated that patients randomized to hydrochlorothiazide had small increases in bone mass over placebo.^{139,140} More data is needed on the effect of thiazides on BMD as well as fracture risk.

Soy Products and Alternative Medicines

There are conflicting data regarding the use of soy products and alternative medicines for the prevention of osteoporosis. Isoflavones are water-soluble chemicals found in plants.¹⁴¹ Soy isoflavones and semisynthetic isoflavones (e.g., Ipriflavone[®]) have been studied for protection against osteoporosis.¹⁴²⁻¹⁴⁴ These studies have been of short duration with small numbers of patients and have demonstrated either a small effect or no effect on bone loss reduction. Overall, data evaluating soy products and alternative medicines have not demonstrated bene-

fit in osteoporosis, especially without fracture data. Furthermore, studies are lacking in their consistency for dosing, product manufacturing and patient characteristics.

Monitoring

Monitoring response to therapy should be done using central bone densitometry.¹⁴ Bone density at peripheral sites does not significantly change in response to drug therapy. The most metabolically active and therefore the most sensitive site for monitoring changes in bone density is the spine.²⁴

However, degenerative changes in the spine that occur due to aging can make measurements at this site less accurate in patients over the age of 65. It can take up to 2 years to see clinically significant changes in bone density. To be 95% confident that the change in bone density observed is significant, the change must be > 2.8 times the precision error of the instrument used (1-2% for central DXA).¹⁴ Therefore, changes of >3-5% at the hip or spine, after 2 years of therapy, must be observed for the change to be considered

significant. If serial monitoring with bone densitometry is to be used, testing is most accurate if performed on the same site and with the same machine and operator (technician). Markers of bone turnover can also be utilized for monitoring early response to therapy and to assist with compliance. They should be obtained at baseline and repeated after 3-6 months of therapy. Decreases of approximately 50% in baseline values of these markers are expected with antiresorptive drug therapy.

VI. Special Populations

Glucocorticoid-induced Osteoporosis (GIOP)

Glucocorticoid use is the most common cause of secondary osteoporosis. Up to 50% of patients taking chronic glucocorticoids sustain osteoporotic fractures.¹⁴⁵ The pathophysiology of GIOP is multifactorial. Corticosteroids can decrease bone formation by decreasing the lifespan and function of osteoblasts. They increase bone resorption by decreasing estrogen and testosterone levels, by decreasing calcium absorption, and by increasing calcium excretion.¹⁴⁵⁻¹⁴⁷

The degree of bone loss associated with glucocorticoid use is dependent on the dose and duration of therapy;¹⁴⁶ the higher the glucocorticoid dose, the greater the risk for fracture.¹⁴⁸ Equipotent

doses of glucocorticoids have equal effects on BMD and alternate day dosing does not appear to decrease the risk of fracture and bone loss. Bone loss associated with glucocorticoids is rapid. Patients can lose as much as 30% of their BMD within 6-12 months.^{145,146} Bone loss occurs mostly in regions high in trabecular bone. Therefore, vertebral frac-

“...bisphosphonate therapy [risedronate] should be considered in any patient beginning therapy with ≥ 5.0 mg/day of prednisone or equivalent for longer than 3 months.”

tures are the most common fractures seen.¹⁴⁶

Management of GIOP is similar to that of other osteoporosis populations. In addition to the dose

and anticipated duration of glucocorticoid therapy, other modifiable and non-modifiable risk factors should be taken into consideration. Preventative therapy, including lifestyle modification, calcium (1500 mg elemental/day), vitamin D (400-800 IU/day), and bisphosphonate therapy should be considered in any patient beginning therapy with ≥ 5.0 mg/day of prednisone or equivalent for longer than 3 months.¹⁴⁹ Risedronate is the only bisphosphonate with a specific indication for the prevention of GIOP. A baseline central bone density evaluation should be performed at the onset of therapy

if the expected duration is > 6 months.^{146,149} Due to the rapid loss of bone that can occur with glucocorticoid therapy, BMD testing can be repeated as early as 6-12

months to evaluate for changes.

Patients receiving chronic glucocorticoid therapy and/or with a documented low bone density (T-score below -1) or fragility fracture, should receive pharmacologic therapy. Risedronate and alendronate are the only agents FDA-approved for the treatment of GIOP.

Risedronate and GIOP

The efficacy of risedronate in the prevention and treatment of GIOP was demonstrated in two 1-year, randomized, controlled trials including a total of 518 men and women. One trial focused on prevention in patients recently started on glucocorticoids.¹⁵⁰ The other trial examined patients on long-term (> 6 months) glucocorticoid therapy who already had low BMD.¹⁵¹ Risedronate 5mg/day resulted in maintenance of spine and hip BMD in the prevention trial and significant increases in BMD in the treatment trial. In both trials, significant decreases in BMD occurred in the placebo groups. There was a trend toward reduction in the incidence of vertebral fractures, however individually the studies were not powered to detect a difference. In a combined, post hoc analysis of these studies, risedronate 5mg/day significantly reduced overall vertebral fracture risk by 70% and multiple vertebral fracture risk by 91%.¹⁵²

Alendronate and GIOP

The efficacy of alendronate for

the treatment of GIOP was also demonstrated in two, 1-year, randomized, controlled trials including a total of 560 patients.¹⁵³ Both studies enroll patients with varying durations of glucocorticoid use. The combined results of this study showed that alendronate 5 mg or 10 mg/day significantly increased BMD compared to placebo. The increases between the 5 mg and 10 mg doses were similar in all patients except postmenopausal women not receiving estrogen. In these women, the 10 mg dose resulted in greater increases in BMD. After one year of therapy, significant reductions in vertebral fractures were not seen. However, after a one-year extension of the trial, a significant reduction in new vertebral fractures was demonstrat-

“Adolescence is a critical time for bone development because 40-60% of peak bone mass is attained during the adolescent years.”

ed in a pooled analysis of the 5mg and 10 mg doses.¹⁵⁴

The ACR and UK recommendations provide useful treatment algorithms for various patient populations taking glucocorticoids. In pre-menopausal women or men with documented low sex hormone levels, hormonal replacement is the therapy of first choice. Testosterone replacement should be utilized in men and high dose oral contraceptives (\geq 50 mcg

ethinyl estradiol) should be tried in pre-menopausal women.

Bisphosphonates are an option for pre-menopausal females, but adequate contraceptive measures should be used. Men with normal gonadal function should receive bisphosphonate therapy. HRT or a bisphosphonate is recommended for postmenopausal women.

Adolescents

Adolescence is a critical time for bone development, because 40-60% of peak bone mass is attained during the adolescent years.^{155,156} It is known that achieving a higher peak bone mass during adolescence protects against postmenopausal osteoporosis.¹⁵⁷ Exercise, proper calcium intake, and regular menses help to reach peak bone mass. However, several factors can contribute to sub-optimal achievement of peak bone mass.

The Recommended Dietary Intake (RDI) of calcium for girls aged 9-18 years is 1300 mg/day.¹⁵⁸ Adolescent girls in the US consume an average of 800 mg calcium/day, only 62% of the RDI and less than 16% meet the RDI.^{159,160} One study proposed that this decreased dairy intake may be due to increased consumption of carbonated beverages among adolescents.¹⁶¹ The author found that 9th- and 10th-grade girls, consuming mostly cola beverages, were three times more likely to have a bone fracture compared to girls not

consuming carbonated beverages. The high phosphorous content of carbonated beverages may have been contributing to decreased bone development on the basis of secondary hyperparathyroidism. In addition to proper calcium intake, it is important for adolescents to obtain positive energy balance from other macronutrients, such as vitamin D, magnesium and phosphorous. The Food and Nutrition Board of the National Academy of Science has deemed these nutrients most related to bone health.

Protein is important for the appropriate synthesis of the bone matrix. Studies have demonstrated that appropriate caloric and protein intake are critical in achieving peak growth potential.¹⁶² Anorexia-nervosa, exercise-associated amenorrhea, and delayed puberty may also contribute to the failure of patients attaining optimal peak bone mass.³⁷ Other risk factors contributing to the development of bone loss include low body mass, sex steroid deficiency, and childhood disease states, such as cystic fibrosis, diabetes, and growth hormone deficiency. Therefore, appropriate nutrition, especially adequate calcium intake, and physical activity should be emphasized in adolescents to achieve optimal peak bone mass.

Perimenopausal Women

Perimenopause is a time period beginning several years prior to the average age of menopause (51

years) and is characterized by abnormal menstrual cycles and episodic symptoms of menopause, like hot flashes and night sweats. Estrogen levels are falling during this time, and various decisions regarding the use of oral contraceptives or HRT may be considered. As a woman prepares to enter menopause, the most critical time for bone loss, a baseline bone mineral density should be considered if risk factors are present and she is willing to consider potential interventions.^{6,7} The pharmacist

“One quarter of all U.S. men over the age of 60 will experience an osteoporotic fracture in their lifetime.”

should provide general education regarding lifestyle modification (weight-bearing exercise, smoking) and calcium + vitamin D intake to this patient population.

Men

There has been increased recognition that osteoporotic fractures in men represent an important healthcare concern. There are approximately 1.5 million American men over the age of 65 who have osteoporosis and another 3.5 million who are at an increased risk.¹⁶³ One quarter of all U.S. men over the age of 60 will experience an osteoporotic fracture in their lifetime.^{20,147} Mortality rates for men are higher for all types of fractures compared to women.¹⁶⁴ Thirty percent of men will die

within one year of a hip fracture compared to 20% of women.¹⁶⁵ The direct healthcare costs associated with osteoporosis in men were estimated in 1995 at 2.7 billion per year. All these figures are expected to rise with the aging of society.

Osteoporosis is less common in men than women for several reasons. Men have a greater accumulation of bone mass during growth and a greater bone size and strength. Men do not undergo a period of rapid bone loss like women experience after menopause and have a lower propensity to fall. Fracture risk in men increases several years later than women, but their average life expectancy is 5 years less.

Classification of osteoporosis in men can be divided into two categories: primary and secondary. Primary causes of osteoporosis are aging (>70 years) and idiopathic. The secondary causes of osteoporosis include hypogonadism, disease states, medications, and lifestyle.¹⁶³ In 40-60% of the cases of osteoporosis in men, a secondary cause for the disease is identified. There are a significant number of men with osteoporosis for which there is no explanation.

Risk factors for osteoporosis in men are similar to those in women. Additional risk factors include quadriceps weakness, high body sway, and falls in the previous 12 months.¹⁶⁶

There are no guidelines for the

diagnosis and treatment of osteoporosis in men. Bone mineral density should be considered in men with evidence of a low trauma fracture or prevalent vertebral deformity, radiographic evidence of osteopenia, height loss of >1.5 inches, conditions known to increase the risk for bone loss and fracture, multiple risk factors, and age greater than 75 years with risk factors.^{163,167} Central BMD testing is the gold standard for men. Peripheral screening is not currently recommended due to the lack of data in this population. Diagnostic thresholds are not available for men. There is data that men and women fracture at similar T-scores.¹⁶⁸ Therefore, the WHO classification is typically applied to men.

There are no drug therapies approved for prevention of osteoporosis in men. Lifestyle modifications and appropriate elemental calcium (1200-1500 mg/day) and vitamin D intake (400-800 IU/day) are the cornerstones of preventative therapy. In men with osteoporosis with or without fracture, drug therapy is indicated. Alendronate at a dose of 10mg/day or 70mg/week is the only agent FDA-approved for the treatment of osteoporosis in men. Efficacy is based on one prospective, randomized trial in men with primary osteoporosis.¹⁶⁹ This study showed statistically significant

increases in spine BMD of 7% and hip BMD of 2% after 2 years of therapy. These increases in BMD are comparable to those seen in postmenopausal women. Although fracture reduction was not a primary endpoint of this study, there was a significant reduction in the incidence of vertebral fractures in the alendronate-treated group.

Risedronate has not been specifically studied in men with primary osteoporosis; however, it is approved for the prevention and treatment of glucocorticoid-induced osteoporosis in men. Risedronate therapy in men with GIOP has shown fracture reductions (66% relative risk reduction) comparable to postmenopausal women.

“In frail elderly with documented osteoporosis (especially with a history of previous fragility fracture), bisphosphonate therapy should be instituted.”

Data regarding testosterone replacement in men with osteoporosis are conflicting. Increases in BMD have been demonstrated in men with documented hypogonadism who receive testosterone replacement therapy.¹⁷⁰ Whether or not eugonadal men achieve a benefit from testosterone replacement remains to be seen. Testosterone replacement is available as a 5mg patch or intramuscular injection. Side effects of testosterone therapy

include weight gain, acne, edema dyslipidemia, and increase in hematocrit, azospermia, gynecomastia, and prostate disorders. It is essential that prostate cancer be ruled out prior to starting men on testosterone therapy.

Frail Elderly

The majority of hip fractures occur in individuals over the age of 70. In the US, the elderly (residents > age 65) are the fastest growing segment of the population. Therefore, the number of frail elderly at risk for hip (and vertebral) fractures will continue to grow. Frail elderly, especially those in nursing homes and other long-term care facilities, are at very high risk for fractures due to advanced age, low BMD, and a

high prevalence for other risk factors: poor physical function, poor nutrition, vitamin D deficiency, dementia/decreased cognition, and multiple medications that can increase falls

and decrease bone mass.⁵ Advanced age, low bone density, fall to the side, and impaired mobility are all independently associated with an increased hip fracture risk in frail, elderly nursing home patients.¹⁷¹ Each risk factor must be addressed to limit sequelae in this high risk population.

It is essential that this population obtains adequate calcium and vitamin D as studies have shown a positive effect on hip fracture

risk.^{172,173} Fall precautions and appropriate exercise that can improve mobility should be instituted. Medication profiles should be evaluated for any medications that are associated with an increased fall risk or impair bone

health. In frail elderly with documented osteoporosis (especially with a history of previous fragility fracture), bisphosphonate therapy should be instituted. As mentioned previously, risedronate and alendronate are most beneficial in

patients who are at the highest risk for fracture. They work quickly to reduce the incidence/risk of hip and vertebral fractures and have been proven beneficial in elderly patient with osteoporosis.^{103,174}

VIII. Role of the Pharmacist

The pharmacist has a great opportunity to become actively involved in the care of nearly all men and women for their bone health. The pharmacist can provide risk factor assessment, screening for osteoporosis, and education for prevention and treatment of osteoporosis. (See Table 12 for an overview of the role of the pharmacist)

Procter & Gamble has a patient education slide show available for pharmacists to help educate patients about osteoporosis, identification of risk factors, and ways

to prevent fracture. This slide show can be found on the Web at www.CEConcepts.net/bone. Risk factor assessment involves taking an accurate patient history to determine the need of further evaluation. Several tools are available to perform this task (Table 3).

Peripheral bone screening can be performed in most community pharmacy settings. This measurement provides valuable information by identifying patients with low bone mass and helps to establish the need for further evaluation.^{6,7} Education about prevention of osteo-

maintaining optimal bone health. Lifestyle modifications include proper diet, exercise, alcohol intake, tobacco use, and fall prevention.

Pharmacists should counsel patients requiring pharmacologic therapy for prevention or treatment of osteoporosis with care and empathy. Medication regimens for osteoporosis are often difficult to adhere to, because most patients are asymptomatic. One study noted that patients with fair-to-poor self-rated health and patients with four or more depressive symptoms were most likely to discontinue study medication.¹⁷⁵ Like other chronic diseases, patients with osteoporosis are often psychologically and socially impacted. Anxiety, depression, and social withdrawal or isolation can become problems if not appropriately addressed.¹⁷⁶ The physical abnormalities that can result from osteoporosis may lead to significant psychological problems. Women with depression are more likely to experience falls and fractures compared to women without depression.¹⁷⁷ The pharmacist must be aware of these potential problems and be responsive to

Table 12: Potential Role of Pharmacist in Management of Osteoporosis

- ◆ Educating public about disease (including good bone health habits)
- ◆ Assessing risk factors
- ◆ Performing peripheral bone mineral density testing
- ◆ Ensuring adequate consumption of calcium/vitamin D
- ◆ Reviewing appropriate and adequate exercise
- ◆ Discussing limits of alcohol and caffeine
- ◆ Advising and assisting with smoking cessation
- ◆ Discussing measures to prevent falls
- ◆ Discussing the emotional, physical, and social impact of osteoporosis
- ◆ Educating patients about osteoporosis medications
- ◆ Assessing compliance/adherence to all issues of medications with emphasis on self care
- ◆ Assess medication regimen for:
 - ✓ Drugs that harm bone health
 - ✓ Drugs that can increase risk of falls
 - ✓ Appropriate medication for high risk patients
- ◆ Developing disease state management program in osteoporosis

porosis should be focused on non-pharmacologic and pharmacologic approaches. Both men and women of all ages can benefit from education about osteoporosis. Lifestyle modification and proper calcium and vitamin D intake are critical in obtaining peak bone mass and

the concerns of patients. Pharmacists should encourage patients to take responsibility for self-management, including taking calcium and vitamin D, performing exercise, practicing home safety, and adhering to medication regimens. This enables patients to take control of their osteoporosis and maintain a higher quality of life.

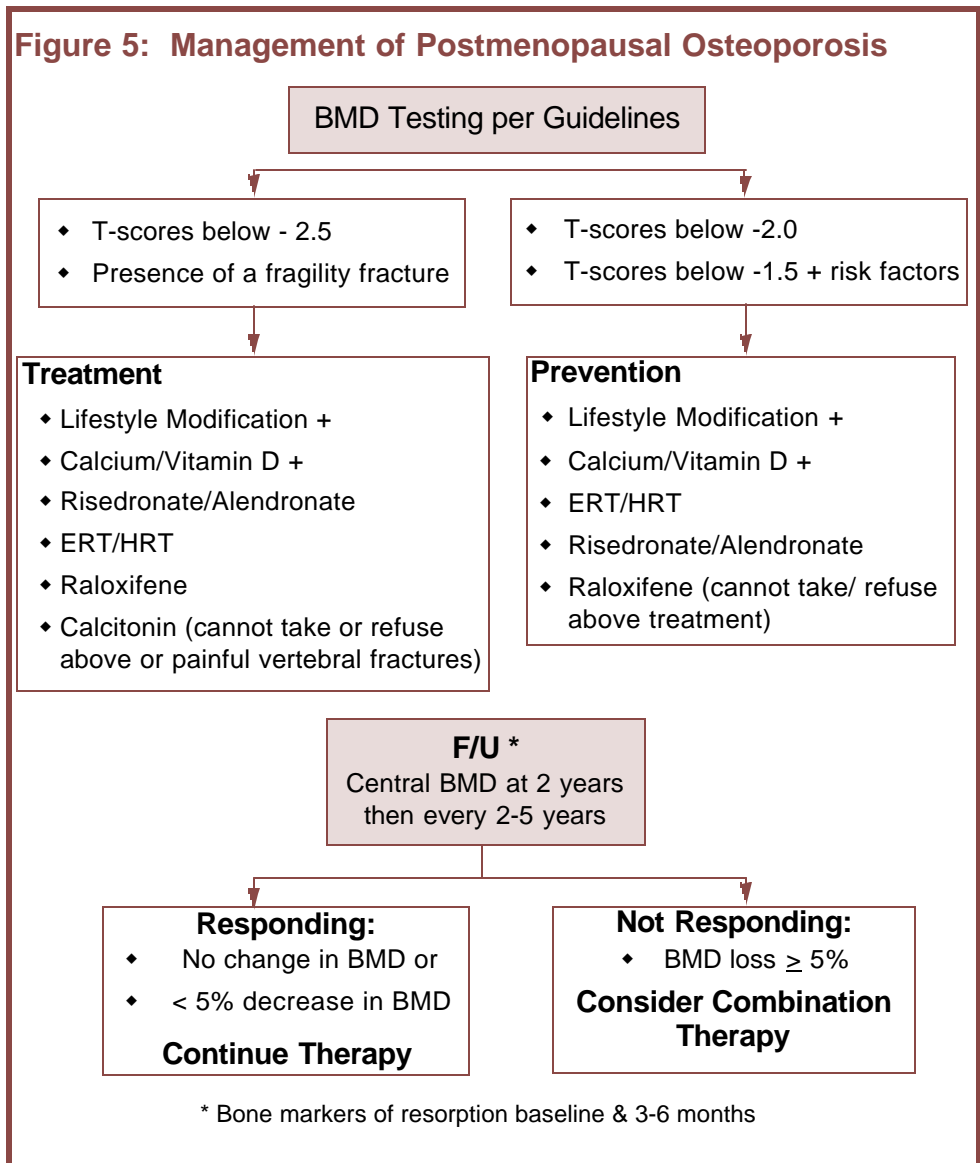
Many pharmacists have taken the initiative to design and implement a disease state management program for osteoporosis. Pharmacists can provide peripheral bone screening and education for osteoporosis. These services can increase customer traffic into the pharmacy and offer companion sales opportunities. However, several things must be considered prior to pursuing this endeavor.¹⁷⁸

Store demographics will be an important factor when deciding who may be eligible for this type of management program. Targeting females > 50 years, males > 65 years and patients taking osteoporosis therapies may be an acceptable starting point. Choosing the appropriate screening technology may include considering the type of peripheral BMD machine, ease of use, size, cost, company support and regulatory implications. Regulatory issues may vary from state to state. These include machine registration and fees, machine transport, operator requirements, inspection and renewal and shielding requirements. Identifying physician "champions" in the community

will be critical to establishing referral sources. When marketing the program, it should be stressed that results should and will be shared with the physicians. Marketing and advertising of the program can include bag stuffers, banners, direct mailings and newspaper, radio and television ads. Lastly, in-store logistics should be modified such that the disease state management program can be delivered in a caring and private to semi-private environment.

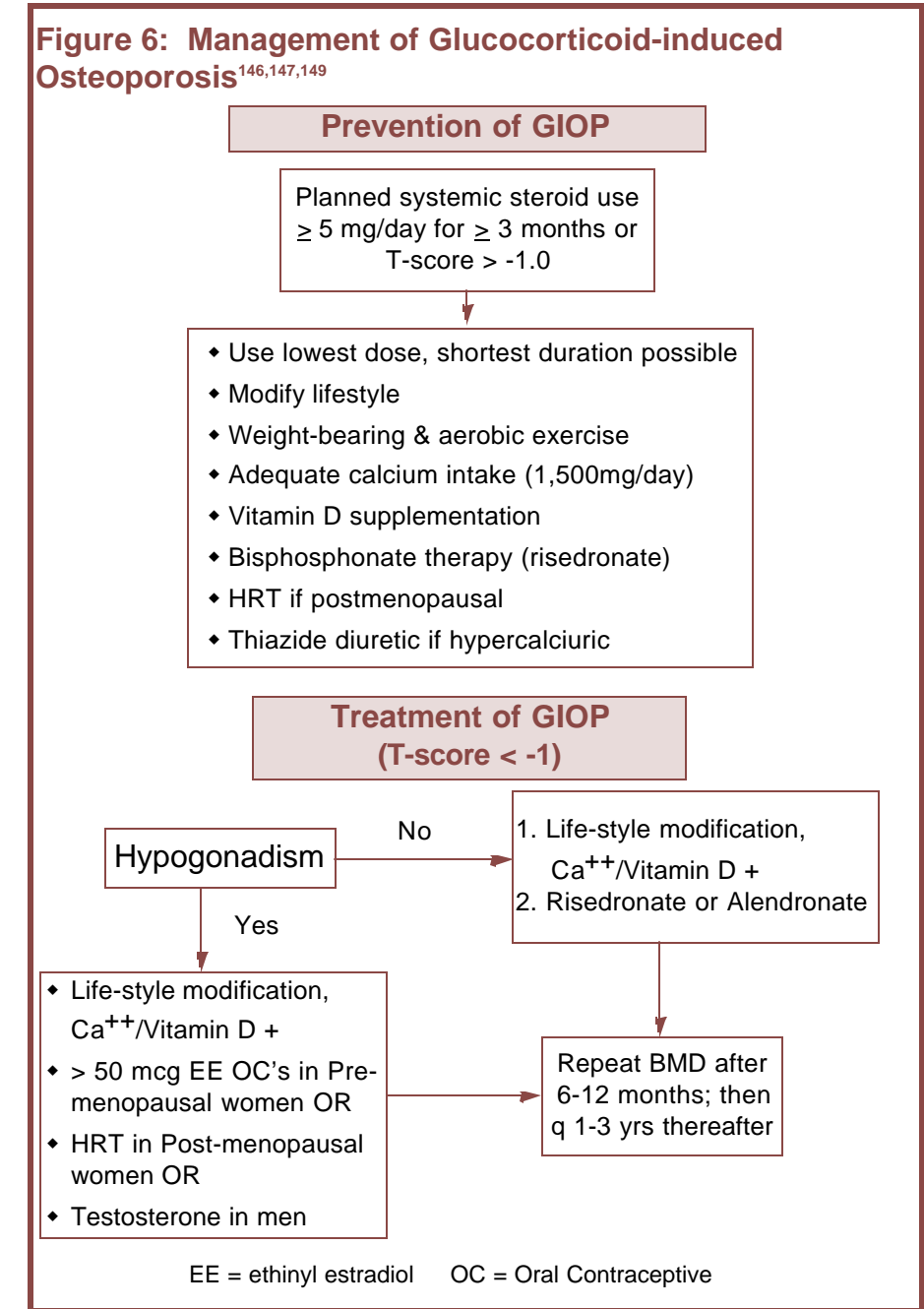
When providing a disease state management program, the poten-

tial and realized reimbursement opportunities should be evaluated and pursued. Options for reimbursement include patient self-pay, contractual agreements, or billing third-party payers. Contractual agreements can be made with managed care organizations, employers, physician groups, and others in a fee for service, capitation, or risk sharing structure. Additionally, reimbursement can be requested for the full service (BMD testing, education, etc) or only for BMD testing. Regardless, all fees must be standardized so that all patients



are charged the same amount for the same service. Most pharmacists charge \$35-\$50 for BMD screening and education when requesting direct payment from patients. When submitting claims to third party payers, pharmacists should submit a claim that includes a provider number (for service provision given by the third party payer), a claim form (i.e., HCFA 1500) and a statement of medical necessity. A cover letter can further explain the request for payment and what services were provided. It is helpful, but not necessary, to provide documentation of services provided. The complete structure and management of reimbursement will be determined by the agreements and protocols set forth between pharmacists and physicians and third party payers in the community.

Pharmacists have a great opportunity to provide pharmaceutical care when screening and educating patients about osteoporosis. The prevention and treatment of osteoporosis can be rewarding, because pharmacists can help decrease the morbidity and mortality of patients susceptible to the consequences of this disease. Pharmacists should remain educated and informed of new develop-



ments in osteoporosis. The flow diagrams found in Figures 5 and 6 are current resources to help with the decision-making process for the prevention and treatment of osteoporosis. However, informa-

tion about osteoporosis is rapidly changing, and pharmacists must be willing to accept the challenges of being life-long learners.

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Continuing Education Examination

Continuing Education Questions

- 1. Which of the following is true regarding trabecular bone?**
 - A. Comprises 80% of the skeleton
 - B. Found mostly in the peripheral skeleton
 - C. More metabolically active than cortical bone
 - D. Stronger than cortical bone
- 2. Which of the following is true regarding Type-1 osteoporosis?**
 - A. Due to "high turnover" bone loss
 - B. Women over the age of 70 years are at greatest risk
 - C. Usually secondary to a disease or medication
 - D. Cortical bone is affected more than trabecular bone
- 3. Which of the following risk factors have been shown to increase the risk of hip fracture?**
 - A. Female gender
 - B. Caucasian race
 - C. Current cigarette smoker
 - D. Sedentary lifestyle
- 4. Which of the following measurements is considered the best for the diagnosis of osteoporosis?**
 - A. Peripheral DXA of the forearm
 - B. Central DXA of the spine
 - C. Ultrasound of the heel
 - D. Urinary markers of bone turnover
- 5. According to the World Health Organization diagnostic criteria using bone mineral density, what T-score indicates osteoporosis?**
 - A. Between -1.0 SD and -2.5 SD from the young adult mean
 - B. Between -1.0 SD and -2.5 SD from age- and sex-matched controls
 - C. Below -2.5 SD from the young adult mean
 - D. Below -2.5 SD from age- and sex-matched controls
- 6. According to the National Osteoporosis Foundation, which of the following patients would be most appropriate to recommend central BMD testing?**
 - A. A 55 year-old woman with two risk factors
 - B. A 62 year-old woman taking estrogen for 12 years
 - C. A 72 year-old woman taking calcium daily
 - D. All of the above
- 7. According to the NIH guidelines, how much calcium should a postmenopausal woman (age 59 years) on hormone replacement therapy consume?**
 - A. 800 mg daily
 - B. 1000 mg daily
 - C. 1200 mg daily
 - D. 1500 mg daily
- 8. Which of the following is true regarding lifestyle modifications in patients concerned about osteoporosis?**
 - A. Swimming 2-3 times per week is beneficial for BMD
 - B. Caffeine should be limited to 4 cups/day
 - C. Weight-lifting 2-3 times per week is beneficial for BMD
 - D. Smoking should be limited to 1/2 pack/day
- 9. Which of the following is true regarding the use of vitamin D in osteoporosis?**
 - A. Vitamin D increases calcium absorption in the GI tract
 - B. The recommended amount is 100-200 IU/day
 - C. Vitamin D can only be obtained from oral supplementation
 - D. Vitamin D alone can decrease fracture rates
- 10. Which of the following is true regarding estrogen therapy in osteoporosis?**
 - A. It is safe to initiate estrogen in a woman who experienced a myocardial infarction 3 months ago.
 - B. It is approved for both prevention and treatment of osteoporosis.
 - C. Estrogen therapy loses its protective effect on bone after it is discontinued.
 - D. There are many prospective trials using estrogen that demonstrate fracture reduction.

- 11. Which of the following is FDA-approved for the prevention of glucocorticoid-induced osteoporosis?**
- A. Risedronate
 - B. Alendronate
 - C. Calcitonin
 - D. Raloxifene
- 12. Which of the following therapies are proven to reduce hip fractures?**
- A. Hormone replacement therapy
 - B. Selective estrogen receptor modulators
 - C. Soy products
 - D. Bisphosphonates
- 13. Reductions in clinical vertebral fractures have been demonstrated as early as 6 months with risedronate.**
- A. True
 - B. False
- 14. Alendronate, but not risedronate, is contraindicated in patients with abnormalities of the esophagus, which delay esophageal emptying such as stricture or achalasia.**
- A. True
 - B. False
- 15. Which of the following is true regarding raloxifene?**
- A. May decrease the risk for breast cancer
 - B. Increases the risk for venous thromboembolism by 3 fold
 - C. Can make hot flashes worse
 - d. All of the above
- 16. Which of the following is true regarding glucocorticoid-induced osteoporosis?**
- A. Alternate-day dosing of the steroid does not protect against bone loss
 - B. BMD loss becomes a concern once a patient has been on therapy for over one year.
 - C. Steroid users can lose an average of 2-4% BMD per year
 - D. BMD loss becomes a concern only in patients receiving > 10mg/day of prednisone (or equivalent)
- 17. Osteoporosis is more common in women than men because...?**
- A. Men absorb dietary calcium better
 - B. Men have a higher accumulation of bone mass during growth
 - C. Men are not genetically prone to osteoporosis
 - D. Men are better able to convert vitamin D to its active form
- 18. Which of the following contribute to optimal peak bone mass during adolescence?**
- A. Adequate calcium intake
 - B. Appropriate protein intake
 - C. Physical activity
 - D. All of the above
- 19. Which of the following components is essential when developing an osteoporosis disease management program?**
- A. Purchasing a central DXA machine
 - B. Ensuring alternative products (i.e., soy) are available for patients
 - C. Establishing a target patient population
 - D. Have a physician in the store during BMD screening to interpret results
- 20. Which of the following is an appropriate role for pharmacists discussing osteoporosis with patients?**
- A. Performing peripheral bone mineral density testing
 - B. Educating patients about osteoporosis medications
 - C. Discussing measures to prevent falls
 - D. All of the above

Notes



Creative Educational Concepts, Inc. is approved by the American Council of Pharmaceutical Education as a provider of continuing pharmaceutical education.


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Start Date: March 15, 2002 Expiration Date: Feb. 28, 2005



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HEALTH CARE

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Practice Opportunities.

Prevention of Osteoporosis and Osteoporotic Fracture

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Name _____

RPh PharmD PhD Other_____

Home Address _____

Soc Sec # _____ Daytime Phone _____

E-Mail _____

Practice Site: _____ Independent Pharmacy _____ Chain Pharmacy
 _____ Grocery Pharmacy _____ Mass Merchandiser
 _____ College or School _____ Other

Evaluation (Please indicate your answers to the following questions.)

	Strongly Disagree		Strongly Agree		
	1	2	3	4	5
The objectives for the program were achieved.	1	2	3	4	5
The program was a valuable learning experience for me.	1	2	3	4	5
The information was covered in sufficient detail.	1	2	3	4	5
The examination was representative of the material presented.	1	2	3	4	5
Approximately how long did it take you to complete this program and Continuing Education Examination?	1	2	3	4	5

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18. A B C D
19. A B C D
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