

Clinician's Guide

to Prevention
and Treatment
of Osteoporosis



Developed by the
**National
Osteoporosis
Foundation**

Clinician's Guide to Prevention and Treatment of Osteoporosis

Developed by the National Osteoporosis Foundation and endorsed by:

American Academy of Physical Medicine and Rehabilitation

American Association of Clinical Endocrinologists

American College of Obstetricians and Gynecologists

American College of Radiology

American College of Rheumatology

American Geriatrics Society

American Orthopaedic Association

American Osteopathic Association

American Society for Bone and Mineral Research

International Society for Clinical Densitometry

International Society of Physical and Rehabilitation Medicine

The Endocrine Society

Attention Clinicians:

It is important to note that the recommendations developed in this Guide are intended to serve as a reference point for clinical decision-making with individual patients. They are not intended to be rigid standards, limits or rules. They can be tailored to individual cases to incorporate personal facts that are beyond the scope of this Guide. Because these are recommendations and not rigid standards, they should not be interpreted as quality standards. Nor should they be used to limit coverage for treatments.

This Guide was developed by an expert committee of the National Osteoporosis Foundation (NOF) in collaboration with a multi-specialty council of medical experts in the field of bone health convened by NOF. Readers are urged to consult current prescribing information on any drug, device or procedure discussed in this publication.

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Disclosure

No member of the Guide Development Committee has a relevant financial relationship with any commercial interest.

Note to Readers

This Guide is designed to serve as a basic reference on the prevention, diagnosis and treatment of osteoporosis in the US. It is based largely on updated information on the incidence and costs of osteoporosis in the US. For those with low bone mass (in whom more than 50 percent of fractures occur) the Guide incorporates an analysis from the World Health Organization (WHO) that assesses 10-year fracture risk. The Guide utilizes an economic analysis prepared by the National Osteoporosis Foundation in collaboration with the WHO (Dr. J. Kanis), the American Society for Bone and Mineral Research, the International Society for Clinical Densitometry and a broad multidisciplinary coalition of clinical experts, to indicate the level of risk at which it is cost-effective to consider treatment. This information combined with clinical judgment and patient preference should lead to more appropriate testing and treatment of those at risk of fractures attributable to osteoporosis.

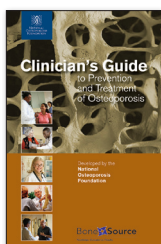
This Guide is intended for use by clinicians as a tool for clinical decision-making in the treatment of individual patients. While the guidance for testing and risk evaluation comes from an analysis of available epidemiological and economic data, the treatment information in this Guide is based mainly on evidence from randomized, controlled clinical trials. The efficacy (fracture risk reduction) of medications was used in the analysis to help define levels of risk at which it is cost effective to treat.

The Guide addresses postmenopausal women and men age 50 and older. The Guide also addresses secondary causes of osteoporosis which should be excluded by clinical evaluation. Furthermore, all individuals should follow the universal recommendations for osteoporosis prevention outlined in this Guide.

The recommendations herein reflect an awareness of the cost and effectiveness of both diagnostic and treatment modalities. Some effective therapeutic options that would be prohibitively expensive on a population basis might remain a valid choice in individual cases under certain circumstances. This Guide cannot and should not be used to govern health policy decisions about reimbursement or availability of services. Its recommendations are not intended as rigid standards of practice. Clinicians should tailor their recommendations and, in consultation with their patients, devise individualized plans for osteoporosis prevention and treatment.

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Osteoporosis: Impact and Overview

EXECUTIVE SUMMARY

Osteoporosis is a silent disease until it is complicated by fractures—fractures that can occur following minimal trauma. These fractures are common and place an enormous medical and personal burden on aging individuals and a major economic toll on the nation.

Osteoporosis can be prevented and can be diagnosed and treated before any fracture occurs. Importantly, even after the first fracture has occurred, there are effective treatments to decrease the risk of further fractures. Prevention, detection and treatment of osteoporosis should be a mandate of primary care providers. Since the National Osteoporosis Foundation first published the Guide in 1999, it has become increasingly clear that many patients are not being given appropriate information about prevention; many patients are not having appropriate testing to diagnose osteoporosis or establish osteoporosis risk; and, once diagnosed (by testing or by the occurrence of a fracture), too many patients are not being prescribed any of the FDA-approved, effective therapies. This Guide offers concise recommendations regarding prevention, risk assessment, diagnosis and treatment of osteoporosis in postmenopausal women and men age 50 and older. It includes indications for bone densitometry and fracture risk thresholds for intervention with pharmacologic agents. The absolute risk thresholds at which consideration of osteoporosis treatment is recommended were guided by a cost-effectiveness analysis.

SYNOPSIS OF MAJOR RECOMMENDATIONS TO THE CLINICIAN

Recommendations apply to postmenopausal women and men age 50 and older.

- Counsel on the risk of osteoporosis and related fractures.
- Check for secondary causes.
- Advise on adequate amounts of calcium (at least 1,200 mg per day) and vitamin D (800-1,000 IU per day) including supplements if necessary for individuals age 50 and older.
- Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.
- Advise avoidance of tobacco smoking and excessive alcohol intake.

- In women age 65 and older and men age 70 and older, recommend bone mineral density (BMD) testing.
- In postmenopausal women and men age 50-69, recommend BMD testing when you have concern based on their risk factor profile.
- Recommend BMD testing to those who have had a fracture, to determine degree of disease severity.
- Initiate treatment in those with hip or vertebral (clinical or morphometric) fractures.
- Initiate therapy in those with BMD T-scores ≤ -2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry (DXA), after appropriate evaluation.
- Initiate treatment in postmenopausal women and men age 50 and older with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability $\geq 3\%$ or a 10-year major osteoporosis-related fracture probability $\geq 20\%$ based on the US-adapted WHO absolute fracture risk model (FRAX[®]; www.NOFOrg and www.shef.ac.uk/FRAX).
- Current FDA-approved pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid), calcitonin, estrogens and/or hormone therapy, parathyroid hormone (teriparatide) and estrogen agonist/antagonist (raloxifene).
- BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss. For patients on pharmacotherapy, it is typically performed two years after initiating therapy and every two years thereafter; however, more frequent testing may be warranted in certain clinical situations.

SCOPE OF THE PROBLEM

Osteoporosis is the most common bone disease in humans, and it represents a major public health problem as outlined in *Bone Health and Osteoporosis: A Report of the Surgeon General*.¹ It is characterized by low bone mass, deterioration of bone tissue and disruption of bone architecture, compromised bone strength and an increase in the risk of fracture. According to the WHO diagnostic classification, osteoporosis is defined by BMD at the hip or spine that is less than or equal to 2.5 standard deviations below the young normal mean reference population. Osteoporosis is an intermediate outcome for fractures and is a risk factor for fracture just as hypertension is for stroke. The majority of fractures, however, occur in patients with low bone mass rather than osteoporosis.

Osteoporosis affects an enormous number of people, of both sexes and all races, and its prevalence will increase as the population ages. Based on data

from the National Health and Nutrition Examination Survey III (NHANES III), NOF has estimated that more than 10 million Americans have osteoporosis and an additional 33.6 million have low bone density of the hip.² About one out of every two Caucasian women will experience an osteoporosis-related fracture at some point in her lifetime, as will approximately one in five men.¹ Although osteoporosis is less frequent in African Americans, those with osteoporosis have the same elevated fracture risk as Caucasians.

MEDICAL IMPACT

Fractures and their complications are the relevant clinical sequelae of osteoporosis. The most common fractures are those of the vertebrae (spine), proximal femur (hip) and distal forearm (wrist). However, most fractures in older adults are due in part to low bone mass, even when they result from considerable trauma. Fractures may be followed by full recovery or by chronic pain, disability and death.² These fractures can also cause psychological symptoms, most notably depression and loss of self-esteem, as patients grapple with pain, physical limitations, and lifestyle and cosmetic changes. Anxiety, fear and anger may also impede recovery. The high morbidity and consequent dependency associated with these fractures strain interpersonal relationships and social roles for patients and their families.

In particular, hip fractures result in 10 to 20 percent excess mortality within one year¹; additionally, hip fractures are associated with a 2.5 fold increased risk of future fractures.³ Approximately 20 percent of hip fracture patients require long-term nursing home care, and only 40 percent fully regain their pre-fracture level of independence.¹ Mortality is also increased following vertebral fractures, which cause significant complications including back pain, height loss and kyphosis. Postural changes associated with kyphosis may limit activity, including bending and reaching. Multiple thoracic fractures may result in restrictive lung disease, and lumbar fractures may alter abdominal anatomy, leading to constipation, abdominal pain, distention, reduced appetite and premature satiety. Wrist fractures are less globally disabling but can interfere with specific activities of daily living as much as hip or vertebral fractures.

ECONOMIC TOLL

Osteoporosis-related fractures create a heavy economic burden, causing more than 432,000 hospital admissions, almost 2.5 million medical office visits and about 180,000 nursing home admissions annually in the US.¹ The cost to the healthcare system associated with osteoporosis-related fractures has been estimated at \$17 billion for 2005; hip fractures account for 14 percent of incident fractures and 72 percent of fracture costs.⁴ Due to the aging population, the Surgeon General estimates that the number of hip fractures and their associated costs could double or triple by the year 2040.

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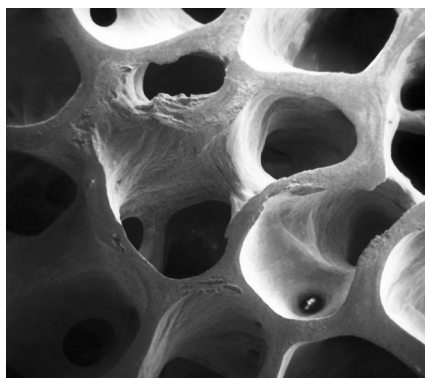
Basic Pathophysiology

Bone mass in older adults equals the peak bone mass achieved by age 18-25 years minus the amount of bone subsequently lost. Peak bone mass is determined largely by genetic factors, with contributions from nutrition, endocrine status, physical activity and health during growth.⁵ The process of bone remodeling that maintains a healthy skeleton may be considered a preventive maintenance program, continually removing older bone and replacing it with new bone. Bone loss occurs when this balance is altered, resulting in greater bone removal than replacement. The imbalance occurs with menopause and advancing age. With the onset of menopause, the rate of bone remodeling increases, magnifying the impact of the remodeling imbalance. The loss of bone tissue leads to disordered skeletal architecture and an increase in fracture risk.

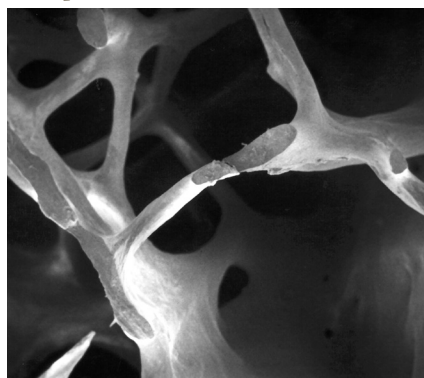
Figure 1 shows the changes within cancellous bone as a consequence of bone loss. Individual trabecular plates of bone are lost, leaving an architecturally weakened structure with significantly reduced mass. Increasing evidence suggests that rapid bone remodeling (as measured by biochemical markers of bone resorption or formation) increases bone fragility and fracture risk.

FIGURE 1. Micrographs of Normal vs. Osteoporotic Bone

Normal bone



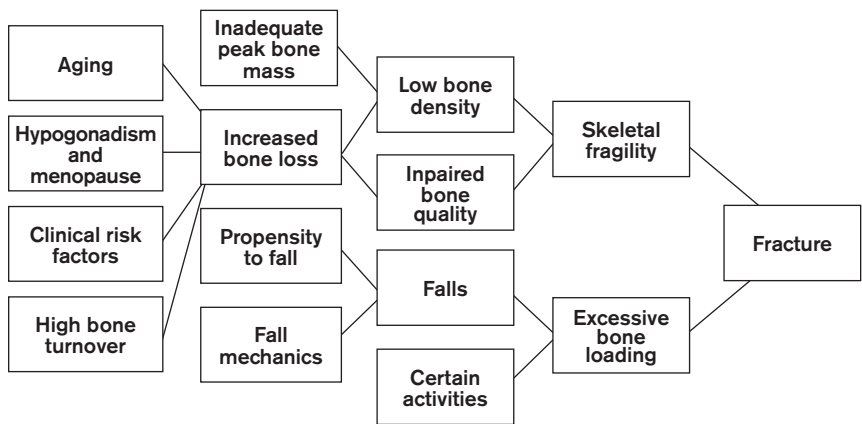
Osteoporotic bone



From: Dempster, DW et al.⁶, with permission of the American Society for Bone and Mineral Research.

Bone loss leads to an increased risk of fracture that is magnified by other aging-associated declines in functioning. Figure 2 shows the factors associated with an increased risk of osteoporosis-related fractures. These include general factors that relate to aging and sex steroid deficiency, as well as specific risk factors, such as use of glucocorticoids, which cause bone loss, reduced bone quality and disruption of microarchitectural integrity. Fractures result when weakened bone is overloaded, often by falls or certain activities of daily living.

FIGURE 2. Pathogenesis of Osteoporosis-Related Fractures



From: Cooper C and Melton LJ⁷, with modification.

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Approach to the Diagnosis and Management of Osteoporosis

NOF recommends a comprehensive approach to the diagnosis and management of osteoporosis. A detailed history and physical examination together with BMD assessment and, where appropriate, the WHO 10-year estimated fracture probability are utilized to establish the individual patient's fracture risk.⁸ Therapeutic intervention thresholds are based on NOF's economic analysis that takes into consideration the cost-effectiveness of treatments and competition for resources in the US.^{9,10} The clinician's clinical skills and past experience, incorporating the best patient-based research available, are used to determine the appropriate therapeutic intervention. The potential risks and benefits of all osteoporosis interventions should be reviewed with patients and the unique concerns and expectations of individual patients considered in any final therapeutic decision.

RISK ASSESSMENT

All postmenopausal women and men age 50 and older should be evaluated clinically for osteoporosis risk in order to determine the need for BMD testing. In general, the more risk factors that are present, the greater the risk of fracture. Osteoporosis is preventable and treatable, but because there are no warning signs prior to a fracture, many people are not being diagnosed in time to receive effective therapy during the early phase of the disease. Many factors have been associated with an increased risk of osteoporosis-related fracture (Table 1).

TABLE 1: Conditions, Diseases and Medications That Cause or Contribute to Osteoporosis and Fractures

Lifestyle factors		
Low calcium intake	Vitamin D insufficiency	Excess vitamin A
High caffeine intake	High salt intake	Aluminum (in antacids)
Alcohol (3 or more drinks/d)	Inadequate physical activity	Immobilization
Smoking (active or passive)	Falling	Thinness

(continued on pg. 7)

Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan syndrome	Riley-Day syndrome
Hemochromatosis	Menkes steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Turner's & Klinefelter's syndromes
Anorexia nervosa and bulimia	Panhypopituitarism	
Athletic amenorrhea	Premature ovarian failure	
Endocrine disorders		
Adrenal insufficiency	Diabetes mellitus	Thyrotoxicosis
Cushing's syndrome	Hyperparathyroidism	
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
GI surgery	Pancreatic disease	
Hematologic disorders		
Hemophilia	Multiple myeloma	Systemic mastocytosis
Leukemia and lymphomas	Sickle cell disease	Thalassemia
Rheumatic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Miscellaneous conditions and diseases		
Alcoholism	Emphysema	Muscular dystrophy
Amyloidosis	End stage renal disease	Parenteral nutrition
Chronic metabolic acidosis	Epilepsy	Post-transplant bone disease
Congestive heart failure	Idiopathic scoliosis	Prior fracture as an adult
Depression	Multiple sclerosis	Sarcoidosis

(continued on pg. 8)

TABLE 1: Conditions, Diseases and Medications That Cause or Contribute to Osteoporosis and Fractures *(continued)*

Medications		
Anticoagulants (heparin)	Cancer chemotherapeutic drugs	Gonadotropin releasing hormone agonists
Anticonvulsants	Cyclosporine A and tacrolimus	Lithium
Aromatase inhibitors	Depo-medroxyprogesterone	
Barbiturates	Glucocorticoids (≥ 5 mg/d of prednisone or equivalent for ≥ 3 mo)	

From: The Surgeon General's Report,¹ with modification.

Since the majority of osteoporosis-related fractures result from falls, it is also important to evaluate risk factors for falling (Table 2). The most important of these seem to be a personal history of falling, along with muscle weakness and gait, balance and visual deficits.¹¹ Dehydration is also a risk factor.

TABLE 2: Risk Factors for Falls

Environmental risk factors
Lack of assistive devices in bathrooms
Loose throw rugs
Low level lighting
Obstacles in the walking path
Slippery outdoor conditions
Medical risk factors
Age
Anxiety and agitation
Arrhythmias
Dehydration
Depression
Female gender
Impaired transfer and mobility
Malnutrition
Medications causing oversedation (narcotic analgesics, anticonvulsants, psychotropics)
Orthostatic hypotension
Poor vision and use of bifocals

(continued on pg. 9)

Previous fall
Reduced problem solving or mental acuity and diminished cognitive skills
Urgent urinary incontinence
Vitamin D insufficiency [serum 25-hydroxyvitamin D (25(OH)D) < 30 ng/ml (75 nmol/L)]
Neuro and musculoskeletal risk factors
Kyphosis
Poor balance
Reduced proprioception
Weak muscles
Other risk factors
Fear of Falling

From: *NOF Rehabilitation Guide*.¹²

Several of these risk factors have been included in the WHO 10-year fracture risk model (Table 3). As suggested by the WHO,⁸ this set of risk factors increases risk independently of BMD and can be combined with BMD measurements and used to assess an individual patient’s risk of future fracture.

TABLE 3: Risk Factors Included in the WHO Fracture Risk Assessment Model

• Current age	• Rheumatoid arthritis
• Gender	• Secondary osteoporosis
• A prior osteoporotic fracture (including morphometric vertebral fracture)	• Parental history of hip fracture
• Femoral neck BMD	• Current smoking
• Low body mass index (kg/m ²)	• Alcohol intake (3 or more drinks/d)
• Oral glucocorticoids ≥5 mg/d of prednisone for ≥3 mo (ever)	

From: *WHO Technical Report*.⁸

CLINICAL EVALUATION

Consider the possibility of osteoporosis and fracture risk in men and women, based on the presence of the risk factors and conditions outlined in Tables 1 and 3. Metabolic bone diseases other than osteoporosis, such as hyperparathyroidism or osteomalacia, may be associated with a low BMD. Many of these diseases have very specific therapies, and it is appropriate to complete a history and physical examination before making a diagnosis of osteoporosis on the basis of a low BMD alone. In patients in whom a specific secondary,

treatable cause of osteoporosis is being considered (Table 1), relevant blood and urine studies (such as serum and urine calcium, serum thyrotropin (TSH), protein electrophoresis, cortisol or antibodies associated with gluten-sensitive enteropathy) should be obtained prior to initiating therapy. For instance, elderly patients with recent fractures should be evaluated for secondary etiologies and, when considering osteomalacia or vitamin D insufficiency, a serum 25(OH) D level should be obtained. In general, biochemical testing (such as serum calcium, creatinine, etc.) should be considered in patients with documented osteoporosis prior to initiation of treatment.

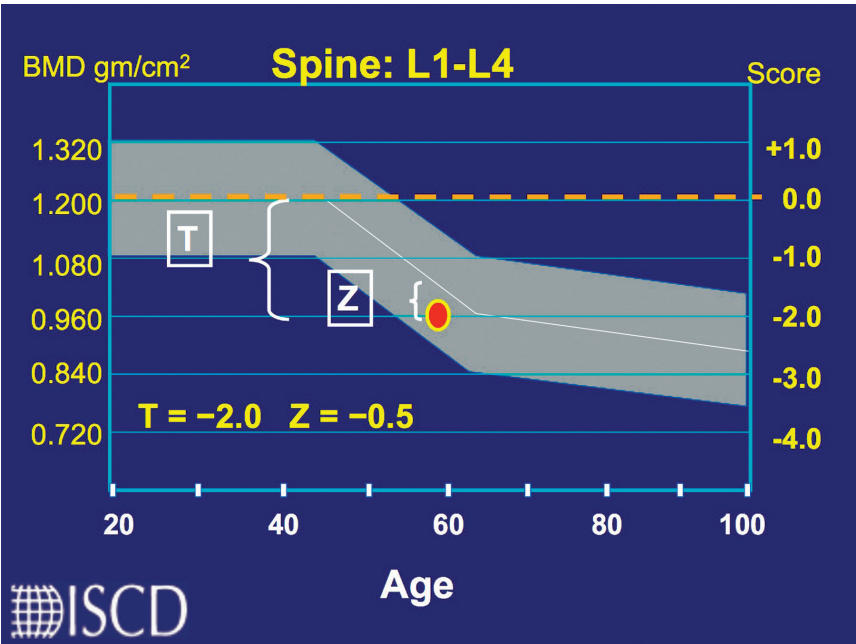
DIAGNOSIS

The diagnosis of osteoporosis is established by measurement of BMD. A clinical diagnosis can often be made in at-risk individuals who sustain a low-trauma fracture.

Bone Mineral Density Measurement and Classification

Dual-energy x-ray absorptiometry (DXA) measurement of the hip and spine is the technology now used to establish or confirm a diagnosis of osteoporosis, predict future fracture risk and monitor patients by performing serial assessments.¹³ Areal BMD is expressed in absolute terms of grams of mineral per square centimeter scanned (g/cm^2) and as a relationship to two norms: compared to the expected BMD for the patient's age and sex (Z-score), or compared to "young normal" adults of the same sex (T-score). The difference between the patient's score and the norm is expressed in standard deviations (SD) above or below the mean. Usually, 1 SD equals 10 to 15 percent of the BMD value in g/cm^2 . Depending upon the skeletal site, a decline in BMD expressed in absolute terms (g/cm^2) or in standard deviations (T-scores or Z-scores) begins during young adulthood, accelerates in women at menopause and continues to progress in postmenopausal women and men age 50 and older (see Figure 3). The BMD diagnosis of normal, low bone mass, osteoporosis and severe or established osteoporosis is based on the WHO diagnostic classification (see Table 4).

FIGURE 3. Z- and T-Scores



From: ISCD Bone Densitometry Clinician Course. Lecture 5 (2008).

TABLE 4: Defining Osteoporosis by BMD

The World Health Organization has established the following definitions based on BMD measurement at the spine, hip or forearm by DXA devices: ¹³
Normal: BMD is within 1 SD of a “young normal” adult (T-score at -1.0 and above).
Low bone mass (“osteopenia”): BMD is between 1.0 and 2.5 SD below that of a “young normal” adult (T-score between -1.0 and -2.5).
Osteoporosis: BMD is 2.5 SD or more below that of a “young normal” adult (T-score at or below -2.5). Patients in this group who have already experienced one or more fractures are deemed to have severe or “established” osteoporosis.
Note: Although these definitions are necessary to establish the presence of osteoporosis, they should not be used as the sole determinant of treatment decisions.

BMD testing is a vital component in the diagnosis and management of osteoporosis. BMD has been shown to correlate with bone strength and is an excellent predictor of future fracture risk. Instead of a specific threshold, fracture risk increases exponentially as BMD decreases. Although available technologies measuring central (spine and hip) and peripheral skeletal sites (forearm, heel, fingers) provide site-specific and global (overall risk at any skeletal site) assessment of future fracture risk, DXA measurement at the hip is the best predictor of future hip fracture risk. DXA measurements of the spine and hip must be performed by appropriately trained technologists on properly maintained instruments. DXA scans are associated with exposure to trivial amounts of radiation.

In postmenopausal women and men age 50 years and older, the WHO diagnostic T-score criteria (normal, low bone mass and osteoporosis) are applied to BMD measurement by central DXA at the lumbar spine and femoral neck.¹³ BMD measured by DXA at the one-third (33 percent) radius site can be used for diagnosing osteoporosis when the hip and spine cannot be measured.

In premenopausal women, men less than 50 years of age and children, the WHO BMD diagnostic classification should not be applied. In these groups, the diagnosis of osteoporosis should not be made on the basis of densitometric criteria alone. The International Society for Clinical Densitometry (ISCD) recommends that instead of T-scores, ethnic or race adjusted Z-scores should be used, with Z-scores of -2.0 or lower defined as either “low bone mineral density for chronological age” or “below the expected range for age” and those above -2.0 being “within the expected range for age.”¹⁴

TABLE 5: Additional Bone Densitometry Technologies

The following bone mass measurement technologies are capable of predicting both site-specific and overall fracture risk. When performed according to accepted standards, these densitometric techniques are accurate and highly reproducible.¹⁴ However, T-scores from these technologies cannot be used according to the WHO diagnostic classification because they are not equivalent to T-scores derived from DXA.

Peripheral dual-energy x-ray absorptiometry (pDXA) measures areal bone density of the forearm, finger or heel. Measurement by validated pDXA devices can be used to assess vertebral and overall fracture risk in postmenopausal women. There is lack of sufficient evidence for fracture prediction in men. pDXA is associated with exposure to trivial amounts of radiation. pDXA is not appropriate for monitoring BMD after treatment.

(continued on pg. 13)

CT-based absorptiometry. Quantitative computed tomography (QCT)

measures volumetric trabecular and cortical bone density at the spine and hip, whereas **peripheral QCT (pQCT)** measures the same at the forearm or tibia. In postmenopausal women, QCT measurement of spine trabecular BMD can predict vertebral fractures whereas pQCT of the forearm at the ultra distal radius predicts hip, but not vertebral fractures. There is lack of sufficient evidence for fracture prediction in men. QCT and pQCT are associated with greater amounts of radiation exposure than central DXA or pDXA.

Quantitative ultrasound densitometry (QUS) does not measure BMD directly but rather speed of sound (SOS) and/or broadband ultrasound attenuation (BUA) at the heel, tibia, patella and other peripheral skeletal sites. A composite parameter using SOS and BUA may be used clinically. Validated heel QUS devices predict fractures in postmenopausal women (vertebral, hip and overall fracture risk) and in men 65 and older (hip and non-vertebral fractures). QUS is not associated with any radiation exposure.

Who Should Be Tested?

The decision to perform bone density assessment should be based on an individual's fracture risk profile and skeletal health assessment. Utilizing any procedure to measure bone density is not indicated unless the results will influence the patient's treatment decision. In agreement with the U.S. Preventive Service Task Force recommendations for postmenopausal women,¹⁵ NOF recommends testing of all women age 65 and older. NOF also recommends testing of men age 70 and older. BMD measurement is not recommended in children or adolescents and is not routinely indicated in healthy young men or premenopausal women.

Indications for BMD Testing:

- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Younger postmenopausal women and men age 50 to 69 about whom you have concern based on their clinical risk factor profile
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk such as low body weight, prior low-trauma fracture or high risk medication
- Adults who have a fracture after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for \geq three months) associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy for osteoporosis
- Anyone being treated for osteoporosis, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

- Postmenopausal women discontinuing estrogen should be considered for bone density testing

Medicare covers BMD testing for many individuals age 65 and older, including but not limited to:

- Estrogen deficient women at clinical risk for osteoporosis
- Individuals with vertebral abnormalities
- Individuals receiving, or planning to receive, long-term glucocorticoid therapy in a daily dose ≥ 5 mg prednisone or equivalent for \geq three months
- Individuals with primary hyperparathyroidism
- Individuals being monitored to assess the response or efficacy of an approved osteoporosis drug therapy

Additional Skeletal Health Assessment Techniques

Biochemical markers of bone turnover. Bone remodeling (or turnover) occurs throughout life to repair fatigue damage and microfractures in bone. Biochemical markers of bone remodeling [e.g., resorption markers—serum C-telopeptide (CTX) and urinary N-telopeptide (NTX) and formation markers—serum bone specific alkaline phosphatase (BSAP) and osteocalcin] can be measured in the serum and urine in untreated patients to assess risk of fracture. They may predict bone loss and, when repeated after 3-6 months of treatment with FDA approved antiresorptive therapies, may be predictive of fracture risk reduction.¹⁶

Vertebral fracture assessment (VFA). Independent of BMD, age and other clinical risk factors, radiographically confirmed vertebral fractures are a strong predictor of new vertebral fractures, and they also predict other fractures. VFA imaging of the thoracic and lumbar spine using central DXA scanners should be considered at the time of BMD assessment when the presence of a vertebral fracture not previously identified may influence clinical management of the patient. International Society for Clinical Densitometry indications for VFA in postmenopausal women and men are available at www.iscd.org.¹⁴

USE OF WHO FRACTURE RISK ALGORITHM (FRAX®) IN THE US

FRAX® was developed to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (defined as clinical vertebral, hip, forearm or proximal humerus fracture) taking into account femoral neck BMD and the clinical risk factors shown in Table 3.⁸ The FRAX® algorithm is available at www.nof.org and at www.shef.ac.uk/FRAX; it should soon be available on newer DXA scanners.

The WHO algorithm used in this Guide was calibrated to US fracture and mortality rates; hence the fracture risk figures herein are specific for the US

population. Economic modeling was performed to identify the 10-year hip fracture risks above which it is cost-effective, from the societal perspective, to treat with pharmacologic agents.⁹ The US-based economic modeling is described in one report,⁹ and the US-adapted WHO algorithm and its clinical application are illustrated in a companion report.¹⁰ The latter analyses generally confirm the previous NOF conclusion¹⁷ that it is cost-effective to treat individuals with a prior hip or vertebral fracture and those with a DXA femoral neck T-score ≤ -2.5 . Previous analyses have established that a spine T-score ≤ -2.5 also warrants treatment.^{17, 18}

FRAX® is most useful in patients with low hip BMD. Utilizing FRAX® in patients with low BMD at the spine but a relatively normal BMD at the hip requires special consideration. Specifically, the WHO algorithm has not been validated for the use of spine BMD. As such, clinicians will need to use clinical judgment in this situation, since FRAX® may underestimate fracture risk in these individuals based on the exclusive use of femoral neck BMD.

Application of US-FRAX® in the US:

- FRAX® is intended for postmenopausal women and men age 50 and older; it is not intended for use in younger adults or children.
- The FRAX® tool has not been validated in patients currently or previously treated with pharmacotherapy for osteoporosis. In such patients, clinical judgment must be exercised in interpreting FRAX® scores.
- In the absence of femoral neck BMD, total hip BMD may be substituted; however, use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated.
- The WHO determined that for many secondary causes of osteoporosis, fracture risk was mediated primarily through impact on BMD.⁸ For this reason, when T-scores are inserted into FRAX®, the secondary osteoporosis button is automatically inactivated.

The therapeutic thresholds proposed in this Guide are for clinical guidance only and are not rules. All treatment decisions require clinical judgment and consideration of individual patient factors, including patient preferences, comorbidities, risk factors not captured in the FRAX model (e.g., frailty, falls), recent decline in bone density and other sources of possible under- or over-estimation of fracture risk by FRAX®. The therapeutic thresholds do not preclude clinicians or patients from considering intervention strategies for those who do not have osteoporosis by BMD (WHO diagnostic criterion of T-score ≤ -2.5), do not meet the cut points after FRAX®, or are not at high enough risk of fracture despite low BMD. Conversely, these recommendations should not mandate treatment, particularly in patients with osteopenia. Decisions to treat must still be made on a case-by-case basis.

4

Universal Recommendations for All Patients

Several interventions to reduce fracture risk can be recommended to the general population. These include an adequate intake of calcium and vitamin D, lifelong participation in regular weight-bearing and muscle-strengthening exercise, avoidance of tobacco use, identification and treatment of alcoholism, and treatment of other risk factors for fracture such as impaired vision.

ADEQUATE INTAKE OF CALCIUM AND VITAMIN D

Providing adequate daily calcium and vitamin D is a safe and inexpensive way to help reduce fracture risk. Controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D can reduce the risk of fracture.

Advise all individuals to obtain an adequate intake of dietary calcium (at least 1,200 mg per day, including supplements if necessary). Lifelong adequate calcium intake is necessary for the acquisition of peak bone mass and subsequent maintenance of bone health. The skeleton contains 99 percent of the body's calcium stores; when the exogenous supply is inadequate, bone tissue is resorbed from the skeleton to maintain serum calcium at a constant level. NOF supports the National Academy of Sciences (NAS) recommendation that women older than age 50 consume at least 1,200 mg per day of elemental calcium.¹⁹ Intakes in excess of 1,200 to 1,500 mg per day have limited potential for benefit and may increase the risk of developing kidney stones or cardiovascular disease.

Table 6 illustrates a simple method for estimating the calcium content of a patient's diet. Men and women age 50 and older typically consume only about 600 to 700 mg per day of calcium in their diets. Increasing dietary calcium is the first-line approach, but calcium supplements should be used when an adequate dietary intake cannot be achieved.

TABLE 6. Estimating Daily Dietary Calcium Intake

STEP 1: Estimate calcium intake from calcium-rich foods*					
Product	Servings/d		Estimated calcium/ serving, in mg		Calcium, in mg
Milk (8 oz.)	_____	x	300	=	_____
Yogurt (6 oz.)	_____	x	300	=	_____
Cheese (1 oz. or 1 cubic in.)	_____	x	200	=	_____
Fortified foods or juices	_____	x	80 to 1,000**	=	_____
STEP 2: Total from above + 250 mg for nondairy sources = total dietary calcium					Calcium, in mg _____

* About 75 to 80 percent of the calcium consumed in American diets is from dairy products.
** Calcium content of fortified foods varies.

Vitamin D plays a major role in calcium absorption, bone health, muscle performance, balance and risk of falling. NOF recommends an intake of 800 to 1,000 international units (IU) of vitamin D per day for adults age 50 and older. This intake will bring the average adult's serum 25(OH)D concentration to the desired level of 30 ng/ml (75 nmol/L) or higher. Chief dietary sources of vitamin D include vitamin D-fortified milk (400 IU per quart, although certain products such as soy milk are not supplemented with vitamin D) and cereals (40 to 50 IU per serving), egg yolks, salt-water fish and liver. Some calcium supplements and most multivitamin tablets also contain vitamin D.

Many elderly patients are at high risk for vitamin D deficiency, including patients with malabsorption (e.g., celiac disease) and chronic renal insufficiency, housebound patients, chronically ill patients and others with limited sun exposure. Serum 25(OH)D levels should be measured in patients at risk of deficiency and vitamin D supplemented in amounts sufficient to bring the serum 25(OH)D level to 30 ng/ml (75 nmol/L) or higher. Many patients, including those with malabsorption, will need more. The safe upper limit for vitamin D intake for the general adult population was set at 2,000 IU per day in 1997¹⁹; recent evidence indicates that higher intakes are safe and that some elderly patients will need at least this amount to maintain optimal 25(OH)D levels.

REGULAR WEIGHT-BEARING EXERCISE

Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures. Among its many health benefits, weight-bearing

and muscle-strengthening exercise can improve agility, strength, posture and balance, which may reduce the risk of falls. In addition, exercise may modestly increase bone density. NOF strongly endorses lifelong physical activity at all ages, both for osteoporosis prevention and overall health, as benefits are lost when the person stops exercising. Weight-bearing exercise (in which bones and muscles work against gravity as the feet and legs bear the body's weight) includes walking, jogging, Tai-Chi, stair climbing, dancing and tennis. Muscle-strengthening exercise includes weight training and other resistive exercises. Before an individual with osteoporosis initiates a new vigorous exercise program, such as running or heavy weight-lifting, a clinician's evaluation is appropriate.

FALL PREVENTION

Major risk factors for falling are shown in Table 2. In addition to maintaining adequate vitamin D levels and physical activity, as described above, strategies to reduce falls include, but are not limited to, checking and correcting vision and hearing, evaluating any neurological problems, reviewing prescription medications for side effects that may affect balance and providing a checklist for improving safety at home. Wearing undergarments with hip pad protectors may protect an individual from injuring the hip in the event of a fall. Hip protectors may be considered for patients who have significant risk factors for falling or for patients who have previously fractured a hip.

AVOIDANCE OF TOBACCO USE AND EXCESSIVE ALCOHOL INTAKE

Advise patients to avoid tobacco smoking. The use of tobacco products is detrimental to the skeleton as well as to overall health. NOF strongly encourages a smoking cessation program as an osteoporosis intervention.

Recognize and treat patients with excessive alcohol intake. Moderate alcohol intake has no known negative effect on bone and may even be associated with slightly higher bone density and lower risk of fracture in postmenopausal women. However, alcohol intake of three or more drinks per day is detrimental to bone health, increases the risk of falling and requires treatment when identified.

5

Pharmacologic Therapy

All patients being considered for treatment of osteoporosis should also be counseled on risk factor reduction. Patients should be counseled specifically on the importance of calcium, vitamin D and exercise as part of any treatment program for osteoporosis. Prior to initiating treatment, patients should be evaluated for secondary causes of osteoporosis and have BMD measurements by central DXA, when available. An approach to the clinical assessment of individuals at risk of osteoporosis is outlined in Table 7.

The percentage of risk reductions for vertebral and non-vertebral fractures cited below are those cited in the FDA-approved Prescribing Information. In the absence of head-to-head trials, direct comparisons of risk reduction of one drug with another should be avoided.

WHO SHOULD BE CONSIDERED FOR TREATMENT?

Postmenopausal women and men age 50 and older presenting with the following should be considered for treatment:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture $\geq 3\%$ or a 10-year probability of a major osteoporosis-related fracture $\geq 20\%$ based on the US-adapted WHO algorithm

TABLE 7: Clinical Assessment of Osteoporosis in Postmenopausal Women and Men Age 50 and Older

Obtain a detailed patient history pertaining to clinical risk factors for osteoporosis-related fracture.
Perform physical examination to evaluate for signs of osteoporosis and its secondary causes.
Modify diet/supplements and other clinical risk factors for fracture.
Estimate patient's 10-year probability of hip and any major osteoporosis-related fracture using the US-adapted WHO algorithm.
Decisions on whom to treat and how to treat should be based on clinical judgment using this Guide and all available clinical information.
Consider FDA-approved medical therapies based on the following:
■ A vertebral or hip fracture
■ A DXA hip (femoral neck) or spine T-score ≤ -2.5
■ Low bone mass and a US-adapted WHO 10-year probability of a hip fracture $\geq 3\%$ or 10-year probability of any major osteoporosis-related fracture $\geq 20\%$
■ Patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels
Consider non-medical therapeutic interventions:
■ Modify risk factors related to falling
■ Consider physical and occupational therapy including walking aids and hip pad protectors
■ Weight-bearing activities daily
Patients not requiring medical therapies at the time of initial evaluation should be clinically re-evaluated when medically appropriate.
Patients taking FDA-approved medications should have laboratory and bone density re-evaluation after two years or more frequently when medically appropriate.

US FDA-APPROVED DRUGS FOR OSTEOPOROSIS

Current FDA-approved pharmacologic options for the prevention and/or treatment of postmenopausal osteoporosis include, in alphabetical order: bisphosphonates (alendronate, alendronate plus D, ibandronate, risedronate, risedronate with 500 mg of calcium carbonate and zoledronic acid), calcitonin, estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene) and parathyroid hormone [PTH(1-34), teriparatide]. **Please see Prescribing Information for specific details of their use.**

The anti-fracture benefits of FDA-approved drugs have mostly been studied in women with postmenopausal osteoporosis. There are limited fracture data in glucocorticoid-induced osteoporosis and no fracture data in men. FDA-approved osteoporosis treatments have been shown to decrease fracture risk in patients who have had fragility fractures and/or osteoporosis by DXA. Pharmacotherapy may also reduce fractures in patients with low bone mass (osteopenia) without fractures, but the evidence is less strong. Thus the clinician should assess the potential benefits and risks of therapy in each patient. Note that the intervention thresholds do not take into account the non-skeletal benefits or the risks that are associated with specific drug use. NOF does not advocate the use of drugs not approved by the FDA for prevention and treatment of osteoporosis. Examples of these drugs are listed in Table 8 for information only.

Bisphosphonates

Alendronate, brand name: Fosamax® or Fosamax Plus D. Alendronate sodium is approved by the FDA for the prevention (5 mg daily and 35 mg weekly tablets) and treatment (10 mg daily tablet, 70 mg weekly tablet or liquid formulation, and 70 mg weekly tablet with 2,800 IU or 5,600 IU of vitamin D₃) of postmenopausal osteoporosis. Alendronate is also approved for treatment to increase bone mass in men with osteoporosis and for the treatment of osteoporosis in men and women taking glucocorticoids. Alendronate is now available as a generic preparation in the US. Alendronate reduces the incidence of spine and hip fractures by about 50 percent over three years in patients with a prior vertebral fracture. It reduces the incidence of vertebral fractures by about 48 percent over three years in patients without a prior vertebral fracture.

Ibandronate, brand name: Boniva®. Ibandronate sodium is approved by the FDA for the treatment (2.5 mg daily tablet, 150 mg monthly tablet and 3 mg every three months by intravenous injection) of postmenopausal osteoporosis. The oral preparations are also approved for the prevention of postmenopausal osteoporosis. Ibandronate reduces the incidence of vertebral fractures by about 50 percent over three years.

Risedronate, brand name: Actonel® or Actonel® with Calcium. Risedronate sodium is approved by the FDA for the prevention and treatment (5 mg daily tablet; 35 mg weekly tablet; 35 mg weekly tablet packaged with 6 tablets of 500 mg calcium carbonate; 75 mg tablets on two consecutive days every month; and 150 mg monthly tablet) of postmenopausal osteoporosis. Risedronate is also approved for treatment to increase bone mass in men with osteoporosis and for the prevention and treatment of osteoporosis in men and women who are either initiating or taking glucocorticoids. Risedronate reduces the incidence of vertebral fractures by about 41-49 percent and non-vertebral fractures by about 36 percent over three years, with significant risk reduction occurring after one year of treatment, in patients with a prior vertebral fracture.

Zoledronic acid, brand name: Reclast®. Zoledronic acid is approved by the FDA for the prevention and treatment (5 mg by intravenous infusion over at least 15 minutes once yearly for treatment and once every two years for prevention) of osteoporosis in postmenopausal women. It is also approved for the prevention and treatment of osteoporosis in men and women expected to be on glucocorticoid therapy for at least 12 months. Zoledronic acid is also indicated for the prevention of new clinical fractures in patients who have recently had a low-trauma hip fracture. Zoledronic acid reduces the incidence of vertebral fractures by about 70 percent (with significant reduction at one year), hip fractures by about 41 percent and non-vertebral fractures by about 25 percent over three years.

Side effects and administration of bisphosphonates. Side effects are similar for all oral bisphosphonate medications and include gastrointestinal problems such as difficulty swallowing, inflammation of the esophagus and gastric ulcer. There have been reports of osteonecrosis of the jaw (particularly following intravenous bisphosphonate treatment for patients with cancer) and of visual disturbances, which should be reported to the healthcare provider as soon as possible. The level of risk for osteonecrosis in patients being treated for osteoporosis with bisphosphonates is not known, but appears extremely small for at least up to five years.²⁰ There was a higher risk of developing atrial fibrillation for patients on zoledronic acid when compared with placebo (1.3 percent vs 0.4 percent); the effect of other bisphosphonates on the incidence of atrial fibrillation is uncertain.

- **Alendronate and risedronate** tablets must be taken on an empty stomach, first thing in the morning, with 8 ounces of plain water (no other liquid). Patients using the **liquid formulation of alendronate** should swallow one bottle (75 ml) and follow with at least 2 oz of plain water. After taking these medications, patients must wait at least 30 minutes before eating, drinking or taking any other medication. Patients should remain upright (sitting or standing) during this interval.

- **Ibandronate** tablets should be taken on an empty stomach, first thing in the morning, with 8 ounces of plain water (no other liquid). After taking this medication, patients must wait at least 60 minutes before eating, drinking or taking any other medication. Patients must remain upright for at least one hour after taking the medication. Ibandronate, 3 mg per 3 ml prefilled syringe, is given by intravenous injection over 15 to 30 seconds, once every three months. Serum creatinine should be checked before each injection.
- **Zoledronic acid**, 5 mg in 100 ml, is given once yearly or once every two years by intravenous infusion over at least 15 minutes. Patients may be pre-treated with acetaminophen to reduce the risk of an acute phase reaction (arthralgia, headache, myalgia, fever). These symptoms occurred in 32 percent of patients after the first dose, 7 percent after the second dose and 3 percent after the third dose.

Calcitonin

Brand name: Miacalcin® or Fortical®. Salmon calcitonin is FDA-approved for the treatment of osteoporosis in women who are at least five years postmenopausal. It is delivered as a single daily intranasal spray that provides 200 IU of the drug. Subcutaneous administration by injection also is available. The effect of nasal calcitonin on fracture risk is not stated in the Prescribing Information. Intranasal calcitonin is generally considered safe although some patients experience rhinitis and, rarely, epistaxis.

Estrogen/Hormone Therapy (ET/HT)

ET brand names: e.g. Climara®, Estrace®, Estraderm®, Estratab®, Ogen®, Ortho-Est®, Premarin®, Vivelle®; **HT brand names:** e.g. Activella®, Femhrt®, Premphase®, Prempro®. Estrogen/hormone therapy is approved by the FDA for the prevention of osteoporosis, relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. Women who have not had a hysterectomy require HT, which contains progestin to protect the uterine lining. The Woman's Health Initiative (WHI) found that five years of HT (Prempro®) reduced the risk of clinical vertebral fractures and hip fractures by 34 percent and other osteoporotic fractures by 23 percent.²¹

The Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein phlebitis during five years of treatment with conjugated equine estrogen and medroxyprogesterone (Prempro®).²¹ Subsequent analysis of these data showed no increase in cardiovascular disease in women starting treatment within 10 years of menopause. In the estrogen only arm of WHI, no increase in breast cancer incidence was noted over 7.1 years of treatment. Other doses and combinations of estrogen and progestins were not studied and, in the absence of comparable data, their risks should be assumed to be comparable. Because of the risks, ET/HT should be used in the lowest effective doses for the shortest

duration to meet treatment goals. When ET/HT use is considered solely for prevention of osteoporosis, the FDA recommends that approved non-estrogen treatments should first be carefully considered.

Estrogen Agonist/Antagonist (formerly known as SERMs)

Raloxifene, brand name: Evista®. Raloxifene is approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women. Raloxifene reduces the risk of vertebral fractures by about 30 percent in patients with a prior vertebral fracture and by about 55 percent in patients without a prior vertebral fracture over three years. Raloxifene is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. Raloxifene does not reduce the risk of coronary heart disease. Raloxifene increases the risk of deep vein thrombosis to a degree similar to that observed with estrogen. It also increases hot flashes (6 percent over placebo).

Parathyroid Hormone

PTH(1-34), teriparatide, brand name: Forteo®. Teriparatide is approved by the FDA for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture. It is also approved for treatment in men and women at high risk of fracture with osteoporosis associated with sustained systemic glucocorticoid therapy. Teriparatide is also indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture. It is an anabolic (bone-building) agent administered by daily subcutaneous injection. Teriparatide in a dose of 20 µg daily was shown to decrease the risk of vertebral fractures by 65 percent and non-vertebral fractures by 53 percent in patients with osteoporosis, after an average of 18 months of therapy.

Teriparatide is well tolerated, although some patients experience leg cramps and dizziness. Because it caused an increase in the incidence of osteosarcoma in rats, patients with an increased risk of osteosarcoma (e.g., patients with Paget's disease of bone) and those having prior radiation therapy of the skeleton, bone metastases, hypercalcemia or a history of skeletal malignancy should not receive teriparatide therapy. The safety and efficacy of teriparatide has not been demonstrated beyond two years of treatment. Teriparatide is used for a maximum of two years. It is common practice to follow teriparatide treatment with an antiresorptive agent, usually a bisphosphonate, to maintain or further increase BMD.

Combination Therapy

Combination therapy (usually a bisphosphonate with a non-bisphosphonate) can provide additional small increases in BMD when compared with monotherapy; however, the impact of combination therapy on fracture rates is unknown. The added cost and potential side effects should be weighed against potential gains.

TABLE 8: Non-FDA-Approved Drugs for Osteoporosis

These drugs are listed for information only. These non-approved agents include:
Calcitriol. This synthetic vitamin D analogue, which promotes calcium absorption, has been approved by the FDA for managing hypocalcemia and metabolic bone disease in renal dialysis patients. It is also approved for use in hypoparathyroidism, both surgical and idiopathic, and pseudohypoparathyroidism. No reliable data demonstrate a reduction of risk for osteoporotic fracture.
Other bisphosphonates (etidronate, pamidronate, tiludronate). These medications vary chemically from alendronate, ibandronate, risedronate and zoledronic acid but are in the same drug class. At the time of publication, none is approved for prevention or treatment of osteoporosis. Most of these medications are currently approved for other conditions including Paget's disease, hypercalcemia of malignancy and myositis ossificans.
Parathyroid hormone PTH(1-84). This medication is approved in some countries in Europe for treatment of osteoporosis in women. In one clinical study PTH(1-84) effectively reduced the risk of vertebral fractures at a dose of 100mcg/d.
Sodium fluoride. Through a process that is still unclear, sodium fluoride stimulates the formation of new bone. The quality of bone mass thus developed is uncertain, and the evidence that fluoride reduces fracture risk is conflicting and controversial.
Strontium ranelate. This medication is approved for the treatment of osteoporosis in some countries in Europe. Strontium ranelate reduces the risk of both spine and non-vertebral fractures, but the mechanism is unclear. Incorporation of strontium into the crystal structure replacing calcium may be part of its mechanism of effect.
Tibolone. Tibolone is a tissue-specific, estrogen-like agent that may prevent bone loss and reduce menopausal symptoms but it does not stimulate breast or uterine tissue. It is indicated in Europe for the treatment of vasomotor symptoms of menopause and for prevention of osteoporosis, but it is not approved for use in the US.

MONITORING EFFECTIVENESS OF TREATMENT

It is important to ask patients whether they are taking their medications and to encourage continued and appropriate compliance with their osteoporosis therapies to reduce fracture risk. It is also important to review their risk factors and encourage appropriate calcium and vitamin D intakes, exercise, fall prevention and other lifestyle measures.

Serial central DXA BMD testing is an important component of osteoporosis

management. Measurements for monitoring patients should be performed in accordance with medical necessity, expected response and in consideration of local regulatory requirements. NOF recommends that repeat BMD assessments generally agree with Medicare guidelines of every two years, but recognizes that testing more frequently may be warranted in certain clinical situations.

The following techniques may be used to monitor the effectiveness of treatment:

- **Central DXA.** Central DXA assessment of the hip or spine is currently the “gold standard” for serial assessment of BMD. Biological changes in bone density are small compared to the inherent error in the test itself, and interpretation of serial bone density studies depends on appreciation of the smallest change in BMD that is beyond the range of error of the test. This least significant change (LSC) varies with the specific instrument used, patient population being assessed, measurement site, technologist’s skill with patient positioning and test analysis, and the confidence intervals used. Changes in the LSC of less than 3-6 percent at the hip and 2-4 percent at the lumbar spine from test to test may be due to the precision error of the testing itself. Information on how to assess precision and calculate the LSC is available at www.ISCD.org.
- **QCT.** Trabecular BMD of the lumbar spine can be used to monitor age-, disease- and treatment-related BMD changes in men and women. Precision of acquisition should be established by phantom data and analysis precision by re-analysis of patient data.

*Note: **pDXA, pQCT and QUS.** Peripheral skeletal sites do not respond in the same magnitude as the spine and hip to medications and thus are not appropriate for monitoring response to therapy at this time.*

Biochemical markers of bone turnover. Suppression of biochemical markers of bone turnover after 3-6 months of specific antiresorptive osteoporosis therapies, and biochemical marker increases after 1-3 months of specific anabolic therapies, have been predictive of greater BMD responses in studies evaluating large groups of patients. Because of the high degree of biological and analytical variability in measurement of biochemical markers, changes in individuals must be large in order to be clinically meaningful. It is critical to appreciate the LSC associated with the biomarker being utilized, which is calculated by multiplying the “precision error” of the specific biochemical marker (laboratory provided) by 2.77 (95% confidence level). Biological variability can be reduced by obtaining samples in the early morning after an overnight fast. Serial measurements should be made at the same time of day and preferably during the same season of the year.

6

Physical Medicine and Rehabilitation

Physical medicine and rehabilitation can reduce disability, improve physical function and lower the risk of subsequent falls in patients with osteoporosis. Rehabilitation and exercise are recognized means to improve function, such as activities of daily living. Psychosocial factors also strongly affect functional ability of the osteoporotic patient.

Recommendations from NOF's Rehabilitation Guide¹²

- Evaluate and consider the patient's physical and functional safety as well as psychological and social status, medical status, nutritional status and medication use before prescribing a rehabilitation program. Strive for an active lifestyle, starting in childhood.
- Evaluate the patient and her/his current medication use and consider possible interactions and risk for altered mental status. Intervene as appropriate.
- Provide training for the performance of safe movement and safe activities of daily living, including posture, transfers, lifting and ambulation in populations with or at high risk for osteoporosis. Intervene as appropriate, e.g., with prescription for assistive device for improved balance with mobility.
- Evaluate home environment for risk factors for falls and intervene as appropriate.
- Implement steps to correct underlying deficits whenever possible, i.e., improve posture and balance and strengthen quadriceps muscle to allow a person to rise unassisted from a chair; promote use of assistive devices to help with ambulation, balance, lifting and reaching.
- Based on the initial condition of the patient, provide a complete exercise recommendation that includes weight-bearing aerobic activities for the skeleton, postural training, progressive resistance training for muscle and bone strengthening, stretching for tight soft tissues and joints and balance training. As long as principles of safe movement are followed, walking and daily activities, such as housework and gardening, are practical ways to contribute to maintenance of fitness and bone mass. Additionally, progressive resistance training and increased loading exercises, within the parameter of the person's current health status, are beneficial for muscle and bone strength. Proper exercise may improve physical performance/function, bone mass, muscle strength and balance, as well as reduce the risk of falling.

- Advise patients to avoid forward bending and exercising with trunk in flexion, especially in combination with twisting.
- Avoid long-term immobilization and recommend partial bed rest (with periodic sitting and ambulating) only when required and for the shortest periods possible.
- In patients with acute vertebral fractures or chronic pain after multiple vertebral fractures, the use of trunk orthoses (e.g., back brace, corset, posture training support devices) may provide pain relief by reducing the loads on the fracture sites and aligning the vertebra. However, long-term bracing may lead to muscle weakness and further de-conditioning.
- Effective pain management is a cornerstone in rehabilitation from vertebral fractures. Pain relief may be obtained by the use of a variety of physical, pharmacological and behavioral techniques with the caveat that the benefit of pain relief should not be outweighed by the risk of side effects such as disorientation or sedation which may result in falls.
- Individuals with painful vertebral fractures that fail conservative management may be candidates for emerging interventions, such as kyphoplasty or vertebroplasty, when performed by experienced practitioners.

NOF's *Health Professional's Guide to Rehabilitation of the Patient with Osteoporosis* provides additional information on this topic and can be accessed at www.nof.org.

Conclusions and Remaining Questions

The Guide has focused on the prevention, diagnosis and treatment of osteoporosis in postmenopausal women and men age 50 and older using the most common existing diagnostic and treatment methods available. Much is known about osteoporosis in this population.

However, many additional issues urgently need epidemiologic, clinical and economic research. For example:

- How can we better assess bone strength using non-invasive technologies and thus improve identification of patients at high risk for fracture?
- There is the need to expand the WHO algorithm to incorporate information on spine BMD.
- How can children, adolescents and young adults maximize peak bone mass?
- What are the precise components (type, intensity, duration, frequency) of an effective exercise program for osteoporosis prevention and treatment?
- What should be done to identify and modify risk factors for falling, and what would be the magnitude of effect on fracture risk in a population?
- How effective are different FDA-approved treatments in preventing fractures in patients with moderately low bone mass?
- What approaches are most effective in treating osteoporosis in disabled populations?
- How long should antiresorptive therapies be continued, and are there long-term side effects as yet unknown?
- Are combination therapies useful and, if so, which are the useful drug combinations and when should they be used?
- Can we identify agents that will significantly increase bone mass and return bone structure to normal?

NOF is committed to continuing the effort to answer these and other questions related to this debilitating disease, with the goal of eliminating osteoporosis as a threat to the health of present and future generations.

For additional resources on osteoporosis and bone health visit www.nof.org or call 1-800-231-4222.

Glossary

Alendronate (Fosamax®): A bisphosphonate approved by the US Food and Drug Administration for prevention and treatment of osteoporosis; accumulates and persists in the bone. Studies indicate about a 50 percent reduction in vertebral and hip fractures in patients with osteoporosis.

Biochemical markers of bone turnover: Biochemical markers of bone remodeling [e.g., resorption markers - serum C-telopeptide (CTX) and urinary N-telopeptide (NTX) and formation markers - serum bone specific alkaline phosphatase (BSAP) and osteocalcin] can be measured in the serum and urine. Elevated levels of markers of bone turnover may predict bone loss, and declines in the levels of markers after 3-6 months of treatment may be predictive of fracture risk reduction.

Bone mineral density (BMD): A risk factor for fractures. By DXA, BMD is expressed as the amount of mineralized tissue in the area scanned (g/cm^2); with some technologies, BMD is expressed as the amount per volume of bone (g/cm^3). Hip BMD by DXA is considered the best predictor of hip fracture; it appears to predict other types of fractures as well as measurements made at other skeletal sites. Spine BMD may be preferable to assess changes early in menopause and after bilateral ovariectomy.

Calcitonin (Miacalcin® or Fortical®): A polypeptide hormone that inhibits the resorptive activity of osteoclasts.

Calcitriol: A synthetic form of 1,25-dihydroxyvitamin D_3 , a hormone that aids calcium absorption and mineralization of the skeleton. Its effectiveness as a treatment for osteoporosis is still uncertain.

Calcium: A mineral that plays an essential role in development and maintenance of a healthy skeleton. If intake is inadequate, calcium is mobilized from the skeleton to maintain a normal blood calcium level. In addition to being a substrate for bone mineralization, calcium has an inhibitory effect on bone remodeling through suppression of circulating parathyroid hormone.

Cancellous bone: The spongy, or trabecular, tissue in the middle of bone (e.g., vertebrae) and at the end of the long bones.

Cortical bone: The dense outer layer of bone.

Cost-effectiveness analysis: As utilized in this Guide, a quantitative analysis that considers the value of treatment by comparing average costs and average health outcomes (quality-adjusted life expectancy) for patients who are treated for osteoporosis relative to untreated patients.

Dual-energy x-ray absorptiometry (DXA): A diagnostic test used to assess bone density at various skeletal sites using radiation exposure about one-tenth that of a standard chest x-ray. Central DXA (spine, hip) is the preferred measurement for definitive diagnosis of osteoporosis and for monitoring the effects of therapy.

Estrogen: One of a group of steroid hormones that control female sexual development; directly affects bone mass through estrogen receptors in bone, reducing bone turnover and bone loss. Indirectly increases intestinal calcium absorption and renal calcium conservation and, therefore, improves calcium balance. See hormone therapy.

Estrogen agonists/antagonists: A group of compounds that are selective estrogen receptor modulators, formerly known as SERMs.

Exercise: An intervention long associated with healthy bones, despite limited evidence for significant beneficial effect on bone mineral density or fracture risk reductions. Studies evaluating exercise are ongoing; however, enough is known about the positive effect of exercise on fall prevention to support its inclusion in a comprehensive fracture prevention program.

Fluoride: A compound that stimulates the formation of new bone by enhancing the recruitment and differentiation of osteoblasts. Studies show varying effects on BMD depending upon the preparation, dose, measurement site and outcomes assessed.

Fracture: Breakage of a bone, either complete or incomplete. Most studies of osteoporosis focus on hip, vertebra and/or distal forearm fractures. Vertebral fractures include morphometric as well as clinical fractures.

FRAX[®]: The World Health Organization Fracture Risk Assessment Tool. www.NOF.org and www.shef.ac.uk/FRAX

Hormone/estrogen therapy (HT/ET) (HT – Activella[®], Femhrt[®], Premphase[®], Prempro[®]; ET – Climara[®], Estrace[®], Estraderm[®], Estratab[®], Ogen[®], Ortho-Est[®], Premarin[®], Vivelle[®]): HT is a general term for all types of estrogen replacement therapy when given along with progestin, cyclically or continuously. HT is generally prescribed for women after natural menopause or bilateral ovariectomy. ET is prescribed for postmenopausal women who have had a hysterectomy. Studies indicate that five years of HT may decrease vertebral fractures by 35 to 50 percent and non-vertebral fractures by about 25 percent. Ten or more years of use might be expected to decrease the rate of all fractures by about 50 percent.

Ibandronate (Boniva[®]): A bisphosphonate approved by the FDA for the prevention and treatment of postmenopausal osteoporosis. Ibandronate reduces the incidence of vertebral fractures by about 50 percent over three years.

Low bone mass (osteopenia): The designation for bone density between 1.0 and 2.5 standard deviations below the mean for young normal adults (T-score between -1.0 and -2.5).

Modeling: The term for skeletal processes that occur during growth (e.g., linear growth, cortical apposition and cancellous modification) and increase bone mass.

Non-vertebral fractures: Fractures of the hip, wrist, forearm, leg, ankle, foot and other sites.

Normal bone mass: The designation for bone density within 1 standard deviation of the mean for young normal adults (T-score at -1.0 and above).

Osteopenia: See low bone mass.

Osteoporosis: A chronic, progressive disease characterized by low bone mass, microarchitectural deterioration of bone tissue and decreased bone strength, bone fragility and a consequent increase in fracture risk; bone density 2.5 or more standard deviations below the young normal mean (T-score at or below -2.5).

Peak bone mass: The maximum bone mass accumulated during young adult life.

Peripheral DXA: A DXA test used to assess bone density in the forearm, finger and heel.

Physiatrist: A physician who specializes in medicine and rehabilitation, or physiatry.

Previous fracture: A risk factor for future fractures, defined here as a history of a previous fracture after age 40.

PTH(1-34), teriparatide, (Forteo®): An anabolic therapy approved for the treatment of osteoporosis. The pivotal study indicates a 65 percent reduction in vertebral fractures and a 53 percent reduction in non-vertebral fractures after 18 months of therapy in patients with osteoporosis.

Quantitative computed tomography (QCT): A diagnostic test used to assess bone density; reflects three-dimensional BMD. Usually used to assess the lumbar spine, but has been adapted for other skeletal sites. It is also possible to measure trabecular and cortical bone density in the periphery by peripheral QCT (pQCT).

Quantitative ultrasound densitometry (QUS): A diagnostic test used to assess bone density at the calcaneus or patella. Ultrasound measurements correlate only modestly with other assessments of bone density in the same patient, yet some prospective studies indicate that ultrasound may predict fractures as well as other measures of bone density.

Raloxifene (Evista®): An estrogen agonist/antagonist (or selective estrogen receptor modulator) approved by the FDA for prevention and treatment of osteoporosis. It lowers the risk of vertebral fracture by about 30 percent in patients with and about 55 percent in patients without prior vertebral fracture.

Remodeling: The ongoing dual processes of bone formation and bone resorption after cessation of growth.

Resorption: The loss of substance (in this case, bone) through physiological or pathological means.

Risedronate (Actonel®): A bisphosphonate approved by the FDA for prevention and treatment of osteoporosis. It lowers the risk of vertebral fracture by about 41-49 percent and non-vertebral fractures by about 36 percent.

Risk factors: For osteoporotic fractures, includes low BMD, parental history of hip fracture, low body weight, previous fracture, smoking, excess alcohol intake, glucocorticoid use, secondary osteoporosis (e.g., rheumatoid arthritis) and history of falls. These readily accessible and commonplace factors are associated with the risk of hip fracture and, in most cases, with that of vertebral and other types of fracture as well.

Secondary osteoporosis: Osteoporosis that is drug-induced or caused by disorders such as hyperthyroidism, renal disease or chronic obstructive pulmonary disease.

Severe or “established” osteoporosis: Osteoporosis characterized by bone density that is 2.5 standard deviations or more below the young normal mean (T-score at or below -2.5), accompanied by the occurrence of at least one fragility-related fracture.

Standard deviation (SD): A measure of variation of a distribution.

T-score: In describing BMD, the number of standard deviations above or below the mean for young normal adults of the same sex.

Teriparatide: See PTH(1-34), teriparatide, (Forteo®).

Vitamin D: A group of fat-soluble sterol compounds that includes ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). These compounds are ingested from plant and animal sources; cholecalciferol is also formed in skin on exposure to ultraviolet light. When activated in the liver and then the kidney, vitamin D promotes calcium absorption and bone mass. Vitamin D replacement also increases muscle strength and lowers risk of falling. A 25(OH) D level of ≥ 30 ng/ml (75 nmol/L) is considered by many to be optimal.

Zoledronic acid (Reclast®): A bisphosphonate approved by the FDA for treatment of postmenopausal osteoporosis. It lowers risk of vertebral fractures by about 70 percent, hip fractures by about 41 percent and non-vertebral fractures by about 25 percent.

Z-score: In describing BMD, the number of standard deviations above or below the mean for persons of the same age and sex.

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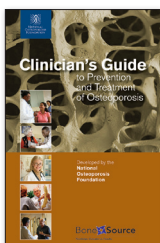
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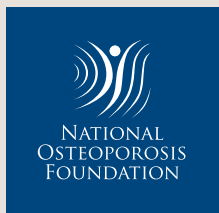
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