Drug-Induced Osteoporosis

PSAP

By Susan K. Bowles, Pharm.D., MSc, FCCP

Reviewed by Mary Beth O'Connell, Pharm.D., FCCP, FASHP, BCPS; and Michelle M. Richardson, Pharm.D., FCCP, BCPS

Learning Objectives

1. Apply an understanding of drug mechanisms to explain drug-induced osteoporosis and its consequences.
2. Use the diagnostic process to develop treatment and monitoring plans for drug-induced osteoporosis.
3. Assess for potential risk factors associated with drug-induced osteoporosis.
4. Evaluate the epidemiologic literature to assess the absolute increase in risk of drug-induced osteoporosis associated with a specific class of agents.

Introduction

Osteoporosis is a disease characterized by low bone mass and deterioration of the bone architecture leading to increased fragility and fractures. A fragility fracture is defined as one that results from no identifiable trauma or minimal trauma, such as a fall from standing height or less. Although a fragility fracture can occur in any bone, fractures of the hip, spine, and wrist are particularly common in individuals with osteoporosis. *Primary osteoporosis* refers to a reduction in bone mass related to aging and menopause, whereas *secondary osteoporosis* results from specific diseases or drugs.

The relationship between osteoporosis and oral glucocorticoids is well understood, but in recent years, many other agents have been reported to affect bone health and should therefore also be considered in the risk assessment for osteoporosis. This chapter reviews new evidence for drugs other than glucocorticoids in the development of secondary osteoporosis and provides a framework for putting risk into context for suitable discussion with patients.

Epidemiology

Osteoporotic fractures are a major public health problem, with about 1.5 million occurring each year. In 2005, the costs associated with osteoporosis were estimated at $17 billion. Epidemiologic reports estimate that 10 million Americans have established osteoporosis, and another 34 million Americans are at risk because of osteopenia. Currently, there are no reliable estimates of the prevalence of drug-induced osteoporosis or osteopenia.

An estimated 80% of those affected by osteoporosis are women, and as discussed in another chapter in this book, men also develop the disease. Although those of Asian or white background are at the highest risk, osteoporosis crosses all ethnic boundaries and can occur in anyone regardless of ethnicity. Bone health behaviors should be assessed regularly in all patients because everyone is at risk of osteoporosis and osteoporotic fractures. Seniors and adults with risk factors generally qualify for bone mineral density (BMD) testing with dual-energy x-ray absorptiometry (DEXA).

Baseline Review Resource

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- O'Connell MB, Vondracek SF. Osteoporosis and other metabolic bone diseases. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 7th ed. New York: McGraw-Hill Medical, 2008[12]:1483–504.
- National Osteoporosis Foundation. Clinicians Guide to Prevention and Treatment of Osteoporosis. 2010. Available at *www.nof.org/professionals/clinicians_guide.htm.* Accessed May 25, 2010.
- Silverman SL, Lane NE. Glucocorticoid-induced osteoporosis. Curr Osteoporos Rep 2009;7:23–6.

Abbreviations in This Chapter

AI	Aromatase inhibitor
BMD	Bone mineral density
DEXA	Dual-energy x-ray absorptiometry
DMPA	Depot medroxyprogesterone acetate
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
H_2RA	H_2-receptor antagonist
LH	Luteinizing hormone
PPI	Proton pump inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TSH	Thyroid-stimulating hormone

Box 1-1. Risk Factors for Osteoporotic Fractures

Nonmodifiable
Advancing age[a]
Female sex[a]
Family history (first-degree relative)[a,b]
Race (non–African American)[a]
Previous fragility fracture[a]
Rheumatoid arthritis[a]
Secondary osteoporosis[a,c]
Past cigarette use
Past glucocorticoid use

Modifiable
Premature menopause (< 45 years)
Amenorrhea (> 1 year)
Low body mass index[a]
Sedentary lifestyle or prolonged immobilization
Low calcium intake
Low vitamin D intake
Alcohol consumption ≥ three drinks/day[a]
Current cigarette smoker[a]
Oral glucocorticoid use[a]
Low bone mineral density[a]
Drugs associated with osteoporosis
Falls

---

[a]Factors included in the WHO fracture risk assessment tool (FRAX).
[b]Only hip fracture of parent included as a FRAX risk factor.
[c]Only these secondary causes—type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition, or malabsorption and chronic liver disease— are included as FRAX risk factors. FRAX does not include prescription drug–induced causes of osteoporosis except for glucocorticoids.

Risk Factors

Among the most important strategies in managing drug-induced osteoporosis is awareness of other factors than can affect bone health and fracture risk (Box 1-1). The most common of these risk factors are age and female sex. Women experience more hip fractures than men; this is thought to be related to a lower peak bone mass and greater effect of menopause. However, one-third of all hip fractures occurring after age 65 occur in men. Therefore, bone health and fracture risk are important to consider in all patients taking drugs with the potential to cause bone loss.

Many osteoporotic fractures are related to falls, so evaluation of risk factors for falls (Box 1-2) is also an important component in the assessment of bone health. Many falls are preventable, and reducing fall rates can prevent fractures and the morbidity and mortality associated with them.

As shown in Figure 1-1, several factors are associated with declining BMD and impaired bone quality. These include factors related to aging and hypogonadism, as well as the clinical risk factors outlined in Box 1-1.

Diagnosis

The diagnosis of osteoporosis is primarily based on the measurement of BMD, but a clinical diagnosis can be

---

Box 1-2. Risk Factors for Falls

Environmental
Lack of assistive devices in bathrooms
Loose throw rugs
Poor lighting
Obstacles in walking path
Slippery sidewalks
Unsafe stairways

Medical
Anxiety
Arrhythmias
Dehydration
Depression
Poor vision
Psychotropic drugs
Previous falls
Urinary incontinence
Vitamin D deficiency
    (serum 25-OH vitamin D < 30 ng/mL)

Musculoskeletal/Neurologic
Impaired mobility
Impaired transfer ability
Cognitive impairment
Kyphosis
Muscle deconditioning
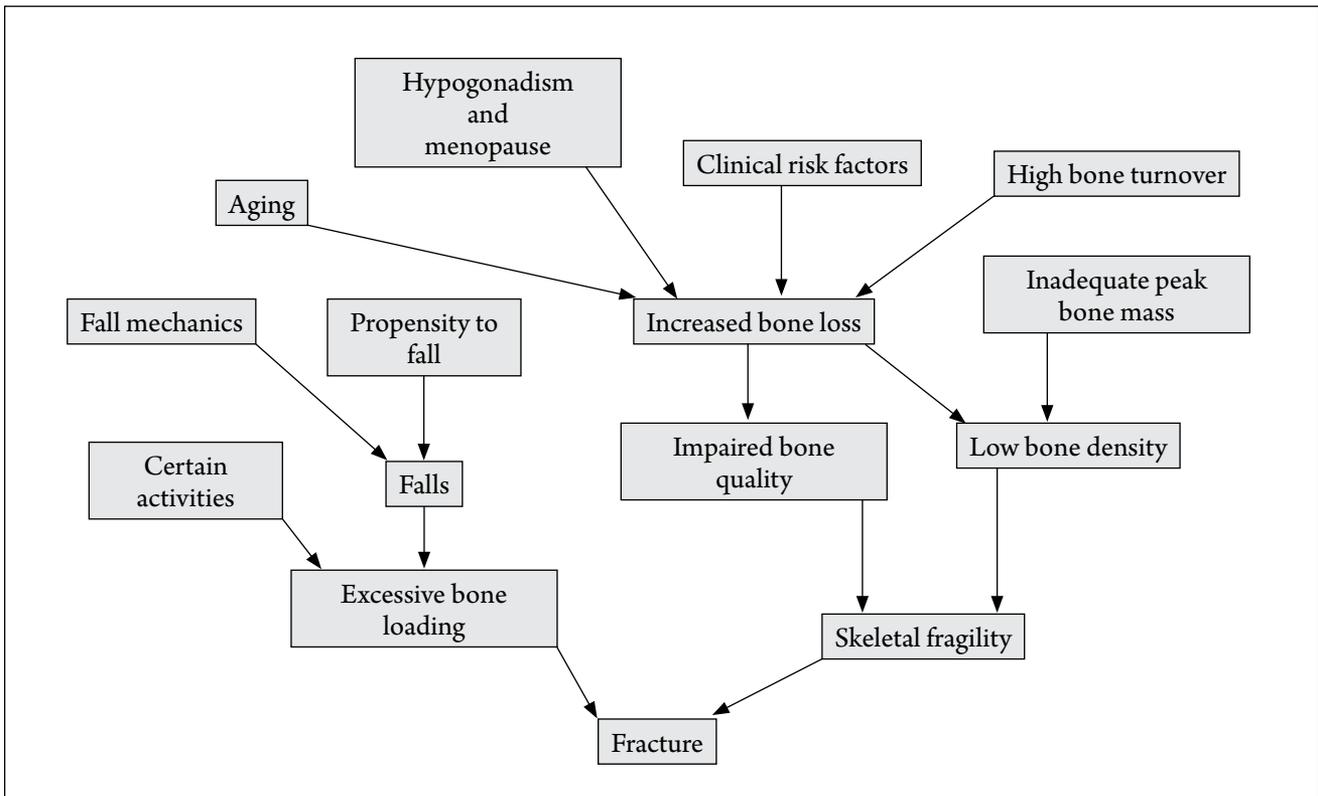
Figure 1-1. Pathogenesis of osteoporotic fractures.

Reproduced with permission from Cooper C, Melton LJ 3rd. Epidemiology of osteoporosis. Trends Endocrinol Metab 1992;3:224–9.

made in someone with several risk factors experiencing a fragility fracture. Methods for measuring BMD include central DEXA, peripheral DEXA, quantitative computed tomography, and quantitative ultrasound densitometry. Although all of these can predict the risk of fragility fractures, evidence supports the use of DEXA as the most accurate method, with the best positive predictive value, to estimate fracture risk in postmenopausal women and men older than 50.

Measurements are taken at common sites for fracture (e.g., forearm, hip, spine) and expressed as grams of

mineral per centimeter scanned. These measurements are then expressed as either a T-score or Z-score. A T-score is essentially a comparison of peak bone mass based on the difference between a patient's BMD and the average found in a white, healthy, young adult of the same sex. The Z-score represents a comparison of a patient's BMD with that expected for someone of the same sex and similar age. Both are expressed as the number of standard deviations (SD) above or below the mean.

The World Health Organization (WHO) has developed a classification for bone health based on BMD, as determined by DEXA, for postmenopausal women and men 50 years or older. As shown in Table 1-1, osteoporosis is defined as a T-score of −2.5 or less. The WHO diagnostic criteria should not be applied to children, premenopausal women, or men younger than 50. In these groups, the International Society for Clinical Densitometry recommends that race-adjusted Z-scores be used. A Z-score of −2.0 or lower is defined as below the expected range for age. A Z-score of greater than −2.0 is considered within the expected range for age. The Z-score can be used to guide treatment decisions for drug-induced osteoporosis in individuals younger than 50 and provide an estimate of fracture risk for discussion with patients.

Table 1-1. WHO Definitions of Bone Health Based on BMD in Postmenopausal Women and Men Older Than 50[a]

Classification	T-score (SD)
Normal	> −1.0
Osteopenia	−1.0 to −2.5
Osteoporosis	< −2.5
Severe osteoporosis	< −2.5 plus one or more fragility fracture

[a]BMD measured by dual-energy x-ray absorptiometry.
BMD = bone mineral density; WHO = World Health Organization.

The WHO has developed a Fracture Risk Assessment Tool (FRAX) that can be used with or without femoral neck BMD measurements (expressed either as grams per square centimeter or a T-score). The machine type should be specified when using FRAX to estimate fracture risk. In general, FRAX is not used if the person is already receiving treatment with osteoporosis prescription drugs. The online FRAX tool (available at *www.shef.ac.uk/FRAX*) can be used to estimate the 10-year probability of fracture risk for overall major osteoporotic fractures (i.e., spine, forearm, hip, and shoulder) and hip fracture for women and men aged 40–90. In general, a 10-year overall fracture risk of less than 10% is considered low risk; 10% to 20% is moderate risk; and greater than 20% is high risk. The only drug-induced osteoporosis drugs evaluated with this tool are glucocorticoids, nicotine, and alcohol. The effect of alcohol use is more related to the risk of falls than to an actual effect on BMD.

The peripheral DEXA and quantitative ultrasound densitometry tests are often used in community pharmacies or ambulatory clinics to identify patients who should be referred for further evaluation by DEXA. However, these methods of measuring BMD should not be used in individuals with several risk factors, fragility fractures, or secondary causes for osteoporosis. They are also not appropriate for children, premenopausal women, or young men unless the patient has at least one major risk factor. Therefore, they do not have a role in the screening of patients for drug-induced osteoporosis.

OSTEOPOROSIS RELATED TO SPECIFIC DRUGS

Hormonal Therapies

Estrogen and testosterone are important regulators of the bone remodeling process, so it is not surprising that osteoporosis is associated with a decline in hormonal concentrations after menopause. Similarly, testosterone deficiency is the most common cause of osteoporosis in men, although the role of testosterone is not as straightforward as once thought. Drugs inhibiting secretion or altering the metabolism of sex hormones have the potential to induce osteoporosis. These drugs include the aromatase inhibitors (AIs) and gonadotropin-releasing hormone (GnRH) agonists used in the treatment of breast and prostate cancers, as well as the contraceptive depot medroxyprogesterone acetate (DMPA).

Thyroid hormones also affect bone metabolism, with increased bone resorption observed in hyperthyroidism. The bone effects result from both endogenous and exogenous causes of hyperthyroidism.

Aromatase Inhibitors

The use of AIs as adjuvant treatment for breast cancer has been shown to improve disease-free survival and decrease the occurrence of metastatic disease in postmenopausal women with estrogen receptor–positive disease. However, the pharmacologic activity of these agents also affects BMD and fracture risk.

After menopause, estrogen is produced in the peripheral tissues by the conversion of adrenal androgens to estrogen. The AIs inhibit the aromatase enzyme, responsible for this conversion, and result in decreased estrogen concentrations. Because many postmenopausal women have several underlying risk factors for osteoporosis, further estrogen loss from treatment with AIs might be expected to cause bone loss and increased fracture risk.

The potential for AIs to affect bone health was anticipated based on their pharmacologic activity and therefore was evaluated during clinical trials studying the efficacy and tolerability of these agents in treating breast cancer. The rate of bone loss associated with AIs varies depending on the patient population studied. However, a decline of about 4% to 6% over 5 years has generally been observed for both anastrozole and letrozole. The relationship between this bone loss and an increased risk of fragility fractures was definitively established for both drugs, with fracture rates of 11% for anastrozole and 8.6% for letrozole reported in randomized controlled clinical trials. Compared with tamoxifen, which is thought to offer bone protection, the absolute risk increase (ARI) for all fragility fractures is 3.3% for anastrazole and 2.8% for letrozole. This translates into one excess fracture for every 30–35 women treated with either AI over 5 years.

Early studies in animals suggest that exemestane, a steroidal AI, does not share the same risk of bone loss and fragility fractures as anastrozole and letrozole. Because of its steroidal structure, exemestane also exhibits some androgenic activity, potentially offsetting the bone loss properties of AI-induced estrogen deficiency. However, this benefit has not been shown in clinical trials, which found the rate of bone loss comparable with that of nonsteroidal AIs. Similarly, when exemestane is compared with tamoxifen, an ARI of 2% for fragility fractures is observed; this translates to one excess fracture for every 50 patients treated with exemestane during a 5-year period.

GnRH Agonists

Gonadotropin-releasing hormone agonists, used in conjunction with chemotherapy, improve disease-free survival in premenopausal women with hormone receptor–positive breast cancer. Although more controversial, these agents are sometimes used in combination with AIs or tamoxifen. The GnRH agonists down-regulate the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in suppression of ovarian function and a corresponding decline in estrogen production. Suppression of ovarian function by GnRH agonists is a treatment strategy also employed in the

management of endometriosis. Regardless of the indication for ovarian suppression, bone metabolism is likely to be affected and result in bone loss.

Whether used alone or in combination with an AI or chemotherapy, goserelin or leuprolide in premenopausal women causes a rapid decline in BMD of about 5% to 6% over 6–12 months. Limited data suggest some recovery in BMD on discontinuation of GnRH agonists, but the degree and time frame are not well understood. As a result, the relationship between GnRH-related bone loss and future risk of fragility fracture has not been established.

The therapeutic effect of GnRH agonists in the treatment of prostate cancer is related to their antiandrogen effects, which result in decreased serum testosterone concentrations. Bone loss is a well-known consequence of hypogonadism, so it follows that decreased BMD is a potential complication of GnRH agonists. Longitudinal studies documented significant bone loss within 1 year of initiating therapy with a GnRH agonist (2% to 5% decrease in BMD, depending on the anatomic site measured). Several small studies have evaluated fracture risk among men receiving treatment with GnRH agonists, but the findings were limited by small sample size and the lack of control groups.

One large retrospective cohort study of more than 50,000 men observed an increased risk of fracture in men receiving androgen deprivation therapy for the management of prostate cancer. The relative risk (RR) during a 5-year period was significantly higher for men who received GnRH agonists in the first year after diagnosis than for men without antiandrogen therapy. The ARI was estimated at 3.6%, resulting in a calculated number needed to harm (NNH) of 28 for all men receiving a GnRH. This means that one excess fracture occurred for every 28 men treated over 5 years. Given an estimated annual incidence of prostate cancer of 220,000 cases per year, and current drug use patterns for GnRH agonists, this translates to about 3000 excess fractures annually.

Furthermore, dose-response and age effects were observed. The NNH declined significantly for men receiving nine or more doses compared with those receiving four or fewer doses. A decline in the NNH is indicative of a higher ARI. For example, the group of men receiving one to four doses had an NNH of 74, whereas the group receiving nine or more doses had an NNH of 18. This suggests that the risk of fracture increases with the number of GnRH doses received. A similar trend toward declining NNH was observed in all dose categories with increasing age, indicating that the risk of fracture increases with age. This is not surprising because older men have lower baseline BMD and would be expected to be at increased risk of fracture when bone loss is accelerated by drugs.

Depot Medroxyprogesterone Acetate

Current drug use patterns indicate that DMPA is the contraceptive of choice for more than 2 million women, including some 400,000 adolescents. This agent prevents pregnancy by inhibiting LH and FSH, causing anovulation and a corresponding decrease in estrogen production.

The potential loss of bone owing to DMPA-related estrogen deprivation is of particular concern for teenage girls and women younger than 30, a time when BMD normally increases. Prolonged use could potentially decrease the peak bone mass and increase the risk of fragility fractures in 20–30 years. Longitudinal data show an annual rate of bone loss of 1% to 3% in adolescents aged 12–18, with the greatest reduction in BMD occurring in the first 2 years of use. Adult women show a similar pattern, with most bone loss observed in the first 2 years of use, slowing thereafter to an annual rate of about 0.5%.

When DMPA is discontinued, adolescent bone mass undergoes full recovery at the spine and at least partially at the hip within 24–36 months. Prospective data indicate that BMD in adults similarly recovers. The long-term effect of continued DMPA use on fracture risk is unknown; however, some research has examined whether the use of DMPA increases the risk of fractures during the short term.

One prospective study of female Army recruits age 16–35 found that DMPA use was associated with increased risk of stress fracture of the calcaneus in white women. Unlike fragility fractures, stress fractures are an incomplete fracture of the bone; caused by unusual or repeated stress, they are often associated with athletic activity such as might be expected in military life. Study participants had several other risk factors, including a lower-than-average BMI and high rates of cigarette smoking and alcohol use.

A second cross-sectional study examined the risk of fracture associated with DMPA use in a cohort of developmentally delayed premenopausal women. Fracture risk, even when corrected for age, race, and concomitant anticonvulsant use, was significantly increased with DMPA use. The overall event rate was small, however, with 3.6% of DMPA users experiencing a fracture compared with 1.6% of nonusers. Although the ARI of 2% (NNH of 50) is similar to that observed with AIs, these findings are from a retrospective cohort study rather than a randomized controlled trial, and not all potentially confounding variables (e.g., seizure activity) could be accounted for using this study design. Larger and longer-term longitudinal studies are needed to accurately determine the association between DMPA use and fractures.

Available data have prompted the U.S. Food and Drug Administration (FDA) to issue a black box warning stating that prolonged use might result in a significant and cumulative bone loss that might not be completely reversible on discontinuation. The caution concerns the use of DMPA beyond 2 years in premenopausal women; the manufacturer recommends BMD testing by DEXA after 2 years of use.

Thyroid Replacement Therapy

Hyperthyroidism and thyroid replacement therapy are both associated with bone loss. Thyroid-stimulating hormone (TSH) receptors have been identified on osteoclastic and osteoblastic precursor cells, with accelerated bone resorption occurring during hyperthyroid states when TSH concentrations are suppressed. Oversupplementation of thyroid replacement hormone causes an exogenous hyperthyroidism, suppressing TSH concentration, with direct effects on bone remodeling that result in bone loss.

Epidemiologic studies have reported an association between bone loss and suppressed TSH concentrations. After adjustment for factors with potential to affect bone density, total hip BMD measurements were decreased by about 4% in men and by almost 8% in postmenopausal women who had serum TSH concentrations below the reference range. In contrast, TSH concentrations within the reference range were associated with preservation of bone mass. A large cross-sectional study of more than 6000 women with self-reported thyroid disease found that women with the lowest TSH concentration (less than 0.5 milli-international unit/L) had lower forearm BMD and the highest prevalence of osteoporosis. There were no differences in BMD between women with TSH concentrations of 0.5–1.49 milli-international units/L and those with concentrations greater than 1.49 milli-international units/L. Hyperthyroidism was also associated with an increase in fracture risk, with a 4.5-fold increase in vertebral fractures and a 3.2-fold increase in nonvertebral fractures when the serum TSH concentration fell below 0.1 milli-international unit/L.

There also appears to be a relationship between TSH concentrations and BMD in euthyroid postmenopausal women. Recent data suggest a relationship between increasing TSH concentrations within the therapeutic range and BMD. The odds ratio (OR) for the median TSH reference range (0.39–1.8 milli-international units/L) versus the higher end of the reference range (1.8–4.5 milli-international units/L) was 3.4 for osteoporosis and 2.2 for osteopenia.. Furthermore, BMD of the total hip was almost 5% lower in white women and 9.7% lower in African American women in the lowest quintile of the reference range than in women with TSH concentrations in the highest quintile.

These data suggest that overt exogenous hyperthyroidism should be avoided with thyroid replacement therapy. Consideration should also be given to dosing adjustments when the TSH concentration falls below the median of the reference range, particularly in women with osteopenia or preexisting osteoporosis.

Central Nervous System Agents

Several classes of central nervous system agents have been associated with an increased risk of fracture. These include anticonvulsants, antidepressants, and antipsychotics.

Anticonvulsants

There are several mechanisms by which anticonvulsants might affect bone metabolism. Initially, it was thought that the anticonvulsants that are potent inducers of cytochrome P450 (CYP) (i.e., carbamazepine, phenobarbital, and phenytoin) might increase the metabolism of vitamin D, leading to a reduction in calcium absorption, subsequent elevation in parathyroid hormone, and increased bone turnover. It has also been suggested that CYP induction leads to lower circulating concentrations of estrogen and testosterone, resulting in bone loss. However, many anticonvulsants that do not affect CYP metabolism are associated with bone loss, indicating that other mechanisms are likely responsible. However, these other mechanisms are poorly understood. Early data in animals suggested that anticonvulsants directly inhibit intestinal calcium absorption. More recently, in vitro studies suggested that anticonvulsants directly inhibit osteoblasts, resulting in decreased bone formation. Further animal and clinical studies are needed to fully elucidate the mechanisms associated with anticonvulsant-related effects on bone metabolism.

Although BMD has been shown to decrease with the use of both CYP-inducing and -noninducing anticonvulsants, it is difficult to quantify the amount and rate of bone loss because studies have enrolled many different patient samples, from children to older adults, and include both single and combination therapy. Reports indicate that Z-scores decline in the range of −0.08 to −0.91 for the spine and −0.09 to −0.90 for the hip. Similarly, measuring the relationship between fracture risk and anticonvulsants is difficult because epilepsy itself may be associated with fractures.

Pooled data from 11 studies showed an overall RR of 2.18 for all fractures among patients with epilepsy; this is much larger than expected considering the degree of bone loss observed with anticonvulsants. One study included in the analysis excluded seizure-related fractures and estimated an RR of 1.3, which is in the expected range of observed BMD measurements. These data suggest that, although there is an increased fracture risk associated with anticonvulsant use, it is not as high as generally thought, and many fractures may be related to the disease rather than the drug.

This result is supported by observations that 34% to 40% of fractures are related to trauma during seizure activity. Furthermore, patients experiencing generalized seizures have been reported to experience more fractures than those with other types of epilepsy. Comorbid conditions and concomitant drug use are important considerations when assessing fracture risk associated with epilepsy and anticonvulsant drugs. Epilepsy might be related to central nervous system neoplasms,

developmental delay, or stroke. Such individuals might be more physically inactive, which can decrease bone density. Some disease states also affect balance and gait, rendering individuals more susceptible to falls. These patients might be taking other psychotropic drugs that further increase fall risk, or they might be taking drugs such as corticosteroids that are known to have a detrimental effect on bone health.

Antidepressants

The serotoninergic system appears to play an important role in bone physiology, which has implications for the effect of selective serotonin reuptake inhibitors (SSRIs) and serotoninergic tricyclic antidepressants (TCAs) on bone health. Specifically, serotonin appears to modulate skeletal response to parathyroid hormone, possibly through receptors and transporters found on osteoblasts and osteocytes. Several studies have shown bone loss among SSRI users, suggesting a clinical effect on bone metabolism. Cross-sectional and longitudinal data in older men and women indicate higher rates of annual bone loss among SSRI users and about a 4% to 5% lower BMD, depending on the anatomic site, compared with nonusers. These studies did not observe a similar decline in BMD among users of nonserotoninergic TCAs, suggesting that the serotoninergic activity of SSRIs has a clinical effect on bone metabolism.

The association between antidepressant use and fractures is well established; however, recent evidence suggests that depression itself is associated with decreased BMD and increased fracture risk. In addition to drugs, behavioral and biologic factors can interact in an individual to negatively affect bone health. Poor health behaviors such as smoking, alcohol use, and physical inactivity are high among depressed individuals. Furthermore, changes to the hypothalamic-pituitary-adrenal axis have been identified in patients with depression, causing elevated cortisol concentrations and lower amounts of sex hormones, both of which can result in lower BMD. Comorbid conditions and concomitant drugs also play a role, potentially increasing the risk of falls. As outlined in Figure 1-1, when all of these factors come together, they result in skeletal fragility and excessive bone loading that ultimately lead to fractures.

Although both SSRIs and TCAs are associated with an increased risk of falls, some data suggest that SSRIs carry a greater risk of fractures than TCAs. This finding might simply be caused by selection bias; clinicians are less likely to prescribe a TCA for the patient at high risk of fracture because of the adverse effect profile. Tricyclic antidepressants might also be used at lower doses, not for their antidepressant activity but for management of neuropathic pain syndromes and insomnia. Most studies also do not differentiate TCAs on the basis of their serotoninergic activity. Nevertheless, assessment of bone health is important to the overall well-being of patients with depression.

Antipsychotic Agents

Similar to antidepressants, a well-established relationship exists between antipsychotic agents and falls and fracture. The postulated biologic mechanism by which antipsychotic agents affect bone physiology is related to their effect on prolactin concentrations. Conventional antipsychotics, in particular, are known to cause a rise in prolactin concentration; this in turn lowers estrogen and testosterone concentrations, potentially leading to bone loss. As with depression, other mental illnesses might also represent an independent risk factor for osteoporosis. Schizophrenia and other psychotic disorders were associated with higher rates of osteoporosis and fragility fractures. Notably, the highest risk of any fracture was reported among premenopausal women, with an RR of 2.5). The risk of hip fracture was increased 5-fold for older women and 6-fold for older men.

Data are limited on the effect of antipsychotic drugs on bone density; however, available data suggest that a higher proportion of premenopausal women taking prolactin-raising agents have lower BMD than those taking prolactin-sparing agents. Spinal BMD has also been observed to be about 20% lower in young men and premenopausal women taking conventional antipsychotics than in those taking atypical agents or in healthy young controls. No BMD differences were seen between patients taking atypical agents and healthy controls. When considered together, these data suggest that conventional antipsychotic agents cause bone loss and that atypical antipsychotic agents do not. However, the effect of behavioral factors could not be accounted for in these studies.

Despite an incomplete understanding of the role of behavioral, biologic, and drug-related factors in individuals taking antipsychotic agents, the potential of these agents to negatively affect bone health should be considered for all patients.

Gastric Acid–Reducing Agents
Proton Pump Inhibitors

Interest in the association between proton pump inhibitor (PPI) use and hip fracture arose from studies that showed decreased calcium absorption in patients taking PPIs. Less potent gastric acid agents, the H_2-receptor antagonists (H_2RAs), were not observed to have the same effect. However, the studies varied in method and may not have used correct testing to document these potential drug-drug or drug-food interactions. Other data suggest that PPIs have a direct effect on bone metabolism. Proton pumps have been identified on osteoclasts and appear to be used during the excretion of hydrogen ions for bone resorption. Inhibition of these proton pumps may interfere with the resorption process, resulting in decreased bone density with time.

Proton pump inhibitors appear to affect BMD in men; a small but significant difference in hip BMD was observed among male PPI users compared with nonusers. However, similar observations were not found in women, suggesting that men are at somewhat increased risk compared with women.

Observations that men are at increased risk of fracture are supported by one epidemiologic study that found a stronger association between duration of PPI use and fracture in men than in women, although the odds of fracture were increased in both. However, this finding was not supported by findings from other epidemiologic studies.

With respect to the overall risk of fracture, two case-control studies found that PPIs were used more often by patients with fracture. The results were consistent between studies, with the adjusted OR reported as 1.44 and as 1.45 for PPI use in the previous year. Therapy duration appeared to be an important factor because the strength of association increased with each year of use. A third study found no association between hip fracture and PPI use for less than 5 years, although PPI use was more frequent in those with any fracture after 5 or more years of use (OR 1.92) or hip fracture (OR 1.62). After 7 or more years of PPI use, the OR increased to 4.55, further supporting the notion that duration of use is an important factor in determining risk.

H$_2$-Receptor Antagonists

In contrast to PPIs, data on H$_2$RA use were equivocal; one study found these agents to have a protective effect on BMD, whereas another showed a significant association between hip fracture and H$_2$RA use, although this association was not as strong as that observed with PPIs.

Although epidemiologic data alone are insufficient to prove a causal relationship between gastric acid–reducing agents (particularly PPIs) and an increase in osteoporotic fracture, gastric acid reducers may contribute to overall risk when assessing bone health in patients using these agents.

Thiazolidinediones

The risk of fracture appears to be increased in individuals with type 2 diabetes, with some suggestion that good glucose control reduces the association between the disease and fracture risk. However, there is an apparent increased risk of fracture associated with the thiazolidinediones rosiglitazone and pioglitazone; this was first identified in randomized controlled trials examining the efficacy of these agents in the management of type 2 diabetes.

A meta-analysis that pooled data from 10 randomized controlled trials showed a small but significant ARI of 0.6% for all fractures in thiazolidinedione users. However, when stratified by sex, the ARI was significantly increased for women at 2.8% compared with no difference in risk for men. In fact, men using thiazolidinedione experienced fewer fractures than the control group of either metformin or sulfonylurea users. Most fractures were observed in the periphery rather than the hip or spine, but this may simply be a reflection of the younger patient sample in the randomized controlled trials (average age 50–60 years). Further supporting this notion is one case-control study that identified a significant association between hip fracture and thiazolidinedione use in older women that was not seen in nonusers.

The sex-based difference in risk observed in the meta-analysis was not confirmed by subsequent epidemiologic studies, which found a significant association between thiazolidinedione use and fractures in both men and women. One of these studies stratified its results by both agent and sex and found a significant association between fractures and both rosiglitazone and pioglitazone in women, but only pioglitazone increased the risk of fracture for men. These data suggested that whereas both men and women taking thiazolidinediones could be at risk of fractures, pioglitazone presents the greater risk for men. However, this finding requires confirmation through further research.

Both randomized controlled trials and observational studies show a consistent decline in BMD over time, suggesting that thiazolidinediones do have an effect on BMD. Thiazolidinedione users show more bone loss (about 1% at the spine and 1.5% at the hip) than nonthiazolidinedione users. These agents are thought to affect bone metabolism through several mechanisms, which include a decrease in osteoblastic function, increasing adiposity of the bone marrow, and reduced aromatase activity. This last mechanism might partially explain why clinical trials have observed women to be at a greater risk than men.

Summary of Drug-Induced Osteoporosis

There is a clear association between bone loss, fragility fractures, and the use of AIs in postmenopausal women and GnRH agonists in men. The use of GnRH agonists and DMPA by premenopausal women is associated with bone loss, but whether this loss is associated with increased risk of fracture remains to be determined. The issue of osteoporosis secondary to central nervous system active agents is difficult to assess in quantifying the risk of bone loss and fracture that can be attributed to drug use. More likely, the overall effect of these drugs is related to complex interactions between the underlying disease state, drugs, comorbid conditions, and lifestyle behaviors. The same holds true for PPIs and thiazolidinediones. Of interest, each of these two drug classes has shown sex differences, with the association between fractures and PPI use stronger in men than women. In contrast, some data with thiazolidinediones suggest a greater risk of fracture for women than men. Furthermore, there is some suggestion that pioglitazone presents a greater risk than rosiglitazone, although this must be confirmed by further study.

Managing Drug-Induced Osteoporosis

Nonpharmacologic Interventions

Limited data exist regarding the effect of nonpharmacologic interventions for the treatment of drug-induced osteoporosis. Lifestyle interventions are important, particularly smoking cessation. Cigarette smoking can decrease sex hormone concentrations and interfere with calcium absorption, and it may impair osteoblastic function. Although not yet studied, there is a potential additive negative effect on BMD, especially among adolescents and young women using DMPA, that could minimize peak bone mass. High rates of smoking and alcohol use in patients with mental illness may contribute to the bone loss associated with antidepressants and antipsychotic agents, further increasing risk of fracture. The same holds true for those taking anticonvulsants.

Physical activity among young women is important to the achievement of peak bone mass. For older people, exercise improves muscle strength, balance, and coordination and assists in maintaining mobility. All medically fit patients should be encouraged to participate in moderate-intensity weight-bearing exercise such as walking for 30 minutes on most days of the week. Ideally, this should be supplemented with some resistance activity two times/week.

Falls and fractures are closely linked, so reducing the risk of falls can decrease the risk of fractures. Living environments should be reviewed to identify factors associated with falls such as poor lighting, unsafe bathrooms or stairs, and tripping hazards. Drug profiles should be reviewed, with drugs known to increase fall risk discontinued whenever possible. Although some clinical trials have shown a significant reduction in falls with vitamin D supplementation, this has not been consistent in all studies.

Pharmacologic Interventions

Several algorithms (Figures 1-1, 1-2, and 1-3) stress the importance of ensuring adequate calcium and vitamin D intake in patients taking drugs associated with increased risk of fracture. Adequate intake is best achieved through dietary intake; however, it is estimated that the daily intake of the average American is only 600 mg of elemental calcium. This level of consumption is well below the recommended daily allowance of 1300 mg for ages 14–18, 1000 mg for ages 19–50, and 1200 mg for those older than 50. Vitamin D deficiency is common, especially among older individuals, those living in northern latitudes or in institutions, or those with poor nutrition.

Vitamin D status is diagnosed by measuring 25-hydroxyvitamin D concentrations, with general definitions of deficiency (less than 20 ng/mL), insufficiency (21–29 ng/mL), and sufficiency (greater than 30 ng/mL). Although this test is expensive and subject to variability between laboratories, it is appropriate in individuals taking drugs known to affect vitamin D catabolism or those at risk of vitamin D deficiency.

There is considerable controversy regarding the currently recommended daily allowance of vitamin D. The National Osteoporosis Foundation recommends 800–1000 units/day for individuals 50 years or older. However, many clinical experts feel that up to 2000–4000 units/day are necessary to maintain a state of vitamin D sufficiency. Patients taking CYP-inducing anticonvulsants may require the higher dose of 4000 units/day to maintain 25-hydroxyvitamin D concentrations greater than 30 mg/mL. Much higher dosages are sometimes prescribed for those with documented vitamin D deficiency, such as ergocalciferol one or two 50,000-unit capsules weekly for 1–3 months. Because of the long half-life of vitamin D, about 3 months of therapy are required before new steady-state 25-hydroxyvitamin D concentrations are observed.

Several drugs have been approved for the treatment of osteoporosis, but only the bisphosphonates, teriparatide, and denosumab have been studied in the management of drug-induced osteoporosis. The bisphosphonates have been studied in glucocorticoid-induced osteoporosis and bone loss secondary to hormonal therapies used in the treatment of breast and prostate cancer. Denosumab has recently been approved for the treatment of osteoporosis related to androgen deprivation therapy of prostate cancer. Teriparatide has been studied in the management of glucocorticoid-induced osteoporosis.

Specific Guidelines
Osteoporosis Induced by AIs and GnRH Agonists in Women

An approach to the management of osteoporosis related to the use of AIs is illustrated in Figures 1-2 and 1-3. When women have additional risk factors or established osteoporosis, the bisphosphonates are considered first-line therapy, either orally or intravenously, although this recommendation is based on limited information. Risedronate, administered as 35 mg once weekly, was studied in 87 postmenopausal women with breast cancer during a 2-year period. Only a few women were receiving an AI (i.e., five in the placebo group and six in the risedronate group). At 24 months, BMD at the spine had declined by almost 5% in the placebo group compared with a 2% loss in the risedronate group.

More recently, zoledronic acid has been studied because of data suggesting that it exhibits antimetastatic and antitumor properties in addition to its preservative effect on bone density. Data on this agent's effect on bone loss from hormonal therapies come primarily from large randomized controlled trials that examined the effect of zoledronic acid on disease-free survival from breast cancer in pre- and postmenopausal women treated with GnRH agonists and/or AIs. The current data are only short term, with patients monitored for no more than 1

Figure 1-2. Algorithm for identifying and managing osteoporosis in postmenopausal women with breast cancer treated with AIs.

AI = aromatase inhibitor; BMD = bone mineral density; BMI = body mass index.

Reproduced with permission from Hadji P, Body JJ, Aapro MS, Brufsky A, Coleman RE, Guise T, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol 2008;19:1413.

year. Zoledronic acid 4 mg administered every 6 months resulted in significant gains in BMD of 3% to 5% among postmenopausal women receiving adjuvant therapy with AIs in early breast cancer. However, it is unknown whether this translates to a reduction of AI-related fractures in this population. The dose used in these studies was also much higher than the annual dose of 5 mg of zoledronic acid indicated for non–drug-induced osteoporosis.

A 5-year study of premenopausal women with breast cancer undergoing ovarian suppression plus hormonal therapy found that BMD stabilized after 36 months of intravenous zoledronic acid 4 mg administered every 6 months. At 5 years, those receiving goserelin plus hormonal therapy with zoledronic acid had an increase of about 4% in BMD at both the spine and hip compared with those receiving placebo. However, this did not translate into a decrease in fractures because the fracture rates were 1.1% for both groups. Similarly, no significant differences were observed when stratified by hormonal therapy, with ARI estimated at 0.7% for the goserelin plus anastrozole group not treated with zoledronic acid compared with treatment.

Osteoporosis Induced by GnRH Agonists in Men

The general approach to managing osteoporosis related to antiandrogen therapy in men with prostate cancer is based on BMD and/or the occurrence of fragility fractures. Men who have experienced fragility fractures should receive counseling regarding adequate calcium and vitamin D intake and be treated with bisphosphonates or denosumab. Men who have not experienced fractures should have their BMD measured. Those with osteoporosis should receive calcium and vitamin D supplements, as well as treatment with bisphosphonates. If the T-score indicates osteopenia, patients should be treated with calcium and vitamin D supplements, with BMD repeated in 6–12 months. Adequate calcium and vitamin D intake should also be ensured in men for whom BMD indicates normal bone, with repeat BMD testing in 2 years.

Similar to osteoporosis related to AIs and GnRH agonists in women with breast cancer, the bisphosphonates play an important role in the management of osteoporosis related to antiandrogen therapy in men. Oral alendronate has been studied in men receiving androgen deprivation
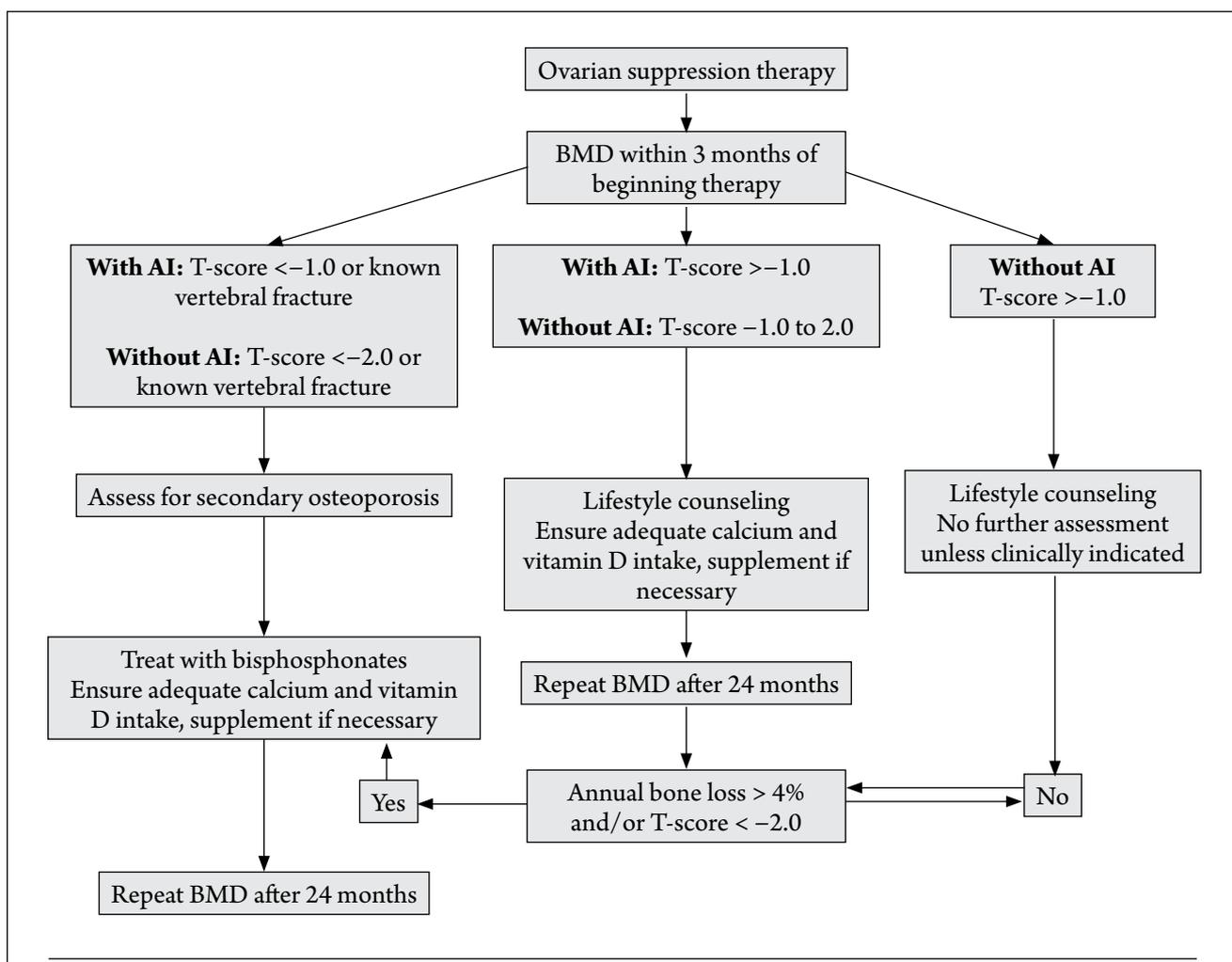
Figure 1-3. Algorithm for identifying and managing osteoporosis in premenopausal women treated with gonadotropin-releasing hormones, with or without concomitant AIs.

Reproduced with permission from Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, et al. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev 2008;34:S12.

AI = aromatase inhibitor; BMD = bone mineral density.

therapy. Men receiving alendronate 70 mg once weekly showed almost a 4% increase in BMD of the spine and 1.6% at the hip at 1 year. In comparison, men in the placebo group had a decline in BMD of about 1% in both the spine and hip.

The effect of zoledronic acid has also been studied in a few men receiving antiandrogen therapy for the treatment of nonmetastatic prostate cancer. Zoledronic acid administered at a dose of 4 mg every 3 months for 1 year resulted in a 5.6% increase in BMD compared with a loss of 2% for those not receiving therapy. A 12-month study of 40 men randomized to either a single 4-mg dose of zoledronic acid or placebo observed an increase in spinal BMD of 4% in men assigned to active treatment compared with a reduction of 3% in men receiving

placebo. At present, no data exist regarding the effect of zoledronic acid on the risk of fracture. A large randomized controlled trial that is currently examining the effect of zoledronic acid on disease outcomes in men with metastatic prostate cancer should provide health care providers with more information regarding the role of this agent on bone health.

Denosumab, a monoclonal antibody against RANKL, was recently studied for the treatment of osteoporosis secondary to androgen deprivation therapy in men with prostate cancer. This randomized controlled trial comparing denosumab 60 mg subcutaneously every 6 months with placebo observed significant increases in BMD of the lumbar spine (7.9%), total hip (5.7%), and distal radius (6.9%) after 3 years of active treatment.

Vertebral fractures were also significantly reduced in the denosumab treatment group, representing an absolute risk reduction of 2.4% and a number needed to treat of 42.

Glucocorticoid-Induced Osteoporosis

Although glucocorticoid-induced osteoporosis is not the focus of this chapter, recent data with teriparatide warrant discussion. Teriparatide 20 mcg once daily was compared with alendronate 10 mg once daily for 18 months in 428 women and men with glucocorticoid-induced osteoporosis. An increase in BMD of the lumbar spine was observed in both treatment groups, but the increase was significantly greater in the teriparatide group (7.2%) than in the alendronate group (3.4%). There were also fewer vertebral fractures in the teriparatide group (0.6%) than in the alendronate group (6.1%), with an absolute risk reduction of 5.5% and a number needed to treat of 18 (i.e., 18 patients with glucocorticoid-induced osteoporosis need to be treated with teriparatide during an 18-month period to prevent one fracture). The incidence of nonvertebral fractures did not differ between the groups.

Current guidelines, which were developed before this study, recommend the use of oral bisphosphonates as first-line therapy in the treatment of glucocorticoid-induced osteoporosis. These recommendations may change when longer-term data comparing teriparatide with the bisphosphonates, as well as a cost-effectiveness evaluation of each approach, become available.

Osteoporosis Related to Other Drugs

Information is limited regarding the management of osteoporosis related to drugs other than AIs, GnRH agonists, and glucocorticoids. Lifestyle counseling is important regardless of the suspect drug, particularly for patients with depression and psychotic disorders. Ensuring appropriate calcium and vitamin D intake, whether by diet or supplements, is equally important. Vitamin D intake might need to be higher in patients receiving anticonvulsant agents with CYP-inducing activity, with these individuals potentially requiring dosages of 2000–4000 units/day to maintain vitamin D sufficiency. Overt hyperthyroidism should be avoided in patients receiving thyroid replacement therapy, and consideration should be given to maintaining the TSH concentration within the median of the reference range.

Although the degree of increased risk related to long-term use of PPIs, H_2RAs, and thiazolidinediones has not been defined, these agents should be used cautiously in patients at high risk of osteoporosis. Based on existing data, H_2RAs may be a more appropriate first-line choice when more potent gastric acid reduction is not necessary. If PPIs are needed, their use should be reassessed on a regular basis. Consideration should be given to the use of other oral antihyperglycemic agents in patients with type 2 diabetes who have several risk factors for osteoporosis. Bone mineral density should be assessed every 1–2 years.

Role of the Pharmacist

Pharmacists providing direct or managed patient care should be aware of the risk factors for osteoporosis in patients taking agents associated with drug-induced osteoporosis. In addition, pharmacists need to be familiar with drugs suspected of causing drug-related osteoporosis and the risk of fracture associated with specific agents. All patients taking drugs associated with an increased risk of fracture should receive a baseline risk assessment, and those at the highest risk should be referred for BMD testing by DEXA.

Based on estimates of the NNH for AIs and GnRH, drug-induced osteoporosis has the potential to contribute significantly to the number of fractures experienced by women and men with hormonal cancers. Pharmacists working in oncology clinics should include assessment of bone health as part of their direct patient care activities and be involved in treatment decisions for the prevention and treatment of osteoporosis. Similarly, health care providers working in other specialty areas (e.g., neurology, psychiatry, diabetes) should be familiar with drugs that might increase the risk of osteoporosis in their patients. Pharmacists also play an important role in educating other health care providers about drug-induced osteoporosis, particularly those working in specialty areas where osteoporosis is not a major focus of care, and helping these providers identify, prevent, and treat drug-induced osteoporosis.

Conclusion

Pharmacists should play a prominent role in recognizing the potential for drug-related osteoporosis and preventing associated fractures. Given the morbidity and mortality of osteoporotic fractures, interventions to reduce this risk may have important public health benefits. Pharmacists should acquire a general understanding of drug-induced osteoporosis and identify patients who require treatment. Prevention of fractures is the overall goal of therapy and requires effective communication with patients and other health care providers alike.

Annotated Bibliography

1. Heneghan C, Badenoch D. Evidence-Based Medicine Toolkit, 2nd ed. Malden, MA: Blackwell Publishing Ltd., 2006.

    Much of the evidence to date regarding drug-induced osteoporosis comes from epidemiologic data rather than randomized controlled clinical trials. This book is an essential reference for clinicians who need to critically appraise this literature so that they can communicate risk

to patients. The first chapter guides the reader through the process of formulating the appropriate clinical question using the PICO approach (i.e., Patient or problem, Intervention, Comparison, Outcome). The chapter addressing appraisal of studies on harm and etiology is particularly useful in the context of drug-induced disease, explaining the differences between case-control and cohort studies, the correct interpretation of the various expressions of risk, and the most appropriate expressions for the type of study. Examples of how to correctly interpret RR increase, ARI, and NNH are also provided.

2. FRAX. The World Health Organization fracture risk assessment tool. Available at *www.shef.ac.uk/FRAX*. Accessed May 26, 2010.

   Clinicians will find the FRAX assessment tool helpful when counseling patients about their risk of osteoporosis-related fractures. The easy-to-use FRAX tool is appropriate for risk assessment in women and men older than 50 who are not taking osteoporosis prescription drugs such as bisphosphonates. The FRAX tool was developed to evaluate the fracture risk of patients based on clinical risk factors, and it also allows the use of femoral neck BMD measurements when available. The FRAX models were developed from population-based cohorts in several countries, including North America. The tool provides 10-year probability of hip fracture, as well as 10-year probability of a major osteoporotic fracture in the spine, forearm, shoulder, or hip. These results are depicted in a figure that can be given to patients. For the U.S. calculation, the correct race/ethnic group (white, African American, Asian American, and Hispanic American) must be selected. Clinical risk factors included in the probability calculation include BMI (based on height and weight), age, sex, previous fracture, parental history of hip fracture, smoking status, current alcohol use (greater than 3 units/day), rheumatoid arthritis, current or past use of oral glucocorticoids, and select secondary causes of osteoporosis. The FRAX tool does not include drugs other than glucocorticoids known to decrease BMD or increase fractures in the risk assessment.

3. Kanis JA, Borgstrom F, De Laet C, Johanasson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int 2005;16:581–9.

   This review provides a summary of the importance of considering clinical risk factors for osteoporotic fractures in addition to results of BMD testing. The literature for these factors that provides information on fracture risk above and beyond that of BMD (e.g., age, prior fragility fracture, premature menopause, family history of hip fracture) is concisely summarized, with a good discussion on the pros and cons of using various expressions of risk. In particular, a review of the use of RR is well presented. There is also a discussion about integrating the presence or absence of risk factors with BMD to estimate the probability of fracture over time, and what appropriate intervention thresholds should be with respect to treatment.

4. Ioannidis G, Papaioannou A, Hopman WM, Akhtar-Danesh N, Anastassiades T, Pickard L, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ 2009;181:265–71.

   This cohort study evaluated the 5-year relationship between incident fractures and mortality in 7753 participants older than 50 years. The cohort was drawn from the Canadian Multicentre Osteoporosis Study, a large national prospective study of ambulatory community-dwelling patients with osteoporosis. Fractures were identified by questionnaires mailed annually to all participants. Reported fractures were confirmed by review of medical records. The primary outcome of the study was the association between fractures and mortality. The absolute mortality rate was 8.1% for no fractures, 16% for vertebral fractures, and 23.5% for hip fractures, resulting in an ARI of 7.9% for vertebral fractures and 15.4% for hip fractures. This translates into one excess death for every 12 vertebral fractures or every six hip fractures. Compared with participants who had no fracture in the 5-year follow-up, those who experienced vertebral fracture during the second year were at increased risk of death (hazard ratio [HR] 2.7, 95% CI, 1.1–6.6). The association was strongest in women, with the ARI for death in women with vertebral fractures being 8.8%. Vertebral fracture was not associated with mortality in men. Those with hip fracture in the first year were also at increased risk of death (HR 3.2; 95% CI, 1.4–7.4), again with the strongest association being in women, with an ARI of 16.9%. As with all cohort studies, residual confounders and bias could potentially influence the results. However, these findings confirm the relationship between fracture and mortality in ambulatory community-dwelling women with osteoporosis. Further research is needed to confirm the association for men and to examine the relationship between multiple fractures and mortality.

5. ATAC Trialists Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years’ adjuvant treatment for breast cancer. Lancet 2005;365:60–2.

   This randomized controlled trial presents the comparative efficacy and tolerability of anastrozole and tamoxifen after a median follow-up of 68 months in 9366 postmenopausal women with localized breast cancer. Treatment with anastrozole resulted in significantly longer disease-free survival and time to recurrence. Fracture rates were monitored throughout the study to determine whether a decline in functional estrogen concentration would be associated with increased fracture risk. Fractures occurred in 11% of women taking anastrozole and 7.7% in the tamoxifen group, representing an ARI of 3.3%. This result translates to an NNH of 30. That is, one excess fracture occurs for every 30 women treated with anastrozole compared with tamoxifen. These data inform clinicians of the risk of fractures associated with anastrozole use and the importance of assessing bone health for women using these drugs in the treatment of breast cancer. Similar results have been observed with the other AIs, letrozole and exemestane, indicating a class effect.

6. Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, et al. Guidance for the management of breast cancer treatment–induced bone loss: a consensus position from a UK Expert Group. Cancer Treat Rev 2008;34:S3–S18.

This consensus statement was developed by a group of clinicians from a range of medical disciplines (e.g., oncology, endocrinology, rheumatology) for the purpose of providing guidelines for the management of bone loss induced by AIs and GnRH agonists during the treatment of breast cancer. A systematic literature review was conducted to identify the evidence around the impact of AIs and ovarian suppression therapy on bone health, as well as the current literature regarding treatment of bone loss secondary to these therapies. This article provides a good overall review of the effect of each breast cancer treatment on bone health. The literature regarding treatment of bone loss was used to develop two algorithms: one for premenopausal women with ovarian suppression, with or without concomitant AI therapy; and a second for postmenopausal women receiving AIs. Although the consensus statement does not provide the level of evidence for each algorithm, it does incorporate the best available evidence to date and provide clinicians with a useful guide in making treatment decisions. However, these recommendations might require revision, particularly the postmenopausal AI algorithm, as new data become available (e.g., the data discussed in annotated bibliography 7). In the current treatment algorithm, treatment decisions for the use of bisphosphonates are made based on the T-score; this might change once the long-term effects on fracture rates of early bisphosphonate therapy, especially intravenous regimens, are determined.

7. Brufsky A, Bundred N, Coleman R, Lambert-Falls R, Mena R, Hadji P, et al. Integrated analysis of zoledronic acid for the prevention of aromatase inhibitor-associated bone loss in post-menopausal women with early breast cancer receiving letrozole. Oncologist 2008;13:503–14.

This article pools the results of the interim 12-month analysis of two large randomized controlled trials (Z-FAST and ZO-FAST) investigating the effect of intravenous zoledronic acid 4 mg every 6 months in combination with letrozole for the treatment of early breast cancer. In both studies, women were randomized in an open-label fashion to receive zoledronic acid early in their letrozole treatment regimen or to delay treatment until their T-score became less than −2.0 or a fragility fracture occurred. The primary purpose of the two randomized controlled trials was to determine whether bisphosphonate treatment improves disease-free survival and reduces distant metastases during a 5-year period. There was also interest in the effect of zoledronic acid on AI-associated bone loss, with fracture as the primary outcome for this substudy. The results of this interim analysis evaluate the surrogate end point of bone loss in a combined total of 1667 women by monitoring BMD using DEXA at 6 months and 12 months. Six-month results showed that those receiving early zoledronic acid experienced a small but significant increase in BMD of the lumbar spine and total hip, whereas the delayed group lost bone at both sites. At 12 months, BMD was 5.2% higher at the lumbar spine and 3.5% higher at the hip in the early zoledronic acid group. Participants in both treatment arms had similar baseline BMD and risk factors, so the difference can be attributed to zoledronic acid. Although these data suggest benefits in BMD, it remains to be determined whether this intervention will lead to a reduction in fractures.

8. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Postlberger S, Menzel C, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360:679–91.

This article presents the results of the Austrian Breast and Colorectal Cancer Study Trial 12, which was designed to evaluate the efficacy of 3 years of treatment with ovarian suppression plus anastrozole or tamoxifen with or without zoledronic acid in premenopausal women with early breast cancer. The primary outcome of this randomized controlled trial is to determine whether the addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival. However, there is again interest in the effect of zoledronic acid on bone health. A previous publication (Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Kainberger F, Kässmann H, Piswanger-Sölkner JC, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 2008;9:840–9) reported the effect of zoledronic acid on BMD, showing significant improvements in bone density with zoledronic acid. However, fracture rates were not reported. This article presents fracture data in the review of adverse effects. In the goserelin plus tamoxifen group, fractures occurred in 1.3% of patients not receiving zoledronic acid and in 0.9% with zoledronic acid. Results were similar for the goserelin plus anastrozole treatment arm, with 1.6% of patients experiencing a fracture without zoledronic acid compared with 0.9% without bisphosphonate. The absolute risk reduction in fracture was small in both endocrine groups, at 0.4% for the tamoxifen group and 0.7% for the anastrozole group. This result is not unexpected given the study population of premenopausal women with an average age of about 45 years, most of whom had baseline BMD within the normal range for their age. Because bone loss at this age is expected to cause fractures later in life, 3 years is probably insufficient to determine whether treatment with zoledronic acid reduces fracture risk in this population. However, this agent may have other beneficial effects for premenopausal women with early breast cancer.

9. Shahinian VB, Kuo YF, Freeman JL, Goodwin SJ. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154–64.

This retrospective cohort study is the largest to examine the risk of osteoporosis and fractures in men receiving androgen deprivation therapy for prostate cancer. Two large databases were used to identify men 66 years or older with a diagnosis of prostate cancer who had received a GnRH agonist or had undergone orchiectomy

6 months or more after diagnosis. The primary outcome was fracture occurrence. Overall, for men receiving a GnRH agonist, the NNH was 28, translating into almost 3000 excess fractures per year based on the annual incidence of prostate cancer and current patterns of GnRH use. Dose-response and age effects were also observed, with fracture incidence increasing with both the number of doses received and increasing age. Although this study was unable to differentiate between fractures related to bone metastases, no decline in fracture risk was observed when early and late stage disease were compared, when fractures are more likely to occur. The findings of this study support the results of smaller studies and show a relationship between the use of GnRH agonists and an increased fracture risk in men with prostate cancer, outlining the need for assessing bone health in men receiving antiandrogen therapies.

10. Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 2007;25:1038–42.

A previous small, randomized controlled trial showed that zoledronic acid reduces GnRH agonist–related bone loss when administered every 3 months to men with non-metastatic prostate cancer. This randomized controlled trial compared the effect on BMD of a 4-mg intravenous dose given annually versus placebo in 40 men with non-metastatic prostate cancer and receiving GnRH agonists. Measurements of BMD were taken at baseline and after 3 months, 6 months, 9 months, and 12 months of therapy. At 12 months, BMD of the lumbar spine had decreased by 3.1% in the placebo group but increased by 4.0% in the group receiving zoledronic acid. Total hip BMD declined by 1.9% in the placebo group compared with a 0.7% increase in those receiving zoledronic acid. These data suggest that one dose of zoledronic acid prevents GnRH agonist–related bone loss in men with early prostate cancer. The data are also consistent with data from other small studies evaluating the effect of zoledronic acid on BMD in men with more advanced prostate cancer. However, the effect of zoledronic acid on fracture rates in men receiving GnRH agonists remains to be determined.

11. Smith MR, Egerdie B, Hernandez Toriz H, Feldman R, Tammela TLJ, et al. Denosumab in men receiving andro-gen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745–55.

The Denosumab Hormone Ablation Bone Loss Trial (HALT) compared the effect of denosumab (60 mg sub-cutaneously every 6 months) with placebo on fracture rates in men receiving androgen deprivation therapy for prostate cancer. Denosumab is a fully human monoclonal antibody, active against RANKL, which is an important mediator of osteoclast formation and function. Of the 734 men randomized to each treatment group, 445 (60.6%) and 467 (63.6%) completed the 3-year study in the placebo and denosumab groups, respectively. At 24 months, the placebo group showed a 1% decline in BMD at the

lumbar spine compared with a 5.6% increase among the denosumab group. Significant increases in BMD were also observed in the total hip, femoral neck, and distal radius with denosumab compared with placebo. Treatment with denosumab also resulted in a significant reduction in new vertebral fractures at 12 months, 24 months, and 36 months. After 3 years of treatment, the absolute risk reduction for new vertebral fractures was 2.4%, translating into a number needed to treat of 42. That is, one fracture will be prevented for every 42 men receiving denosumab therapy during a 3-year period. No significant differences in fracture rates were observed at other anatomic sites, including the hip or distal radius, despite demonstrated increases in BMD. These findings support the use of denosumab for the treatment of osteoporosis related to androgen deprivation therapy in men with prostate cancer.

12. The American Congress of Obstetricians and Gynecologists (ACOG). Depot medroxyprogesterone acetate and bone effects. Obstet Gynecol 2008;112:727–30.

This opinion piece from the ACOG Committee on Adolescent Health Care and Gynecologic Practice addresses the controversial issue of long-term DMPA use in young women, particularly adolescents. The evidence regarding bone loss associated with DMPA use is thoroughly reviewed and concisely summarized, as are the findings of BMD recovery after discontinuation of DMPA and the limited data regarding fractures. The FDA recommendation to limit use to 2 years or to conduct BMD testing by DEXA after that time is disputed on the basis of evidence suggesting that bone loss slows with longer-term DMPA use and is reversible on discontinuation; DMPA use is therefore unlikely to place women at increased risk of fracture in future years. Based on their review of the literature, the authors conclude that DMPA is a safe and effective means of long-term contraception in which the risks of DMPA-associated bone loss must be weighed against the risks of pregnancy, particularly in adolescents. The importance of counseling about the benefits of adequate calcium and vitamin D intake and physical activity is stressed. The use of estrogen supplements to prevent DMPA-associated bone loss is not recommended.

13. Vestergaard P. Epilepsy, osteoporosis and fracture risk – a meta-analysis. Acta Neurol Scand 2005;112:277–86.

This meta-analysis pools data from 11 epidemiologic studies to differentiate the effect of seizures and anticonvulsant-related bone loss on fracture risk. When patients with epilepsy were compared with those without, large and significant RR increases were observed for any fracture (220%; RR 2.2; 95% CI, 1.9–2.5), for hip fracture (530%; RR 5.3; 95% CI, 3.2–8.8), and for lumbar spine fracture (620%; RR 6.2; 95% CI, 2.5–15.5). This risk was much higher than expected based on reports of anticonvulsant-related bone loss. Of note, however, is that the ARI could not be determined from the case-control study and many of the cohort studies in this analysis. Relative risk increase is usually much larger than the ARI and must be considered in the appropriate context. Nevertheless,

a significant association was identified, indicating that patients with epilepsy were at greater risk of experiencing a fracture. To address this issue, the proportion of fractures related to seizure activity was identified in four studies, with an estimated 35% of fractures related to seizures. These data suggest that the RR increase observed among patients taking anticonvulsants was partially caused by fractures occurring secondary to seizures. Even when this is considered, an increased risk of fractures continues to be observed among anticonvulsant users and is consistent with the degree of bone loss associated with the use of anticonvulsant drugs.

14. Richards JB, Papaioannou A, Adachi J, Joseph L, Whitson H, Prior JC, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med 2007;167:188–94.

    This prospective cohort study of 5008 community-dwelling adults age 50 or older determined the association between daily SSRI use and incident clinical fragility fractures. Other outcomes of interest were prevalent falls reported at the time of enrollment and baseline differences in BMD. *Incident clinical fractures* refer to the number of new fractures reported during the study follow-up period, whereas *prevalent falls* refer to the number of patients reporting a fall in the month before study enrollment. Participants were drawn from the Canadian Multicentre Osteoporosis Study, a large population-based longitudinal study, and were monitored for 5 years. Use of SSRIs was identified by interview, and incident clinical fractures were tracked through annual questionnaires sent to all participants. All self-reported incident clinical fragility fractures were confirmed radiographically. Daily SSRI use was low, reported in only 137 study subjects with an average age of about 65 years. However, after adjusting for potential confounding factors, it was associated with a substantially increased risk of incident clinical fragility fractures (HR 2.1). The HR can be interpreted similarly to the RR, so the RR increase of fracture is about 210% with daily SSRI use. This compares with the insignificant 20% RR increase estimated for the 162 participants reporting daily TCA use (HR 1.2; 95% CI, 0.7–2.2). Of note, an RR increase should not be interpreted in the same manner as the ARI. Depression, measured by validated instruments, was not found to be associated with fracture risk in either univariate or multivariate analysis. Baseline evaluation of prevalent falls revealed a doubling of the adjusted odds of falling among daily SSRI users (OR 2.2; 95% CI, 1.4–3.5). Daily SSRI use was also associated with lower BMD of about 4% at the hip and 2.4% at the lumbar spine compared with nonusers. These data indicate that SSRI use is associated with more falls, greater bone loss, and increased risk of fractures.

15. Abel KM, Heatlie HF, Howard LM, Webb RT. Sex- and age-specific incidence of fractures in mental illness: a historical, population-based cohort study. J Clin Psychiatry 2008;69:1398–403.

    This retrospective cohort study of more than 300,000 patients is the largest to estimate the risk of fracture in patients with mental illness compared with the general population. Specifically, age- and sex-specific fracture risks were estimated in psychotic illnesses, nonpsychotic affective disorders, and all other psychiatric conditions using the UK General Practice Research Database. This database captures the primary care records of about 5% of the UK population, recording prescriptions, clinical events, specialist care, and hospital admissions. The risk of any fracture was observed to be highest among women 18–44 years old with a diagnosis of psychotic illness (RR 2.53; 95% CI, 1.49–4.32). Likewise, the risk of any fracture among patients with a psychotic disorder using a prolactin-raising antipsychotic drug was highest in young women (RR 2.74; 95% CI, 1.50–4.98), although risk was significantly increased in women of all age groups. Not unexpectedly, the risk of hip fracture increased with age and was highest in both women and men aged 45–74 years with psychotic disorders (RR 5.12; 95% CI, 2.73–9.63, and RR 6.41; 95% CI, 2.55–16.11, respectively). The same pattern was observed for users of prolactin-raising antipsychotic agents. Despite a large sample size, this study was not able to identify and account for important confounding variables such as alcohol use, cigarette smoking, or physical inactivity. In addition, duration of treatment with prolactin-raising antipsychotic drugs could not be determined. However, these data point to an increased risk of fracture in individuals with psychiatric illness, particularly those with diagnoses of psychotic disorders. Furthermore, it identifies a relationship between antipsychotic agents with prolactin-raising effects and fracture that warrants further study.

16. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton-pump inhibitor therapy and risk of fracture. JAMA 2006;296:2947–53.

    This study is the largest of three case-control studies examining the association between PPIs and hip fracture. Using the UK General Practice Research Database, 13,556 hip fracture cases occurring at least 1 year after initiation of PPI therapy were matched with 135,386 controls for sex, year of birth, index date, and duration of follow-up. Adjustment for potential confounding factors (e.g., drugs, other medical conditions that could increase hip fracture risk) was made in the statistical analysis. Because this was a case-control study, the association between PPI use and hip fracture is expressed as the adjusted OR. Overall, the odds of experiencing a hip fracture with PPIs was significantly increased at 1 year (OR 1.22; 95% CI, 1.15–1.3), with the magnitude of effect increasing with increased duration of therapy (OR at 2 years 1.41; 95% CI, 1.28–1.56, OR at 3 years 1.54; 95% CI, 1.37–1.73, and OR at 4 years 1.59; 95% CI, 1.39–1.80). Sex differences were also noted, with the association between PPI therapy and hip fracture stronger in men (OR 1.78; 95% CI, 1.42–2.22) than in women (OR 1.37; 95% CI, 1.22–1.53), although a significant relationship was observed for both. The finding of a significant association between PPI use and hip fracture is consistent with other studies, although there is inconsistency regarding sex differences and increasing risk with duration of therapy. Proton pump inhibitors are among the drugs most commonly prescribed to older

individuals, many of whom have several risk factors for hip fracture. The results of this study and others outline the need for clinicians to consider the indications for PPI therapy and whether long-term use is warranted.

17. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes; a meta-analysis. CMAJ 2009;180:32–9.

This meta-analysis pooled data from 10 randomized controlled trials to determine the OR and absolute risk of fractures with thiazolidinedione therapy. There were 13,715 participants in the 10 randomized controlled trials that compared the effect of thiazolidinediones on other oral agents in the management of type 2 diabetes. Overall, the odds of having a fracture were significantly increased with thiazolidinedione therapy (OR 1.45; 95% CI, 1.18–1.79). However, with 3% of patients in the thiazolidinedione group experiencing fractures, compared with 2.4% in the control groups, the ARI increase was only 0.6%. Data in five randomized controlled trials were available to stratify by sex, with the odds of experiencing a fracture doubled in women (OR 2.23; 95% CI, 1.65–3.01) but not in men (OR 1.00; 95% CI, 0.72–1.39). The ARI increase among women was 2.8%, translating into one excess fracture for every 35 women treated with a thiazolidinedione. Based on current drug use patterns in an estimated 2 million American women using thiazolidinediones, about 30,000 excess fractures in women with type 2 diabetes could be expected. These data, taken in context with concerns regarding the cardiovascular effects of thiazolidinediones, suggest clinicians need to carefully balance the benefits of this therapy with the apparent skeletal and cardiovascular risks.

Self-Assessment Questions

Questions 1–3 pertain to the following case.

Y.K. is a 65-year-old Asian woman (height 5′1″, weight 49.5 kg). She was given a diagnosis of stage IIA estrogen receptor–positive breast cancer 2 years ago and, since then, has been receiving adjuvant therapy with anastrozole 1 mg once daily. Her medical history is significant for a previous wrist fracture after slipping on the ice about 8 years ago. She has also received citalopram 20 mg once daily for depression for the past 6 months, which she reports has improved her appetite, sleep, and mood. Her other drugs include calcium carbonate 1250 mg (500 mg of elemental calcium) two times/day and vitamin D 1000 units/day. She quit smoking 7 years ago, but before that, she had a 35 pack-year history. Y.K. reports occasional alcohol use of about one or two glasses of wine per month. She denies any falls in the past year. Her parents have not experienced any fractures. All laboratory values are within normal limits. Her serum 25-hydroxyvitamin D concentration was 45 ng/mL. Y.K. was recently referred for bone mineral density (BMD) testing by dual-energy x-ray absorptiometry (DEXA), and her T-scores were as follows: lumbar spine −3.3, femoral neck −3.2, and total hip −3.1.

1. **Based on the WHO fracture risk assessment tool (FRAX) (scroll to T-scores on item 12 on the FRAX tool), which one of the following best represents Y.K.'s 10-year probability of experiencing a major fragility fracture?**

   A. No increased risk.
   B. Less than 10%.
   C. Between 10% and 20%.
   D. Greater than 20%.

2. **Which one of the following represents the most appropriate intervention to reduce Y.K.'s risk of fracture?**

   A. Initiate therapy with risedronate 150 mg/month.
   B. Increase the vitamin D dose to 5000 units/day.
   C. Discontinue anastrozole and start exemestane.
   D. Discontinue citalopram and start amitriptyline.

3. **Which one of the following represents the most important factor in determining Y.K.'s risk of fragility fractures secondary to anastrozole?**

   A. Concomitant use of citalopram.
   B. Current calcium intake.
   C. Vitamin D deficiency.
   D. Baseline T-score.

4. A 41-year-old premenopausal white woman has been given a diagnosis of stage IIIB breast cancer and is scheduled to start adjuvant therapy with leuprolide in addition to her anthracycline-based chemotherapy. Baseline BMD testing reveals a T-score of −1.5 for the total hip. **Which one of the following is the most appropriate intervention for this patient's bone health?**

   A. Initiate zoledronic acid 4 mg intravenously every 6 months.
   B. Initiate alendronate 70 mg once weekly.
   C. Initiate raloxifene 60 mg once daily.
   D. Initiate adequate calcium and vitamin D intake.

5. Your patient is a 58-year-old white man (height 5′6″, weight 66.4 kg) who received a diagnosis of stage T3 prostate cancer 8 months ago. He began radiation therapy and adjuvant treatment with goserelin, and his current dosage is 10.8 mg by depot injection every 3 months. His medical history is significant for dyslipidemia and hypertension, which are well controlled with atorvastatin 40 mg/day and ramipril 5 mg/day. His history is negative for oral glucocorticoid use, and he has had no fragility fractures. The patient is a nonsmoker and reports occasional alcohol use of no more than one or two drinks per month. He denies using recreational drugs. His family history is significant for osteoporosis, and his mother has had two hip fractures. All laboratory results are within normal limits, and his 25-hydroxyvitamin D concentration is reported as 50 ng/mL. The patient recently underwent BMD testing by Hologic DEXA, and his results are as follows: lumbar spine 0.759 g/cm^2; femoral neck 0.683 g/cm^2; and total hip 0.686 g/cm^2. **Incorporating his risk based on the FRAX tool, which one of the following interventions is most appropriate for this patient?**

   A. Ensure his elemental calcium intake is at least 1200 mg/day.
   B. Initiate ergocalciferol 100,000 units/week for 3 months.
   C. Initiate therapy with nasal calcitonin.
   D. Initiate therapy with intravenous zoledronic acid 5 mg/year.

Questions 6 and 7 pertain to the following case.

E.K. is a 34-year-old African American woman (height 5′8″, weight 72 kg) who presents for administration of depot medroxyprogesterone acetate (DMPA) 150 mg for contraception. She has received DMPA every 3 months for the past 12 months. In addition to DMPA,

E.K. takes 400 units of vitamin D daily and has a 12-year history of valproic acid use to manage her epilepsy. E.K. reports a lifelong lactose intolerance and has not tolerated dairy products since she was a small child, using soy milk instead. She does not smoke or use recreational drugs, and she reports only occasional alcohol use. E.K. is physically active, running 5 km two times/week with her running group, and takes part in resistance training two times/week. Her parents, alive and well in their early 70s, have not experienced any fragility fractures.

6. **Which one of the following places E.K. most at risk of developing an osteoporosis-related fracture?**

    A. Use of DMPA.
    B. African American ethnicity.
    C. Low calcium intake.
    D. Excessive physical exercise.

7. **Which one of the following is the most appropriate intervention to make with respect to E.K.'s bone health?**

    A. Counsel E.K. to increase her vitamin D intake to 2000 units/day.
    B. Refer E.K. for BMD testing using DEXA.
    C. Recommend switching from valproic acid to phenytoin.
    D. Counsel E.K. to initiate calcium carbonate 1250 mg (500 mg of elemental calcium) two times/day.

8. The following information was observed in the Arimidex, Tamoxifen, Alone or in Combination trial after 5 years of therapy:

Anastrozole fracture rate per 1000 woman-years = 22.6
Tamoxifen fracture rate per 1000 woman-years = 15.6
HR = 1.44; 95% CI, 1.21–1.68
Proportion of fractures in anastrozole-treated patients = 11%
Proportion of fractures in tamoxifen-treated patients = 7.7%

Using these data, which one of the following represents the most accurate expression of the absolute increased risk of experiencing a fracture during the next 5 years with anastrozole compared with tamoxifen?

    A. 44%.
    B. 11%.
    C. 7%.
    D. 3.3%.

Questions 9 and 10 pertain to the following case.
J.R. is a 77-year-old man admitted to the orthopedic service for arthroplasty of the hip after a fall at his nursing home. His medical history is significant for Alzheimer disease, pedal edema, esophageal reflux, hypertension, and osteoarthritis. J.R.'s drug regimen and history includes pantoprazole 20 mg/day for 1 month; furosemide 120 mg two times/day for 3 years; ramipril 2.5 mg/day for 3 years; and acetaminophen 500 mg four times/day for 5 years. Vital signs include the following: temperature 98°F, supine blood pressure 148/72 mm Hg, standing blood pressure 102/68 mm Hg, and pulse rate 58 beats/minute supine increasing to 72 beats/minute on standing.

9. **Which one of the following drugs is most likely responsible for J.R.'s fall?**

    A. Pantoprazole.
    B. Acetaminophen.
    C. Furosemide.
    D. Ramipril.

10. **Which one of the following patient-specific factors is most likely to increase J.R.'s risk of hip fracture associated with pantoprazole use?**

    A. Age.
    B. Sex.
    C. Dose.
    D. Duration of use.

Questions 11 and 12 pertain to the following case.
S.D. is a postmenopausal 56-year-old white woman (height 5′4″, weight 77 kg) recently given a diagnosis of type 2 diabetes. She was initially treated with metformin 500 mg three times/day but experienced severe gastrointestinal upset requiring discontinuation of therapy. Consideration is being given to starting therapy with rosiglitazone 4 mg once daily with titration as necessary. Other drugs in her regimen include ramipril 10 mg/day for hypertension and atorvastatin 80 mg/day for dyslipidemia. S.D. is a nonsmoker, does not drink alcohol, and has not experienced any fractures. Her mother was given a diagnosis of osteoporosis and experienced a hip fracture when in her 80s. S.D. recently had BMD testing by DEXA, and her T-scores were reported as −0.8 at the lumbar spine, −0.7 at the femoral neck, and −0.7 for total hip.

11. **Which one of the following risk factors is most significant in determining S.D.'s risk of developing fractures related to use of rosiglitazone?**

    A. Lumber spine T-score.
    B. Female sex.
    C. Family history of hip fracture.
    D. Postmenopausal status.

12. Six months later, S.D. is doing well on rosiglitazone. Her glycosylated hemoglobin and fasting blood glucose values are within target, and she has not experienced any edema, shortness of breath, or other signs or symptoms suggestive of heart failure. However, S.D. expresses concern regarding her potential risk of fracture after reading several media reports and doing some reading on the Internet. On review of the literature, the following information is obtained from a meta-analysis examining the association between fractures and thiazolidinediones:

| Number of fractures in women taking thiazolidinediones over 5 years = 111/1903 |
| Number of fractures in women taking other oral antihyperglycemics over 5 years = 76/2497 |
| OR 2.23, 95% CI, 1.65–3.01 |

Which one of the following best represents the number of women needed to treat with a thiazolidinedione compared with other oral antihyperglycemic agents over 5 years to cause one excess fracture?

A. 23.
B. 35.
C. 76.
D. 111.

13. **Which one of the following individuals is at greatest risk of developing a drug-related osteoporotic fracture?**

A. A 28-year-old white woman receiving DMPA and pantoprazole for the past 6 months.
B. A 60-year-old African American man receiving rosiglitazone and pantoprazole for the past 6 months.
C. A 46-year-old Hispanic woman receiving olanzapine and citalopram for the past 3 years.
D. A 63-year-old African American woman receiving letrozole and pioglitazone for the past 3 years.

Questions 14 and 15 pertain to the following case.
M.W. is a 68-year-old postmenopausal woman (height 5′4″, weight 76 kg) with a 32-year history of bipolar disorder. Her disease is currently well managed with valproic acid 500 mg three times/day and olanzapine 5 mg two times/day. Other drugs include risedronate 35 mg once weekly, ramipril 5 mg/day, and calcium carbonate 1250 mg two times/day. Although M.W. has a 35 pack-year history of smoking, she no longer smokes or drinks alcohol. At a recent appointment, laboratory tests revealed a 25-hydroxyvitamin D concentration of 15 ng/mL.

14. **Which one of the following factors is most likely responsible for M.W.'s current vitamin D status?**

A. Valproic acid.
B. Inadequate vitamin D3 intake.
C. Inadequate calcium intake.
D. Olanzapine.

15. **Which one of the following represents the most appropriate daily dose of vitamin D supplementation for M.W.?**

A. 600 units.
B. 800 units.
C. 1000 units.
D. 4000 units.

16. Your patient is a 65-year-old man with Down syndrome who resides in a long-term care facility. His medical history is significant for Alzheimer dementia and a generalized seizure disorder, for which he receives donepezil 10 mg/day, risperidone 1.0 mg two times/day, and phenytoin 250 mg/day. His 25-hydroxyvitamin D concentration is measured at 8 ng/mL. **Which one of the following vitamin D dosages is most appropriate for this patient?**

A. 1000 units of vitamin D daily.
B. 50,000 units of ergocalciferol once monthly.
C. 50,000 units of ergocalciferol once weekly for 8 weeks, followed by 1000 units of vitamin D daily.
D. 50,000 units of ergocalciferol twice weekly for 3 months; then 1000 units of vitamin D daily.

17. A 51-year-old woman with a 15-year history of schizophrenia presents for BMD testing after a Colles fracture of the wrist. Her T-scores are reported as −2.0 at the hip and −2.5 at the lumbar spine. Her drug is depot fluphenazine decanoate for the past 8 years, which has substantially improved her adherence to therapy and reduced her number of hospital admissions. **Which one of the following interventions is most appropriate to manage this patient's bone health?**

A. Discontinue fluphenazine decanoate and start oral olanzapine.
B. Initiate daily calcium and vitamin D supplementation.
C. Initiate intravenous infusion of zoledronic acid 4 mg every 6 months and daily calcium and vitamin D supplementation.
D. Initiate monthly oral bisphosphonate therapy and daily calcium and vitamin D supplementation.

18. Your patient is a 56-year-old woman treated with L-thyroxine 150 mcg/day for the past 6 years after the removal of her thyroid gland secondary to a malignancy. Her recent thyroid-stimulating hormone concentration was measured at 1.0 milli-unit/L. Her BMD, measured 1 month ago, produced T-scores of −1.2 at the spine and −0.8 for the total hip. **Which one of the following is most appropriate for the management of this patient's bone health?**

   A. Add calcium and vitamin D supplementation and decrease the L-thyroxine dose to 137 mcg/day.
   B. Add calcium and vitamin D supplementation, decrease the L-thyroxine dose to 137 mcg/day, and add risedronate 150 mg/month.
   C. Add calcium and vitamin D supplementation and discontinue L-thyroxine.
   D. Add calcium and vitamin D supplementation, discontinue L-thyroxine, and add risedronate 150 mg/month.

19. Your patient, a 54-year-old man with rheumatoid arthritis, has required many courses of prednisone for several months during the past 5 years. He recently lost his job and has no health insurance. Recent BMD testing reveals a T-score of −3.0 at the spine and a T-score of −2.6 for the total hip. **Which one of the following represents the most appropriate treatment for this patient?**

   A. Calcium and vitamin D supplementation.
   B. Generic alendronate 70 mg/week; calcium and vitamin D supplementation.
   C. Intravenous zoledronic acid 4 mg every 6 months; calcium and vitamin D supplementation.
   D. Teriparatide 20 mcg subcutaneously daily; calcium and vitamin D supplementation.

20. Your patient is a 72-year-old white man (height 5′11″, weight 72 kg) with early prostate cancer treated with goserelin depot injection 10.8 mg every 3 months. His medical history was insignificant before his diagnosis of prostate cancer. He recently experienced a vertebral fragility fracture, and BMD revealed a T-score of −3.0. Denosumab is being considered for treatment of his osteoporosis. Data from the Hormone Ablation Bone Loss Trial (HALT) show the following regarding the cumulative incidence of vertebral fractures at 36 months:

Cumulative incidence of vertebral fractures in placebo group at 36 months: 3.9%
Cumulative incidence of vertebral fractures in denosumab group at 36 months: 1.5%
RR: 0.38 (95% CI, 0.19–0.78)

Using these data, which one of the following represents the most accurate expression of the RR decrease for experiencing a fracture during the next 3 years with denosumab compared with placebo?

A. 1.5%.
B. 2.4%.
C. 62%.
D. 38%.