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Medication-induced osteoporosis: screening and treatment strategies

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***Abstract*:** Drug-induced osteoporosis is a significant health problem and many physicians are unaware that many commonly prescribed medications contribute to significant bone loss and fractures. In addition to glucocorticoids, proton pump inhibitors, selective serotonin receptor inhibitors, thiazolidinediones, anticonvulsants, medroxyprogesterone acetate, aromatase inhibitors, androgen deprivation therapy, heparin, calcineurin inhibitors, and some chemotherapies have deleterious effects on bone health. Furthermore, many patients are treated with combinations of these medications, possibly compounding the harmful effects of these drugs. Increasing physician awareness of these side effects will allow for monitoring of bone health and therapeutic interventions to prevent or treat drug-induced osteoporosis.

Keywords: anticonvulsants, aromatase, calcineurin, osteoporosis, glucocorticoids, medroxyprogesterone, proton pump, serotonin, thiazolidinediones

Introduction

Osteoporosis is characterized by low bone mineral density (BMD) and loss of the structural and biomechanical properties that are required to maintain bone homeostasis. Physicians are knowledgeable about the association of osteoporosis with aging, postmenopausal status, and secondary causes, including chronic illnesses or lifestyle issues that promote osteoporosis. However, many widely used medications have now been shown to cause decreases in BMD and increase fractures, and physicians may not be aware of these effects. Epidemiologic studies provide valuable information about medications that place patients at risk for drug-induced osteoporosis. While glucocorticoids (GCs) are most commonly associated with drug-induced osteoporosis, the use of several other therapeutic agents increase the risk of significant bone loss and fracture. These medications include proton pump inhibitors (PPIs), selective serotonin receptor inhibitors (SSRIs), thiazolidinediones (TZDs), anticonvulsants, medroxyprogesterone acetate (MPA), hormone deprivation therapy, calcineurin inhibitors, chemotherapies, and anticoagulants. This article reviews the common medications associated with bone loss, the pathogenesis, and possible treatment options.

Bone remodeling

Bone is a metabolically active tissue that undergoes remodeling throughout life, with roughly 5% remodeled at any time [Martin *et al.* 2008]. Over several weeks, a bone remodeling unit, termed basic multicellular unit (BMU), will develop that incorporates several cell types, including osteoclasts, osteoblasts, and osteocytes. Bone remodeling is held in check by osteocyte secreted sclerostin, a Wnt inhibitor that prevents bone formation by osteoblasts, until osteocytes sense bone stress or microdamage and undergo apoptosis. The loss of sclerostin and alterations in other secreted cytokines and chemotactic factors promote BMU's formation. Osteoclasts are recruited into the area by gradients of macrophage colony-stimulating factor and receptor activator of nuclear factor κB ligand (RANKL). Osteoclasts attach and excavate bone over several weeks prior to apoptosing. RANKL is antagonized by osteoprotegrin (OPG), a decoy RANK receptor, and alterations in the ratio of RANKL to OPG contribute to excessive bone remodeling. Following osteoclast apoptosis, pre-osteoblasts are recruited to the eroded surface and differentiate into osteoblasts. Mature osteoblasts secrete unmineralized bone called osteoid that subsequently becomes mineralized over several months. Mineralization of osteoid requires adequate vitamin D and

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calcium as well as osteoblast-secreted osteocalcin. The coupling of osteoclast resorption to osteoblast bone formation is critical to preserve bone homeostasis. Postmenopausal osteoporosis is one example of uncoupling with increased osteoclast activity compared with osteoblastic activity. Many drugs alter the coupled cellular responses of osteoclasts and osteoblasts, leading to clinically evident osteopenia or osteoporosis.

Glucocorticoids

GCs are used to treat a wide variety of diseases, including autoimmune, inflammatory, dermatological, respiratory diseases, malignancies, and solid organ transplants. Around 30–50% of patients receiving GCs develop fractures [Canalis *et al.* 2007]. GCs at doses as low as prednisone 3–10 mg are associated with fractures [Van Staa *et al.* 2003; Steinbuch *et al.* 2004]. GCs have a wide variety of direct and indirect effects on bone, which were recently reviewed in detail by Henneickle and colleagues [Henneicke *et al.* 2014]. In the early phase, there are multiple direct effects on bone cells, including osteocytes, osteoblasts, and osteoclasts. GC stimulation of osteoclasts induces prolonged survival allowing excessive bone resorption primarily in the trabecular rich regions of the spine. GCs also induce osteocyte apoptosis contributing to early fracture risk occurring before the BMD is reduced. Finally, GCs reduce the recruitment of osteoblast precursors leading to decreased osteoblast differentiation and function, resulting in decreased bone formation. Indirect effects contributing to GC-induced bone loss include decreases in calcium resorption [Canalis *et al.* 2007], suppression of growth hormone [Mazziotti and Giustina, 2013], alteration in sex hormones [Canalis *et al.* 2007; Van Staa, 2006], and changes in parathyroid pulsatility [Bonadonna *et al.* 2005; Canalis *et al.* 2007]. Importantly, fracture risk increases even before declines in BMD appear, and fractures occur at higher BMD than seen in postmenopausal osteoporosis [Van Staa *et al.* 2003].

Data suggest that the daily dose of GC predicts fracture more than the cumulative dose [Van Staa *et al.* 2003, 2000b]. While doses over 7.5 mg of prednisone have a fivefold higher risk of spine and hip fractures, even daily 2.5 mg doses are associated with an increased risk of spine fractures [Van Staa *et al.* 2000a; Vestergaard *et al.* 2008b]. Highlighting the sensitivity of vertebrae to GCs, prednisone 10 mg daily for more than 90 days leads to a 17-fold increase in vertebral fractures compared with a sevenfold increase in hip fractures [Steinbuch *et al.* 2004]. Although all patients are at risk for GC-induced bone loss, postmenopausal women and older men are at highest risk when doses are greater than 20 mg daily [Tatsuno *et al.* 2009]. Additional factors that independently increase the risk of developing GC-induced fractures include low body mass, smoking, parental hip fracture, more than three alcoholic drinks a day, and intravenous pulse steroids [Grossman *et al.* 2010; Weinstein, 2012]. After discontinuation of GCs, fracture risk gradually declines to baseline over a year or two [Van Staa *et al.* 2000c; Vestergaard *et al.* 2008b]

Bisphosphonates, oral or intravenous, are effective at preventing GC-induced BMD decline [Saag *et al.* 1998; Grossman *et al.* 2010; Lekamwasam *et al.* 2012]. Decisions to prevent or treat GC-induced bone loss are currently based on a varying set of guidelines that vary by agency and country. Because fracture risk increases before changes in BMD are detected, the measurement of BMD has limited predictive value in GC-induced osteoporosis [Van Staa *et al.* 2003]. FRAX (World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK) analysis may underestimate the risk of GC-induced fracture because it assesses the average dose and not the individual or cumulative doses. Despite these limitations, there is consensus in the guidelines to recommend a baseline BMD measurement or FRAX analysis before the initiation of GC. Vitamin D, calcium, renal and hepatic panels are additional studies recommended at baseline and before the decision to prevent or treat GC-induced bone loss [Grossman *et al.* 2010; Lekamwasam *et al.* 2012; Hoes *et al.* 2007]. GC-induced bone loss may be mitigated by minimizing the steroid dose in addition to concurrent treatment with supplemented calcium, vitamin D, and bisphosphonates or teriparatide [Grossman *et al.* 2010; Lekamwasam *et al.* 2012].

Bisphosphonates are currently the standard of care for prevention and treatment of GC-induced bone loss [Lekamwasam *et al.* 2012; Grossman *et al.* 2010]. Oral or intravenous bisphosphonates are effective at preventing reductions in BMD and in some cases vertebral fractures induced by GCs [Reid *et al.* 2009; Adachi *et al.* 2001; Saag *et al.* 1998, 2007]. Yearly intravenous zoledronic acid may provide more rapid protection from GC-induced bone loss and might be appropriate

for patients on high doses of GCs or already on GCs for more than 90days [Henneicke *et al.* 2014]. For patients intolerant of bisphosphonates or at very high risk of fracture, teriparatide is an alternative. Compared with alendronate, in an 18-month randomized, double-blinded, head-to-head trial, teriparatide increased spinal BMD faster and to a greater extent than bisphosphonates and also reduced vertebral fractures (0.6% *versus* 6.1%, $p = 0.004$) [Saag *et al.* 2007]. The anabolic effect of teriparatide is more effective at counteracting the deleterious effects of GCs and prevents osteoblast and osteocyte apoptosis resulting in reduced fracture risk. Although not approved by the US Food and Drug Administration for the treatment of GC-induced osteoporosis, denosumab improves the BMD of patients with rheumatoid arthritis receiving oral GCs (average dose $\leqslant$ 15 mg/day) and may be considered an alternative therapy for appropriate patients [Dore *et al.* 2010].

There are many guidelines published concerning prevention and treatment of GC-induced bone loss, including the American College of Rheumatology (ACR), the International Osteoporosis Foundation (IOF), and the Belgian Bone Club (BBC) [Grossman *et al.* 2010; Lekamwasam *et al.* 2012; Devogelaer *et al.* 2006]. All guidelines recommend calcium and vitamin D supplementation. The BBC has the most general guidelines and recommends bisphosphonates for any adult taking at least 7.5 mg of prednisone daily for at least 3 months. The IOF is more conservative and recommends treatment for postmenopausal women and men aged 70 years or over, or with a previous fragility fracture, taking at least 7.5 mg of prednisolone daily for at least 3 months. Based on FRAX analysis, younger patients with risk of hip fracture greater than 3% or risk of a major fracture greater than 20%, bisphosphonate therapy should be offered. Premenopausal women and younger men under 50 years, who have had a fragility fracture, should be offered preventive treatment.

ACR guidelines are the most aggressive in terms of treating patients to prevent GC-induced bone loss. It recommends several tiers of therapy based on FRAX analysis and risk factors. For postmenopausal women and men above age 50 considered low risk ($<$10% risk of major fracture), oral bisphosphonates are recommended for prednisone dosing of at least 7.5 mg/day. For patients at moderate risk (10–20% risk of major fracture) in that age group, oral bisphosphonates are recommended for any dose of GCs, and intravenous zoledronic acid can be considered for prednisone dosing at least 7.5 mg/day. For higher risk ($>$20% risk of major fracture or T score $\leqslant -2.5$) postmenopausal women and men older than 50 years, it is recommended they take a bisphosphonate when starting any dose of GC. Patients in this high-risk group taking at least 5 mg/day of prednisone for up to 1 month or any GC dose for more than 1 month may alternatively be treated with teriparatide [Grossman *et al.* 2010]. Premenopausal women who do not have childbearing potential, and men under 50 years old may be offered oral bisphosphonate therapy for prednisone doses above 5 mg/day. If the GC dose is at least 7.5 mg/ day, then intravenous zoledronic acid or teriparatide may be considered. For women of childbearing potential who are at high risk and are taking at least 7.5 mg/day of prednisone for at least 3 months, bisphosphonates or teriparatide are options. However, there are inadequate data about the risk of bisphosphonates and teriparatide on fetal skeletons in child-bearing women and these agents should be used with caution.

Proton pump inhibitors

PPIs have been widely used since their introduction in the late 1980s. Several large observational studies suggest that PPI use is associated with a modest increase in osteoporotic fracture risk [Yang *et al.* 2006; Yu *et al.* 2008; Vestergaard *et al.* 2006b; Targownik *et al.* 2008]. Based on these and two other studies, the US Food and Drug Administration revised labeling for PPIs in May 2010 to include information about the potential risk of hip, spinal, or radial fractures.

The mechanism by which PPIs increase fracture risk is not known. There is considerable speculation that PPIs, by suppressing acid secretion, decrease intestinal absorption of calcium, leading to increases in bone resorption and osteoporosis [Recker, 1985]. Studies evaluating PPI use and BMD have found no clear association, suggesting that other properties of bone metabolism or bone strength are altered with PPI exposure [Targownik *et al.* 2010; Gray *et al.* 2010].

Many studies have evaluated the association of PPI use and fracture. Although some studies have not shown significant effects [Targownik *et al.* 2010], many studies evaluating PPI use for more

than 1 year have consistently demonstrated an increased risk of hip fracture (20–62%) and an increased risk of vertebral fracture (40–60%) [Lau and Ahmed, 2012]. In some but not all studies, a duration effect has been seen. Short-term PPI use is not associated with an increased fracture risk, whereas long-term use for over 1 year increases the odds ratio (OR) to around 1.44, and with more than 7 years of exposure, the OR increases to 4.55 [Yang *et al.* 2006 ; Roux *et al.* 2009 ; Corley *et al.* 2010]. Thus, fracture risk is dependent on duration of therapy [Corley *et al.* 2010]. PPI dose effects are difficult to quantitatively analyze because of incompatible definitions of doses among the studies; however, several studies have shown that fracture risk is increased when high doses are given compared with lower doses [Yu *et al.* 2011]. However, a recent meta-analysis found an association of hip fracture with both high- and low-dose PPI exposure [Ngamruengphong *et al.* 2011]. Another meta-analysis covering over a million patients, found PPI, but not histamine-2 receptor antagonist (H2 blocker) exposure to be associated with fractures of the spine and hip [Kwok *et al.* 2011].

Fortunately, fracture risk is reduced when PPIs are discontinued [Vestergaard *et al.* 2006a; Corley *et al.* 2010]. No formal studies have been published prospectively examining the effect of bisphosphonates on PPI-induced fracture risk. However, several studies suggest that patients on bisphosphonates who also take PPIs have a further increased risk of fracture [Van der Kallen *et al.* 2014; Lee *et al.* 2013; de Vries *et al.* 2009]. In a Korean population-based study of 24,710 cases and 98,642 controls all over 65 years of age, the OR for hip fracture related to PPI use was 1.34 [95% confidence interval (CI) 1.24–144] but was increased to 1.7 (95% CI 1.31–2.23) in patients taking bisphosphonates and PPIs [Lee *et al.* 2013]. The increased risk of hip fracture in PPI and bisposphonate users was present even when adjusted for multiple medications, such as GCs, warfarin, antiepileptic drugs (AEDs), antidepressants and others, as well as medical conditions known to be associated with secondary osteoporosis. Higher cumulative doses of PPIs (>30 mg) given in association with a bisphosphonate led to higher risk of hip fracture. Another population-based cohort study examined the predictors for fractures while taking bisphosphonates for more than 6 months in a Spanish cohort of 5 million. They found that PPI use was associated with fractures in bisphosphonate users with an OR of 1.22 (95% CI 1.02–1.46) [Prieto-Alhambra *et al.* 2014]. Based on these data, H2 blockers should be considered when possible in patients already taking a bisphosphonate. If PPIs are indicated, then the shortest duration should be considered and the need for continued PPI use assessed frequently. Patients on PPIs should also be on calcium and vitamin D supplementation.

Antiepileptic drugs

In addition to epilepsy, which affects roughly 50 million people worldwide, AEDs are used for the treatment of migraine headaches, psychiatric disorders, chronic pain, and neuropathy. In epilepsy, AEDs are associated with reductions in bone density in postmenopausal women and men older than 65 years [Lyngstad-Brechan *et al.* 2008; Ensrud *et al.* 2004, 2008]. Unfortunately, the adverse effects of AEDs on bone metabolism, especially phenytoin, are also seen in young patients [Pack *et al.* 2008].

Several theories exist concerning the mechanisms of AED-induced bone loss. The cytochrome P450 enzyme-inducing AEDs, such as phenytoin, phenobarbital, and carbamazepine, accelerate inactivation of vitamin D which decreases calcium uptake, drives secondary hyperparathyroidism and accelerates bone loss [Valsamis *et al.* 2006]. Animal studies suggest a direct inhibitory effect of phenytoin on osteoblast proliferation and decreases in carboxylated osteocalcin, leading to poor bone mineralization [Pack *et al.* 2004]. It is unclear how nonenzyme-inducing AEDs reduce BMD and increase fractures. However, valproic acid has been associated with fractures due to the development of hypophosphatemia secondary to Fanconi syndrome [Dhillon and Hogler, 2011].

All AEDs, both enzyme inducers (phenytoin, phenobarbital, carbamazepine) and enzyme noninducers, such as valproate, are associated with accelerated bone loss and subsequent increased risk of osteoporotic fracture [Cummings *et al.* 1995; Vestergaard *et al.* 1999; Souverein *et al.* 2006; Carbone *et al.* 2010; Shen *et al.* 2014]. A meta-analysis found AED therapy to be associated with increased risk of fracture, with the relative risk (RR) of 2.2 (95% CI 1.9–2.5) [Vestergaard, 2005]. The fracture risk is dependent on the duration and cumulative dose of AEDs. A recent retrospective study evaluated nearly 16,000 patients over 50 years of age using AEDs for epilepsy and nonepilepsy indications. Use of

carbamazepine, clonazepam, gabapentin, phenobarbital, and phenytoin were associated with a significant increase in nontraumatic fractures, while valproate was not [Jette *et al.* 2011]. Newer AEDs, including topiramate and lamotrigine, were also associated with increased fractures [Jette *et al.* 2011]. Another meta-analysis that included 22 studies found a significant increase in fractures for both enzyme-inducing and nonenzyme-inducing AEDs [Shen *et al.* 2014]. In this study, the highest risk of fractures occurred with exposures to phenobarbital, phenytoin, and topiramate; while valproic acid, gabapentin, lamotrigine, and carbamazepine had nonsignificant effects on fracture risk. However, in other studies, gabapentin has been shown to increase bone loss and fracture risk [Ensrud *et al.* 2008; Jette *et al.* 2011]. Levetiracetam has not been associated with increases in biochemical markers of bone turnover or decreases in BMD after 1 year of treatment, suggesting that it may not have the significant adverse bone health problems that older agents carry [Koo *et al.* 2013]. However, long-term studies with these newer agents are needed to assess fracture risk. Thus most studies have concluded that AEDs are associated with a moderate to severe risk of fractures with prolonged use.

Evidence-based strategies for prevention, screening, monitoring, and treating bone loss and osteoporosis associated with AEDs are limited. Routine evaluation of 25-hydroxy vitamin D before treatment and every 6–12 months of AED therapy is recommended to ensure adequate vitamin D levels [Meier and Kraenzlin, 2011]. Patients on nonenzyme-inducing AEDs generally require 1000–1200 IU/day of vitamin D while those on enzyme-inducing AEDs need 2000–4000 IU/ day to maintain adequate vitamin D levels [Bartl, 2007; Drezner, 2004]. Patients should also receive adequate calcium supplementation. When safe to do so, patients with epilepsy should be encouraged to actively ambulate and participate in regular weight-bearing exercises as tolerated.

Until further evidence from additional randomized trials is available, recommendations are that patients on long-term AEDs should be screened with dual energy X-ray absorptiometry (DXA) or FRAX analysis. Postmenopausal women and men over 50 years of age with osteoporosis or osteopenia and a 10-year probability of hip fracture greater than 3% or major fracture greater than 20% should be treated as per the guidelines of the National Osteoporosis Foundation [Bartl, 2007; Meier and Kraenzlin, 2011]. A recent prospective randomized trial evaluated the effects of risedronate 35 mg daily with vitamin D and calcium in men with epilepsy taking chronic AEDs. This study found bisphosphonate therapy superior to vitamin D and calcium alone in improving BMD and preventing fractures in this epileptic population [Lazzari *et al.* 2013]. Similarly, bisphosphonates with calcium and vitamin D supplementation improves BMD in children with cerebral palsy on chronic AED therapy [Iwasaki *et al.* 2012]. Larger randomized studies are needed to validate the prophylactic use of bisphosphonates in AED users, especially in younger patients. Careful review of risks and benefits should occur with women of child-bearing age who are on AEDs and considering bisphosphonates.

Medroxyprogesterone acetate

Hormonal contraceptives are among the most effective and most widely used contraceptives. More than 11 million American women successfully use this method of contraception. While oral hormone contraception is not associated with bone loss [Lopez *et al.* 2012], MPA, which is widely used for the treatment of endometriosis and as a contraceptive agent, is associated with bone loss. Depot MPA (DMPA), given intramuscular or subcutaneously every 3 months, inhibits gonadotropin secretion and suppresses ovulation as well as estrogen production. Due to the reduction in estrogen, DMPA induces bone loss similar to pregnancy, with a decrease of 2–8% in BMD [Cromer *et al.* 2006, 2008].

Bone loss appears to decline rapidly in the first 2 years of treatment followed by a plateau [Cromer *et al.* 2008; Scholes *et al.* 2002; Clark *et al.* 2004]. Most studies have shown that DMPA-induced bone loss is reversible, with improvement occurring quicker in the spine than the hip [Clark *et al.* 2006; Scholes *et al.* 2005; Kaunitz *et al.* 2006]. Several studies have shown a slight increase in fracture risk associated with DMPA [Watson *et al.* 2006; Vestergaard *et al.* 2008a; Meier *et al.* 2010]. This risk occurs in patients under 30 years of age as well as those over 30, and appears to be highest after 2–3 years of treatment [Meier *et al.* 2010]. However, women who chose DMPA may have baseline characteristics that place them at higher risk for traumatic fractures, including smoking, alcohol use, and exercise patterns [Lappe *et al.*

2001]. A recent retrospective study confirmed this finding and showed that incident fracture rates of DMPA users was higher than never users both prior to initiation of DMPA and after initiation of DMPA. Importantly, the fracture rate ratios (prior to DMPA, 1.28, and post DMPA, 1.23) did not significantly increase as a result of DMPA use [Lanza *et al.* 2013]. More data from prospective long-term studies are needed to fully address the impact of DMPA exposure on fracture risk.

The role of screening bone health with DXA in DMPA users is controversial. Guidelines from the American College of Obstetrics and Gynecology, the Society for Adolescent Health and Medicine, and the World Health Organization do not recommend routine DXA evaluation for premenopausal women using DPMA [American College of Obstetricians & Gynecologists Committee on Gynecologic Practice, 2008; WHO, 2005; Cromer *et al.* 2006]. All DMPA users should have vitamin D levels checked and calcium and vitamin D supplements given. Patients should be encouraged to exercise, stop smoking, and limit alcohol intake. Studies have shown that prescribing low-dose estrogen replacement to DMPA users can prevent bone loss in premenopausal women on DMPA [Cundy *et al.* 2003; Cromer *et al.* 2005]. The use of bisphosphonates or other agents has not been explored in this patient population and is currently not recommended [Cromer *et al.* 2006; WHO, 2005; American College of obstetricians & Gynecologists Committee on Gynecologic Practice, 2008].

Aromatase inhibitors

Aromatase inhibitors (AIs), including letrozole, anastrozole, and exemestane, provide effective adjuvant hormone therapy for estrogen-receptor-positive breast cancer in postmenopausal women. AIs inhibit the peripheral conversion of androgens to estrogens, resulting in lower estrogen levels beyond what is normally achieved in menopause and promote accelerated bone loss [Hadji, 2009].

Prevention of AI-induced bone loss with antiresorptive drugs has been well studied. Data from clinical trials in over 4100 patients support the use of intravenous or oral bisphosphonates and denosumab to prevent AI-induced bone loss in postmenopausal women with breast cancer [Hadji *et al.* 2011]. Compared with risedronate, zoledronic acid (4 mg intravenously every 6 months) is more effective at preventing AI-induced bone loss and increases disease-free survival in patients with breast cancer [Brufsky *et al.* 2008; Greenspan *et al.* 2008; Gnant *et al.* 2009]. In several large trials, intravenous zoledronic acid is effective when started simultaneously with AIs or when delayed after a period of AI therapy [Eidtmann *et al.* 2010; Brufsky *et al.* 2009; Hines *et al.* 2009].

Current recommendations from most professional groups recommend DXA for all women beginning AI therapy in addition to adequate calcium and vitamin D supplementation [Body *et al.* 2007; Reid *et al.* 2008; Gralow *et al.* 2013]. All groups recommend beginning a bisphosphonate simultaneously with AI therapy for patients with T scores less than 2.5 or a history of fragility fracture. The Belgian Bone club recommends bisphosphonate treatment in patients taking AIs with T scores between −1.0 and −2.5 [Body *et al.* 2007]. The UK Expert Group recommends bisphosphonates for women treated with AIs who are over 75 years old and have one or more risk factor independent of BMD [Reid *et al.* 2008]. For younger women with osteopenia, it recommends starting a bisphosphonate at a T score of less than −2.0. Additionally, the UK Expert Group recommends bisphosphonates at a T score of less than −1.0 in younger premenopausal women receiving ovarian suppression. If patients choose not to start a bisphosphonate, DXA analysis should be repeated every other year to monitor bone loss. Denosumab is an alternative prevention and treatment strategy for AI-induced bone loss. Teriparatide is generally not recommend in patients with cancer receiving AIs if they have had prior radiation, due to the risk of developing osteosarcomas.

Gonadotropin-releasing hormone agonists and androgen-deprivation therapy

Gonadotropin-releasing hormone agonists (GnRHs) are used to treat polycystic ovary syndromes, endometriosis, uterine myomas, breast cancer in premenopausal women, and prostate cancer. GnRHs inhibit gonadotropins leading to a hypogonadal state that resembles menopause in women and chemical castration in men. Androgen-deprivation therapy (ADT) provides a survival benefit to men with invasive or

metastatic prostate cancer. GnRH analogs bind to GnRH receptors in the pituitary and downregulate the gonadotropin-producing cells, limiting luteinizing hormone and follicle-stimulating hormone secretion. This in turns limits the production of testosterone and estradiol, leading to chemical castration. As such, GnRH therapy, including leuprolide, goserelin, triptorelin, and histrelin, lead to decreases in BMD. After ADT is started, the BMD declines by 2–5% in the first year and the risk of hip and vertebral fractures increases to 20–50% at 5 years [Smith *et al.* 2005; Shahinian *et al.* 2005]. Patient age, rate of BMD decline, and duration of ADT exposure correlate with fracture risk [Ahlborg *et al.* 2008; Barr *et al.* 2010].

Bisphosphonates can prevent and treat ADT-induced bone loss [Smith *et al.* 2001, 2003; Greenspan *et al.* 2007; Klotz *et al.* 2013]. However, limited data are available showing bisphosphonates prevent fractures in patients treated with ADT [Planas *et al.* 2009]. Other treatments that do provide fracture reduction include selective estrogen receptor modulators (SERMs), such as raloxifene and toremifene [Smith *et al.* 2004a, 2010] and denosumab [Smith *et al.* 2009a, 2009b]. Alternatives to ADT include antiandrogens, such as bicalutamide, flutamide, and nilutamide, in men without bone metastases. These drugs maintain BMD compared with ADT because they inhibit testosterone binding to androgen receptors without lowering testosterone levels [Smith *et al.* 2004b].

Current recommendations, in addition to calcium and vitamin D supplementation, include DXA evaluation. Bisphosphonates are indicated for men beginning ADTs if their T score is less than −2.5, or between −1.0 and −2.0 if other risk factors exist [Greenspan, 2008]. Depending on patient factors, alternative treatments include SERMs, denosumab, and antiandrogens. In some cases, women can be treated with additions of estrogen to the GnRH to maintain BMD [Mitwally *et al.* 2002]. Bisphosphonates are also effective at maintaining BMD in premenopausal women undergoing 6-month cycles of GnRH therapy [Ripps *et al.* 2003].

Selective serotonin reuptake inhibitors

SSRIs including fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram, as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine are now widely prescribed for depression, anxiety disorders, premenstrual syndrome, peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain. Several studies have shown that SSRIs are associated with bone loss and increased fracture risk [Pacher and Ungvari, 2001; Liu *et al.* 1998; Ensrud *et al.* 2003; Richards *et al.* 2007]. Two recent meta-analyses confirmed this association [Wu *et al.* 2012; Eom *et al.* 2012; Rabenda *et al.* 2013]. Eom and colleagues calculated the adjusted OR for fracture among SSRI users to be 1.69 (95% CI 1.51–1.90; r^2 = 89.9%) [Eom *et al.* 2012], while Wu and colleagues found a similar OR of 1.73 (95% CI 1.51–1.9; $p < 0.001$) [Wu *et al.* 2012]. Fracture risk was highest at the hip and nonvertebral sites compared with the spine [Rabenda *et al.* 2013]. Dose and duration of SSRIs also contribute to fracture risk, with both an early increased risk (<6 weeks) and a late risk associated with prolonged use for more than 3–5 years [Richards *et al.* 2007; Eom *et al.* 2012]. A recently published large 10-year longitudinal cohort study [Moura *et al.* 2014] examined fracture risk in SSRI and SNRI users over the age of 50. They found SSRI and NSRI use increased fragility fractures with a hazard ratio (HR) of 1.88 (95% CI 1.48–2.39). This risk remained elevated even after multiple confounders were adjusted, with a HR of 1.69 (95% CI 1.32–2.14). Several studies reported increased fracture risk is highest for postmenopausal women and older men [Richards *et al.* 2007; Liu *et al.* 1998].

Mechanistically, the effect of SSRIs on bone formation and resorption are complex and incompletely understood. Serotonin receptors found on osteoblasts and osteoclasts regulate bone homeostasis via endocrine, autocrine, paracrine, and neuronal serotonin pathways. Surprisingly, SSRI exposure related fractures occur in the absence of declines in BMD, indicating that SSRIs likely have alternative effects on bone homeostasis [Wu *et al.* 2012].

There are no published guidelines on prevention or treatment of SSRI-induced bone loss. Clinicians should ensure appropriate calcium and vitamin D supplementation. Patients considering treatment with SSRIs who have other risk factors for osteoporosis or fracture might benefit from DXA or FRAX analysis. Treatment decisions should be individualized based on osteopenia or osteoporotic T scores or fractures risks greater than 3% for hip and greater than 20% for major

fractures. At this time, there is no literature to support the use of bisphosphonates to prevent SSRI fracture risk.

Thiazolidinediones

TZD are insulin sensitizers used for the treatment of type 2 diabetes mellitus. Two TZDs, rosiglitazone and pioglitazone, are currently available in the United States and are agonists of peroxisome proliferator-activated receptor γ (PPARγ). PPARγ is expressed in stromal cells of the bone marrow, osteoblasts, and osteoclasts, and plays an important role in the differentiation of precursor cells into osteoblasts. TZDs impair the differentiation of osteoblast precursors, thereby preventing bone formation leading to osteoporosis. TZDs may act on bone remodeling by increasing adiposity of bone marrow, decreasing aromatase activity, and promoting osteoclast differentiation, leading to increased bone resorption [Grey, 2009]. Thus, TZDs reduce bone formation and increase bone resorption, increasing osteoporosis and fracture risk.

There is sufficient evidence from the published data both in animal models and in humans that TZDs decrease BMD at the lumbar spine and the hip, and increase fracture risk. A meta-analysis of 10 randomized trials and two large observational studies indicate TZDs double fractures in women with type 2 diabetes but not in men [Loke *et al.* 2009]. A meta-analysis of three population-based European cohort studies also found a 1.2–1.5-fold increase in fractures in women but not men taking TZDs [Bazelier *et al.* 2013]. This study further reveals that prolonged use of TZDs (>25 prescriptions) increases the risk of extremity fractures more so than vertebral fractures. However, a UK-based observational study utilizing a large population from general practice research data found that TZDs significantly increased the risk of nonvertebral fractures independent of age and sex [Douglas *et al.* 2009]. Fracture risk is increased even in young women without other risk factors for osteoporosis.

No proven strategies exist for reducing the risk of fracture induced by TZDs. Before starting TZDs, patients should be evaluated for fracture risk by FRAX analysis or DXA. According to the International Diabetes Foundation, metformin and sulfonylureas should be used as first- and second-line drugs for type 2 diabetes followed by TZDs and other agents. TZDs should be avoided in patients with established osteoporosis and should be stopped in those with a high risk of fracture [Kahn *et al.* 2008; Mancini *et al.* 2009].

Calcineurin inhibitors

Calcineurin inhibitors, including cyclosporine (CsA) and tacrolimus (FK506), have been widely used as immunosuppression to prevent organ transplant rejection and for autoimmune disorders. Both are associated with bone loss and increased fracture, although the exact mechanisms are not known. *In vitro*, calcineurin inhibitors inhibit osteoclastogenesis and osteoclast activity via reductions in Nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) [Miyazaki *et al.* 2007; Zawawi *et al.* 2012]. However, in animal models and humans, these drugs cause dose- and duration-dependent bone loss with excessive osteoclastogenesis [Movsowitz *et al.* 1988, 1989; Kulak *et al.* 2006]. Additionally, there are indirect effects on osteocalcin and vitamin D metabolism, leading to secondary hyperparathyroidism and subsequent high bone turnover osteopenia [Stein *et al.* 1991].

The adverse bone effect of calcineurin inhibitors in humans is difficult to delineate due to the confounding effects of poor bone health prior to organ transplantation and the use of GCs post transplantation. Several studies suggest that calcineurin inhibitors cause bone loss and fragility fractures in transplant patients and the effect is dose and duration dependent [Cueto-Manzano *et al.* 2003; Tannirandorn and Epstein, 2000; Julian *et al.* 1991]. However, when CsA or FK506 are given as monotherapy or in low-GC (10 mg daily) treatment plans, BMD is preserved and even increased [Goffin *et al.* 2002; Ezaitouni *et al.* 1998]. CsA use in rheumatic diseases at doses below 5 mg/kg/day has not been reported to have clinically significant bone loss [Ferraccioli *et al.* 1996]. A multicenter, cross-sectional study of women with rheumatoid arthritis on CsA found that only women treated for over 24 months had a decrease in BMD, but this decrease was not associated with an increased risk of fracture [Mazzantini *et al.* 2007].

Data on the prevention or treatment of post-transplant osteoporosis are limited in terms of large, placebo-controlled studies. Many small studies in kidney, liver, and heart transplant show BMD preservation with bisphosphonates [Cohen *et al.* 2004; Shane *et al.* 1998; Bishop

et al. 1999; Valero *et al.* 1995]. Guidelines from the National Kidney Foundation support BMD evaluation with DXA prior to transplantation and 1 and 2 years post transplantation. If the T score is −2.0, in addition to calcium and vitamin D supplementation, bisphosphonates are indicated [Kasiske *et al.* 2010]. Given the disparate studies showing preservation of BMD and significant BMD loss in various populations, further studies are needed to provide guidance for monitoring and treating bone health in the presence of calcineurin inhibitors.

Anticoagulants

Heparin has been in clinical use for over 50 years for the prevention and treatment of venous thromboembolism. Although short-term use is not associated with reductions in BMD or increased fractures, long-term use leads to reductions in BMD and increased fractures. Mechanistically, unfractionated heparin inhibits osteoblast differentiation and function, leading to decreases in bone formation [Rajgopal *et al.* 2008]. Additionally, heparin increases bone resorption by leading to reductions in OPG, favoring RANKL-induced osteoclast differentiation [Rajgopal *et al.* 2008].

Several studies have shown that up to 30% of heparin-treated pregnant women will have decreases in BMD with 2.2–3.6% developing fractures despite their young age [Douketis *et al.* 1996; Barbour *et al.* 1994; Dahlman, 1993]. The incidence of vertebral fractures in nonpregnant women on long-term heparin is 15% and often occurs within 6 months of starting heparin therapy [Monreal *et al.* 1994]. Heparin-induced bone loss is dose dependent and highly reversible upon discontinuation [Dahlman, 1993; Barbour *et al.* 1994]. Small studies suggest that low molecular weight heparin (LMWH) is associated with fewer fragility fractures compared with unfractionated heparin [Monreal *et al.* 1994; Pettila *et al.* 1999]. However, a large prospective study in pregnant patients found no differences between unfractionated heparin and LMWH [Backos *et al.* 1999]. Newer heparins, including fondaparinux, have no effect on osteoblast differentiation or function *in vitro* and are predicted to be bone neutral [Handschin *et al.* 2005; Matziolis *et al.* 2003]. Clinical studies supporting this hypothesis are lacking at this time.

Controversy surrounds the effects of the oral anticoagulant, warfarin, on bone density and fracture. Mechanistically, warfarin decreases the γ carboxylation and calcium-binding properties of osteocalcin and is predicted to negatively impact BMD [Lian and Gundberg, 1988]. Many small cross-sectional and retrospective studies indicate that warfarin is associated with reductions in BMD and increases in vertebral and rib fractures [Fiore *et al.* 1990; Philip *et al.* 1995; Caraballo *et al.* 1999]. However, other studies have found no significant effects on BMD or fractures in warfarin users compared with controls [Piro *et al.* 1982; Jamal *et al.* 1998; Woo *et al.* 2008]. At this time, data are inconclusive as to the impact of warfarin on bone.

There are no published guidelines for the prevention or treatment of heparin or oral anticoagulant-induced bone loss. Because most patients on long-term heparins are pregnant, bisphosphonates have not been studied in these patients due to concerns for the fetal skeleton. In addition to calcium and vitamin D supplementation in patients at high risk for osteoporosis, LMWH or fondaparinux may be preferred over unfractionated heparin for thromboprophylaxis.

Chemotherapy agents

Some chemotherapeutic agents are associated with excessive bone loss. High-dose methotrexate can directly cause bone loss [Schwartz and Leonidas, 1984]; whereas ifosfamide leads to bone loss secondary to renal tubular phosphate wasting [Pfeilschifter and Diel, 2000]. Other drugs, like cyclophosphamide, indirectly induce bone loss due to negative effects on gonadal tissues.

Summary

Many medications that are commonly prescribed have harmful effects on bone homeostasis, leading to decreases in BMD and increases in fractures. Increasing our awareness of these deleterious effects will improve our ability to appropriately risk stratify our patients, use alternative medications when possible, and use prevention measures when necessary. We have summarized our findings and the current recommendations in Table 1. Further studies are needed to determine the best prevention and treatment strategies for many drugs that increase bone loss or fractures.

Table 1. Commonly prescribed medications that have harmful effects on bone homeostasis leading to decreases in bone mineral density and increases in fractures.

Drug class	Mechanism of action	Reversibility on medication discontinuation	Screening recommendation	Management recommendation	Alternate medication
Glucocorticoids (GC)	Decreased bone formation and increased bone resorption	Fracture risk decreases to baseline within 2 years	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation Bisphosphonate or teriparatide according to fracture risk DXA scan every 2 years	Limit dose and duration of GC Use alternative immunosuppressive agents according to underling disease condition
Proton pump inhibitors (PPIs)	Unknown but maybe due to decreased intestinal absorption of calcium	Fracture risk reverses within 1 year	No recommendation	Calcium and vitamin D supplementation If possible, avoid PPI use with bisphosphonates	H_2 blockers
Antiepileptic drugs (AEDS)	Uncertain but may include inactivation of vitamin D	Unknown	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels every 6–12 months	Calcium and increased vitamin D supplementation: nonenzyme-inducing AEDs give 1000–1200 IU vitamin D and for enzyme-inducing AEDs give 2000-4000 IU vitamin D daily Bisphosphonates in postmenopausal women and men >50 years	Newer agents like levetiracetam
Medroxyprogesterone acetate (MPA)	Reduced estrogen level leading to increased bone resorption	Partial to full recovery of bone loss at spine and hip	DXA scan controversial in this premenopausal population Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation Limit therapy to 2–3 years No data on bisphosphonates prophylaxis and is currently not recommended	Oral hormonal contraceptives, low-dose estrogen replacement with depot MPA, other birth control methods
Aromatase Inhibitors	Reduced estrogen production leading to increased bone resorption	Unknown	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation Bisphosphonates for moderate- to high-risk patients Denosumab as alternative DXA scan every 2 years while on treatment	Not applicable

(Continued)

Table 1. (Continued)

Drug class	Mechanism of action	Reversibility on medication discontinuation	Screening recommendation	Management recommendation	Alternate medication
GnRH agonists	Prevent the production of LH and FSH thereby decreasing testosterone and estradiol leading to increased bone resorption	May be reversed in 2 years depending on dose and duration of therapy	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels	Bisphosphonates, denosumab, raloxifene, or toremifene for moderate- to high-risk patents DXA scan every 2 years while on treatment	Second line: androgen receptor blockers in men without bone metastasis
Serotonin selective reuptake inhibitors	Uncertain	Probable	Fracture risk analysis with DXA or FRAX for patients with other osteoporosis risk factors Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation	Alternative classes of antidepressants
Thiazolidinediones	Decreased bone formation	Unknown	Fracture risk analysis with DXA or FRAX for patients with other osteoporosis risk factors Monitor vitamin D and calcium levels	Avoid in established osteoporosis No data for prevention	Metformin, sulfonylureas, insulin
Calcineurin inhibitors	Excessive osteoclasts and bone resorption with glucocorticoids	Unknown	DXA/FRAX analysis prior to kidney transplant Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation DXA prior to and every 2 years post organ transplant Bisphosphonates for T score < -2.0	
Heparin	Osteoblast inhibition with decreased bone formation; increased bone resorption	Near complete reversal of BMD	No published recommendations	No published recommendations	Fondaparinux if applicable
Warfarin	Decreases bone mineralization	Unknown	No published recommendations	No published recommendations	

BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone agonist; LH, luteinizing hormone.

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Conflict of interest statement

The authors declare no conflict of interest in publishing this article.

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