

**ADR Focus** by Elizabeth Rudy, DVM, RPh

**Update: Drugs That Cause Osteoporosis**

The most common metabolic bone disease in the world is osteoporosis.<sup>1</sup> The National Osteoporosis Foundation estimates that osteoporosis presents a major health threat to ~44 million Americans.<sup>2</sup> As reported by the National Institute on Aging, 10 million Americans already have the disease, and another 34 million are at risk for developing osteoporosis due to low bone mass (osteopenia).<sup>2</sup> Osteoporosis causes fractures, and there are ~1.5 million fractures annually in this country.<sup>1</sup> This results in a significant amount of disability and a huge burden on the health care system. The total cost associated with treatment of complications due to osteoporosis was estimated at \$17 billion in 2001.<sup>1</sup>

Osteoporosis occurs when resorption of bone tissue by osteoclasts becomes greater than the build up of bone tissue by osteoblasts, and bone demineralization results, causing bone to become more porous.<sup>2</sup> The condition is characterized by low bone mass and micro architectural deterioration of bone tissue, resulting in increased bone fragility and a subsequent enhanced risk for fracture.<sup>3</sup> The disease most commonly occurs after menopause and in the elderly, and is rarely observed in normal young adults without predisposing risk factors. Contributing risk factors for osteoporosis are numerous (see Table I). Although women are affected by osteoporosis at a rate of four to one when compared to men, more than 2 million American men currently have osteoporosis and 3.5 million more are at risk for developing the disease due to osteopenia.<sup>2</sup> Osteoporosis can be classified as either primary osteoporosis, which includes postmenopausal and age-related osteoporosis, or as secondary osteoporosis, defined as osteoporosis caused by disease or identifiable agents such as drugs (see Table II).<sup>1,3</sup> The purpose of this *ADR Focus* is to provide practitioners with a second look at medications that are associated with bone loss that can lead to osteoporosis.

**Glucocorticoids** are a well-known cause of osteoporosis. One source estimates that long-term glucocorticoid treatment may result in fractures in ~50% of patients.<sup>3</sup> Glucocorticoid-induced osteoporosis appears to be dose related.<sup>3,4</sup> Moderate to high dose daily therapy with 5mg or more of prednisone may result in significant bone loss and an increased risk of fracture. However, low dose prednisone therapy (1-5mg/day) may also cause the condition. Inhaled steroids are probably less likely to cause bone loss, but high dose, prolonged use of these agents may still be a concern.<sup>3</sup> The mechanism by which these drugs cause bone loss is multifactorial.<sup>3</sup> Three major mechanisms appear to be involved: 1) an effect on calcium homeostasis, resulting in reduced calcium absorption and increased excretion; 2) suppression of sex hormones that cause bone formation; and 3) a direct effect on bone, with inhibition of osteoblasts and activation of osteoclasts, leading to bone loss.<sup>3,5</sup>

The **calmodulin-calcineurin phosphatase inhibitors**, cyclosporine and tacrolimus, mainstays of organ transplant therapy and used to treat many immunologic disorders, cause increased bone turnover that can result in osteoporosis.<sup>6,7</sup> Because the majority of patients taking these drugs are concurrently on glucocorticoid therapy, the mechanism by which cyclosporine/tacrolimus cause bone loss has been difficult to delineate; and additionally, detrimental effects on bone could be additive.<sup>3,7</sup> (Continued on page 38)

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Table I: Risk Factors for Osteoporosis<sup>1,3</sup>

-Age
-Cigarette smoking
-Estrogen deficiency
-Excessive alcohol intake
-History of osteoporotic fracture in a 1st-degree relative
-Hypogonadism
-Inadequate calcium intake
-Low body weight
-Personal history of fracture as an adult
-Race
-Recurrent falls
-Sedentary life style
-Sex
-Vitamin deficiency

**Data from two new clinical studies indicate that women who use medroxyprogesterone as an injectable contraceptive may lose significant bone mineral density, which may not return completely once use of medroxyprogesterone has been discontinued. This is of particular concern in adolescence when bone mineral density should instead be increasing.<sup>18</sup>**

Table II: Drugs That Cause Bone Loss

-Alcohol
-Antacids (aluminum containing)
-Anticonvulsants
-Aromatase inhibitors
-Cholestyramine
-Cyclosporine/Tacrolimus
-Glucocorticoids
-Gonadotropin-releasing hormone agonists
-Heparin
-Lithium
-Marijuana
-Medroxyprogesterone
-Methotrexate
-Neuroleptics
-Thyroxine (high dose)
-Vitamin A (long-term use at doses >10,000 units/day)
-Vitamin D (doses > 2,000 units/day)

Chronic anticonvulsant drug (**phenytoin, phenobarbital, carbamazepine, primidone, valproic acid**) therapy can lower bone mineral density in patients of all ages.<sup>3,8</sup> The previously listed anticonvulsants, with the exception of valproic acid, are inducers of the P450 hepatic enzymes that increase the metabolism of sex steroids and vitamin D that can, in turn, lead to bone loss. Valproic acid rarely causes osteoporosis; however, there have been reports of osteoporosis in children on chronic valproic acid therapy.<sup>3</sup> The drug may induce osteoporosis by increasing renal calcium excretion.<sup>3</sup> At this time, it is not known if the newer antiepileptic drugs have a similar effect on bone.<sup>9</sup>

In one study, **lithium**, indicated for the treatment of bipolar disorder, was found to cause bilateral osteopenia in the forearms of 16% of 98 treated patients.<sup>3</sup> Chronic lithium therapy may result in hyperparathyroidism in up to 40% of treated patients, leading to hypercalcemia and bone loss.<sup>3</sup> Neuroleptic drugs (primarily **phenothiazine and butyrophenone derivatives**) used in the treatment of psychoses, have been implicated as a cause of osteoporosis. Treatment with these medications may induce hyperprolactinemia and subsequent hypogonadism that can result in bone resorption.<sup>3,10,11</sup> It should be noted that schizophrenic patients may have additional factors such as decreased physical activity, decreased exposure to sunlight, and nutritional deficiencies that can all contribute to decreased bone mineral density.<sup>3</sup>

The folic acid antagonist, **methotrexate**, used to treat rheumatologic, dermatologic, and oncologic diseases, was first shown to cause osteopathy in children with leukemia treated with high dose therapy.<sup>3</sup> The drug's bone wasting effects appear to be dependent upon dose and duration of treatment, and result from reduced osteoblast activity and increases in bone resorption.<sup>3</sup> Patients treated with low-dose methotrexate have also exhibited bone abnormalities, but one study showed no correlation without concurrent corticosteroid therapy.<sup>12</sup>

The **gonadotropin-releasing hormone agonists** such as leuprolide, and goserelin when used to treat prostate carcinoma in men, cause a decrease in testosterone levels that may result in hypogonadism and lead to osteoporosis.<sup>3</sup> Osteoporotic fractures have been reported in 5% of men treated with these drugs.<sup>13</sup> Additionally, women treated with the gonadotropin-releasing hormone agonist nafarelin for various gynecologic disorders may experience a reduction in the production of estrogen by the ovaries and subsequent bone loss.<sup>3</sup>

High-dose **medroxyprogesterone**, used to treat various gynecological disorders (including endometriosis, pelvic pain syndrome, breast cancer, and premenstrual syndrome), has been associated with bone loss in premenopausal women.<sup>3</sup> Medroxyprogesterone decreases serum estrogen levels and this can lead to bone mineral density loss.<sup>14</sup> Recent research indicates that medroxyprogesterone when administered as an injectable contraceptive at a dose of 150mg every three months can also result in significant loss of mineral bone density.<sup>14</sup>

Chronic high-dose **heparin** therapy can result in osteoporosis. The mechanism of heparin-induced osteoporosis has not been elucidated, but appears to involve the collagenolytic action of the drug.<sup>3,4</sup> Studies indicate that to see adverse effects on bone, the dose of heparin must be >15,000 units/day for longer than 3 months.<sup>3</sup> Low molecular weight heparins (LMWHs) can have similar effects on bone, but the degree of bone loss is generally less severe.<sup>3,15</sup> Sivakumaran et al., described an osteoporotic lumbar spinal fracture in a female patient treated with low-dose LMWH for 3 months.<sup>16</sup>

High-dose administration of **thyroxine** (in doses that suppress TSH), **vitamin A** (long-term use at doses >10,000 units/day), or **vitamin D** (doses >2,000 units/day) may also result in bone loss.<sup>4,5</sup> **Phosphate binding antacids**, such as aluminum hydroxide, bind to phosphate in the gastrointestinal tract and cause hypercalciuria, hypophos-

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**Although osteoporosis is four times more common in women, more than 2 million American men currently have osteoporosis and 3.5 million more are at risk for developing osteopenia.<sup>2</sup>**

phatemia, and hypophosphaturia. This can result in bone resorption and osteomalacia.<sup>3</sup> Cases of antacid-induced bone disease and fracture have been reported in the literature.<sup>4,17</sup>

Prevention may well be the most important intervention for drug-induced osteoporosis.<sup>1</sup> Several strategies may be employed to minimize the risk that bone loss will occur in patients taking these medications. These include: (1) awareness of the potential of certain drugs to adversely affect bone; (2) careful use of these medications and assessment of concurrent factors and medications that may compound risks for bone loss; (3) utilization of the lowest effective dose; (4) cessation of use when possible; (5) frequent monitoring with bone mineral density measurements; (6) pharmacologic treatment with calcium, vitamin D and its analogs, hormone replacement therapy, bisphosphonates, raloxifene, calcitonin, or parathyroid hormone where indicated; and (7) life style changes such as exercise, dietary changes, and avoidance of tobacco and alcohol.<sup>1,3</sup>

## Oral Mineral Replacement

by Jennifer Namba, Pharm.D.

Strolling down a typical vitamin and mineral aisle at the local drugstore reveals a myriad of products in different strengths, sizes, and combinations. Even for healthcare professionals familiar with the general principles of supplementation, selecting the appropriate product can be a confusing prospect. Imagine then, the difficulties that patients face when trying to determine which bottle corresponds with the recommendation or prescription from their provider. Mineral supplementation is commonly prescribed for the treatment of medical conditions such as anemia and osteoporosis. Therefore, accurately communicating proper dosing and product selection is an integral component of patient care.

Several issues should be considered when recommending mineral replacement. Patients and practitioners should understand the difference between the total and elemental content of supplements such as calcium, magnesium, phosphorus, and iron. The elemental content also varies depending on the salt formulation. Therefore, the elemental content should be specified on all prescriptions and labels to reduce patient confusion and assure appropriate supplementation. The FDA does not regulate commercial labeling of mineral supplements and as a result, elemental content is often not included on the ingredient list. The recommended daily allowance (RDA) provides an alternative way of determining the elemental content. For example, the RDA for calcium is 1 gram. Each 500mg TUMS<sup>R</sup> tablet then provides 200mg elemental calcium, or 20% of the RDA.

**Calcium:** The NIH Consensus Conference and The National Osteoporosis Foundation recommend that adults receive 1.2-1.5 grams of elemental calcium daily. Calcium carbonate requires an acidic environment for absorption, and should be taken with food. In contrast, calcium citrate can be taken on an

**Table I: Elemental Content of Oral Calcium Salts**

Note: 20mg elemental calcium = 1mEq

Calcium Salt	% Ca	Strength	Elemental Calcium
Carbonate	40%	500mg	200mg
		1500mg	600mg
Citrate	21%	950mg	200mg

empty stomach because it is not affected by the level of acidity. Vitamin D facilitates calcium ab-

sorption and is supplemented in doses of 400 units per day. However, excessive doses of vitamin D can cause toxicity and patients should be warned against taking combination products with calcium.

**Magnesium:** Oral supplementation should be limited to patients with documented magnesium deficiency or those taking medications known to cause hypomagnesemia (diuretics, cyclosporine, tacrolimus). Similar to calcium, the elemental magnesium content varies with the salt formulation (Table II). Magnesium oxide provides the highest elemental content per dose and is typically recommended for

**Table II: Elemental Content of Oral Magnesium Salts**

(Note: 1g magnesium = 83.3mEq = 41.7mmol)

Magnesium Salt	% Mg	Strength	Elemental Magnesium
Oxide	60%	400mg	241.3mg (19.8mEq)
Hydroxide	44%	400mg/5mL	167mg/5mL (13.7mEq)

supplementation. However, the use of magnesium-containing antacids or laxatives should also be taken into consideration when prescribing replacement. Diarrhea is the most common dose-limiting adverse effect associated with magnesium replacement. Dose reduction or more frequent monitoring of magnesium levels is recommended in patients with renal impairment (ClCr <25 mL/min). There is no evidence that magnesium prevents osteoporotic fractures; in fact, supplementation was associated with an increased fracture risk in the Women's Health Initiative study. Therefore,

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Formulary Actions	
<b>IV Immune Globulins</b>	It was the decision of the P&T Committee to ADD a sucrose-free IVIG product and an IgA-depleted IVIG product to formulary pending development of an order form that restricts these IVIG products to the appropriate patients.
<b>Insulins</b>	Lente and ultralente insulin will be DELETED from the UW Medicine drug formulary following a 3-month phase out.

## Oral Mineral Replacement (continued)

patients should avoid using the combination products of calcium, vitamin D and magnesium that are commonly promoted for the treatment of osteoporosis.

**Phosphorus:** Oral phosphorus replacement is typically limited to patients with chronic phosphate wasting, symptomatic hypophosphatemia or hypercalcemia. Daily doses of 2.5 to 3.5 grams (80 to 110 mmol) should be given in divided doses. Osmotic diarrhea is the primary dose-limiting adverse effect associated with phosphorus replacement. Dose reduction is recommended in patients with moderate-severe renal insufficiency to minimize excessive phosphorus retention.

Table III: Mineral Content of Phosphorus Products  
(Note: 1g phosphorus = 32.3mmol)

Phosphate Product	Phosphate	Potassium	Sodium
Neutra-Phos	250mg (14.25mEq)	278mg (7mEq)	164mg (7mEq)
Neutra-Phos K		556mg (14mEq)	0
K-Phos Neutral		45mg (1.1mEq)	298mg (13mEq)

**Iron:** The recommended daily dose for iron deficiency is 150 to 300 mg elemental iron given in 3 divided doses. The dose should be titrated up slowly to minimize adverse effects. The length of therapy depends upon the cause and severity of the iron deficiency, but approximately 4–6 months of oral iron replacement is generally required to reverse uncomplicated iron deficiency anemias. The presence of food can decrease the absorption of iron by 50%. However, taking iron with meals can reduce gastrointestinal side effects such as abdominal pain, constipation, diarrhea, nausea and vomiting. Iron absorption decreases with concomitant calcium administration and these supplements are best absorbed when taken separately.

Table IV: Elemental Content of Iron Salts

Iron Salt	% Iron	Strength	Elemental Iron
Fumarate	33%	63mg	20mg
Sulfate	20%	325mg	65mg
		300mg/5mL	60mg/5mL
Gluconate	12%	300mg	34mg

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