



# The Pharmacological Management of Osteoporosis

by Amy E. Riek, MD & Dwight A. Towler, MD

**While the benefits of osteoporosis therapy are clear – and far outweigh the risks for therapy -- the accrual of rare, individual, and time-dependent side effects are just now becoming evident.**

## Abstract

Pharmacotherapy is effective in decreasing the incidence of osteoporotic fracture, morbidity, and mortality. This benefit is pronounced in patients at highest risk for fracture: those with prior osteoporotic fracture, very low bone mineral density, or receiving chronic corticosteroid treatment. We review the best pharmacotherapeutic options currently available for treating osteoporosis.

## Introduction

Osteoporosis afflicts 10 million Americans, and another 30 million Americans have low bone mass that puts them at risk for development of osteoporosis<sup>1</sup>. The overall risk for a 50-year-old Caucasian or Asian woman to sustain an osteoporotic fracture during her lifetime is 50%. While men, African Americans, and Hispanics have lower risks, the health impact is still substantial. One-third of all hip fractures occur in men, and with our aging populace hip fracture incidence in men will eventually approach that of women<sup>1</sup>. A femoral neck or trochanteric fracture is associated with mortality of approximately 20%<sup>1</sup>. Of survivors, only one in three return to pre-fracture mobility<sup>1</sup>. Vertebral fractures deform the posture either with or without pain, and reduce musculoskeletal vitality. Ten year mortality for a woman with an incident vertebral fracture is increased two-fold, indicating that vertebral

fracture is a harbinger of frailty<sup>1</sup>.

Fortunately, effective pharmacotherapies for treatment of osteoporosis in both women and men have been developed.<sup>2</sup> Aminobisphosphonates were the first drugs unambiguously established to reduce hip and vertebral fracture, followed shortly thereafter by estrogen<sup>3</sup> and denosumab<sup>4</sup>. Raloxifene – a selective estrogen receptor modulator (SERM)– and teriparatide – an anabolic PTH fragment – both decrease vertebral fracture and non-vertebral fracture without clearly impacting hip fracture<sup>3</sup>. Here we review the diagnosis of osteoporosis and how to match the needs of the osteoporotic patient with appropriate pharmacotherapy. Osteoporosis in children and hormone replacement will not be discussed, but the reader is referred to suitable reviews<sup>3,5</sup>.

## Definitions and Diagnoses

Osteoporosis diagnostics can be complicated. The World Health Organization (WHO) defined osteoporosis as a systemic skeletal disease characterized by low bone mass with microarchitectural deterioration of bone tissue, thus increasing bone fragility and susceptibility to fracture<sup>1</sup>. For screening purposes, osteoporosis was defined by the WHO as a bone mineral density (BMD) at any site equal to or greater than 2.5 standard deviations below the fracture resistant mean peak bone mass of young adulthood.

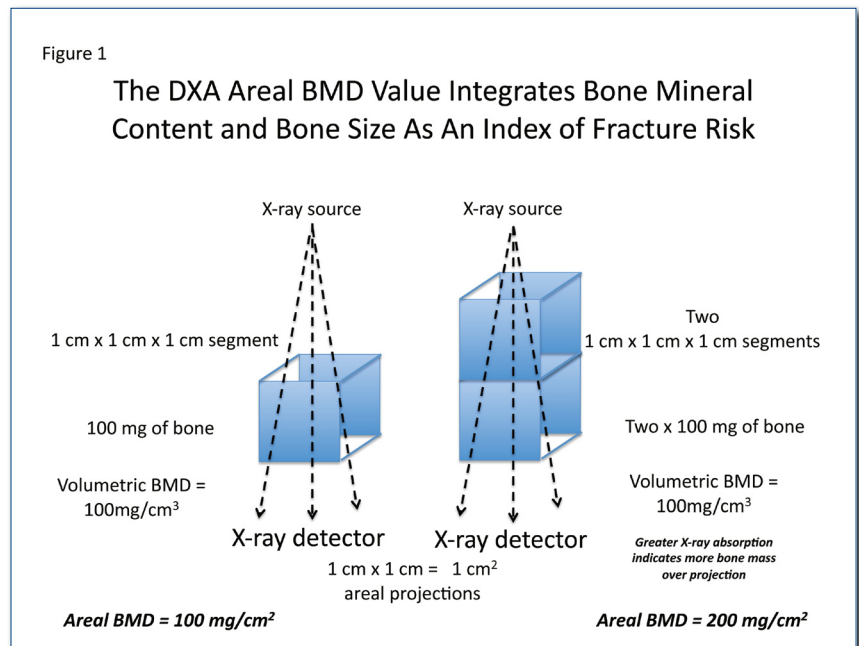


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Denoted a “T score” rather than a “Z score” because the referent population for those at risk (older individuals) is a younger cohort, the utility of the T-score  $\leq -2.5$  has revolutionized our approach to fracture prevention. Screening by dual electron X-ray absorptiometry (DXA) identifies those without fracture who are at greatest risk for future fracture<sup>6</sup>. DXA evaluation is an “areal” BMD expressed as grams of bone mass/cm<sup>2</sup>, achieved by quantitative projection of bone content in three dimensions onto the two-dimensional plane of the X-ray detector (See Figure 1).

Because larger bones have more total bone mass in all directions – including the height of bone perpendicular to the image projection plane of DXA analysis – areal BMD is greater for larger bones. Moreover, because larger bones are harder to break, the DXA value integrates bone mineral content and bone size into a single number that predicts fracture risk. A 10% reduction in BMD, or a -1 change in T score, doubles the risk for fracture<sup>7</sup>. DXA screening is recommended in women  $\geq 65$ , men  $\geq 70$ , and middle-aged adults at increased clinical risk for osteoporosis (prior fracture as an adult; family history of osteoporosis; chronic tobacco and/or corticosteroid use; low body weight) (<http://www.nof.org/professionals/clinical-guidelines>). Younger women with early menopause are also at risk. Benefits of DXA monitoring following initiation of therapy are more equivocal, but repeat DXA evaluation two years after the first screen provides sufficient time to detect a significant change ( $\sim 3\%$ ).

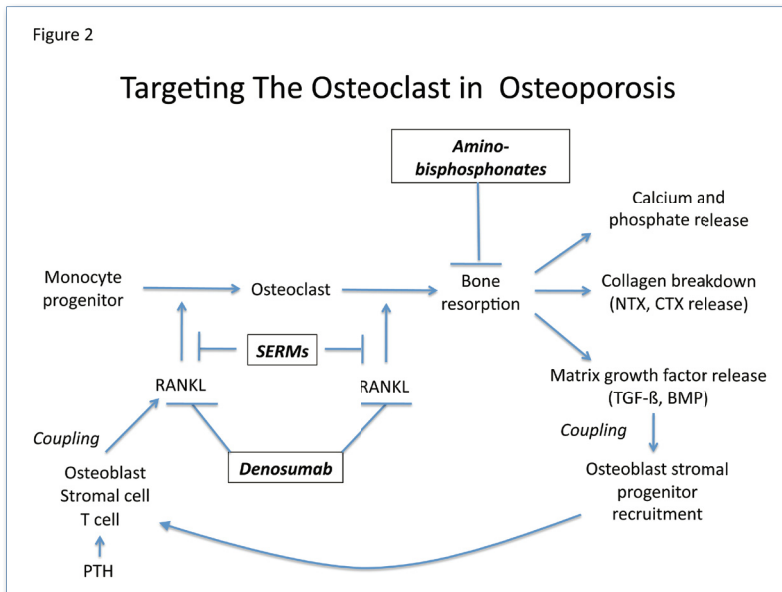
Osteoporosis was a clinical diagnosis made well before DXA analysis was available. Low-energy fragility fractures, loss of height, and vertebral deformity with or without skeletal radiolucency on X-ray were all implemented as diagnostic criteria. Because of the greater prevalence of DXA-designated osteopenia vs. osteoporosis, the majority of fractures occur in individuals with osteopenia because of greater numbers of those at risk. Thus, therapeutic decisions must incorporate other clinical features that convey fracture risk in addition to the DXA value<sup>6</sup>. For example, the most significant risk factor for future fracture is a personal history of prior fracture as an adult. Prior fracture may be asymptomatic; a 15% deformation in anterior vertebral height on lateral x-ray or  $> 2$  inch loss in maximum adult height represent fracture equivalents<sup>6</sup>. Even those individuals suffering fracture in motor vehicle accidents (MVA) are also at increased risk



for future low-impact osteoporotic fracture at any given bone mineral density<sup>8</sup>. Why might this occur? DXA provides information relevant to bone strength but not bone quality – the composite material properties that convey biomechanical toughness. Prior fracture in response to mechanical challenge brings “out of the woodwork” those individuals whose integrated bone size, bone mineral content, and bone quality convey fragility.

Recently, the WHO developed an algorithm for considering such clinical factors to calculate the 10-year risk for fracture<sup>6</sup>. The WHO Fracture Risk Assessment Tool, or FRAX, is available online at <http://www.sheffield.ac.uk/FRAX/> and as an iPhone App. Age, gender, ethnicity, geographic local, height, weight, personal and parental fracture history, presence of rheumatoid arthritis, corticosteroid and tobacco use, alcohol consumption, and femoral neck areal BMD are integrated to estimate fracture risk. The National Osteoporosis Foundation recommends treatment in patients 50 or older with (a) a history of prior osteoporotic or vertebral fracture; (b) a DXA T score  $< -2.5$  or lower at the femoral neck or spine; or (c) 10 year risk for hip fracture is  $> 3\%$  or major osteoporotic fracture is  $> 20\%$  by FRAX in those with a T score between -1.0 and -2.5<sup>9</sup> (<http://www.nof.org/professionals/clinical-guidelines>).

Potential secondary causes of osteoporosis must be addressed along with nutrition (See Table 1). The 25-hydroxyvitamin D (25-OHD) level should be  $> 30$  ng/ml; if not, ergocalciferol 100,000 IU weekly for five to six weeks followed by repeat 25-OHD evaluation is required<sup>10</sup>. Thereafter, a total of 1000 IU vitamin D3 and 1200 mg elemental calcium daily are required in most adults<sup>11</sup>.



hypocalcemia, renal insufficiency (GFR < 30 mL/min/1.73 m<sup>2</sup>), and the inability to stand or sit for 30 minutes (oral regimens). Potent IV aminobisphosphonates such as zoledronic acid are contraindicated in pregnancy, while oral compounds are classified as pregnancy category C. While children with osteogenesis imperfecta or secondary osteoporosis have been treated with bisphosphonates, this should only be implemented by a pediatric bone health specialist<sup>5</sup>. In children and pregnant women with osteoporosis, an expert in bone health should be consulted.

Complications may include gastrointestinal distress in about 10% of patients, and the rare but serious erosive esophagitis related to pill “reflux” is minimized by the above dosing

**Table 1**  
Important Contributors to Osteoporotic Fracture Risk

Vitamin D deficiency or insufficiency  
Hypercortisolism/Cushing’s syndrome and glucocorticoid therapy  
Multiple myeloma or MGUS  
Alcoholism, tobacco abuse  
Hypogonadism  
Rheumatoid Arthritis  
Chronic renal insufficiency  
Hemochromatosis, metal intoxication/  
chronic low – level cadmium exposure

Renal calcium “leak” / idiopathic hypercalciuria  
Chronic gastrointestinal disease (celiac disease, Crohn’s disease, hepatobiliary disease, short gut syndrome, lactose intolerance)  
Hyperthyroidism  
Hyperparathyroidism  
Chronic immobilization, neuromuscular disease, stroke  
Type I > Type II diabetes  
Chronic antidepressant, proton pump inhibitor, thiazolidinedione use  
Hereditary collagen disorders

**Aminobisphosphonates**

Alendronate, risedronate, ibandronate, and zoledronic acid<sup>12</sup> reduce fracture risk by 50% within the first year of therapy in both genders. These aminobisphosphonates are pyrophosphate analogs that inhibit farnesyl diphosphate synthase, an enzyme that regulates G-proteins controlling osteoclast function<sup>12</sup>. Thus, aminobisphosphonates inhibit osteoclast-mediated bone resorption in vivo (See Figure 2). Aminobisphosphonates are orally poorly bioavailable, undergo renal clearance without metabolism, and deposited in bone<sup>3</sup>. The depot-like actions at this site allow IV formulations for zoledronic acid and ibandronate to be dosed every 12 months and 3 months, respectively<sup>12</sup>. Oral treatment with aminobisphosphonates requires the medicine to be taken on an empty stomach with an 8-ounce glass of water, avoiding recumbency and other oral intake for 30 minutes. Once weekly or once monthly oral regimens has improved adherence, but gastrointestinal upset may still limit use. IV ibandronate and zoledronic acid have improved the therapeutic landscape (See Table 2).

Contraindications include drug class hypersensitivity,

recommendations<sup>3</sup>. Conflicting data address a questionable increase in risk for esophageal cancer<sup>13</sup>. This uncertain potential outcome is far outweighed by the benefits of osteoporosis pharmacotherapy, which decreases mortality and morbidity<sup>2</sup>. Oral aminobisphosphonates should not be used in patients with Barrett’s esophagus or gastroesophageal disease<sup>13</sup>. With IV bisphosphonates, a “flu-like” acute phase response may occur in 10% of patients, and pretreatment with 650 mg PO acetaminophen is helpful<sup>12</sup>. Renal failure is a reportable complication of IV aminobisphosphonates<sup>14</sup>, and since the drugs cleared by the kidney, serum creatinine must be checked prior to each yearly dose of zoledronic acid or when pamidronate is given. For unclear reasons, this rare association is not seen with ibandronate. Once a GFR ≥ 30 ml/min as estimated from the initial serum creatinine has been established, repeated serum creatinine values are not currently required when dosing with IV ibandronate<sup>14</sup>.

A more concerning complication is osteonecrosis of the jaw<sup>15</sup>, which may be observed in 1/10,000 to 1/100,000 patients treated, related to concomitant oral bone trauma and infection. Initiation of aminobisphosphonate therapy should

**Table 2**  
**Typical Pharmacotherapeutic Dosing Regimens For Treatment of Osteoporosis**

Alendronate	10 mg PO q Day, 70 mg PO q Week
Risedronate	5 mg PO q Day, 35 mg PO q Week, 150 mg PO q Month
Ibandronate	150 mg PO q Month, 3 mg IV q 3 Months (15-30 second infusion)
Zoledronic acid	5 mg IV q Year (15 minute infusion) (5 mg IV q 2 Years for osteoporosis prevention)
Raloxifene	60 mg PO q Day
Denosumab	60 mg SC q 6 Months
Teriparatide	20 micrograms SC q Day, maximum of 24 months

be postponed until elective oral surgery is performed, and oral surgery should be avoided when on these drugs<sup>15</sup>. Cumulative IV aminobisphosphonate administration conveys increased risk in the setting of malignancy, particularly multiple myeloma. A recent position statement provides details<sup>15</sup>.

Recently, an uncommon subtrochanteric fracture type has been potentially linked with aminobisphosphonate therapy, denoted “atypical femoral fracture.” While subtrochanteric fractures represent approximately 7% of all hip fractures, few exhibit the signs of brittle bone failure<sup>16</sup>. This atypical clinical scenario describes a non-traumatic, non-comminuted fracture of the subtrochanteric or diaphyseal femur. A history of femur or groin pain may precede an atypical fracture for months, with a periosteal reaction resembling a “stress fracture” or “dreaded black line” radiolucency on femoral radiographs. The explanation may relate to accumulation of “microtrauma” in at-risk individuals with abnormal bone quality. Many with atypical fracture will have other health issues, including diabetes or chronic glucocorticoid treatment.

Of note, ~6% of atypical femur fractures are observed in patients never treated with aminobisphosphonates. In addition, the incidence of femoral neck, trochanteric, and intertrochanteric hip fractures has declined following approval of aminobisphosphonate therapy, while that of subtrochanteric and femoral shaft fractures has not changed<sup>16</sup>. Thus, the pathobiology of the atypical femur fracture may be distinct from that of typical femur fractures -- and may not respond to aminobisphosphonate therapy in those at high risk for any type of femur fracture. If truly a complication of therapy, perhaps 1 atypical fracture arises for each 100 “routine” femur fractures prevented by aminobisphosphonate therapy<sup>16</sup>. While causality has not been established, increased awareness of this rare potential complication is appropriate, and FDA implemented a labeling change for these drugs in October 2010. In patients who lack severe osteoporosis or do not have severely reduced BMD ( $T \leq -3.5$ ), a drug holiday may be considered after five years of therapy. In previously compliant patients, a drug holiday of < 2 years appears acceptable and is not associated with significantly increased fracture risk<sup>16</sup>. In those at significantly increased risk for future fracture (prior osteoporotic fracture,  $T \text{ score} \leq -3.5$ ), benefits of

continued therapy clearly outweigh risks. In patients on aminobisphosphonates with thigh or groin pain, plain radiography, MRI, or scintigraphy should be performed<sup>16</sup>. If periosteal reaction or “stress fracture” is apparent, therapy should be stopped and orthopedic nailing offered<sup>16</sup>. If an

atypical fracture occurs, therapy should be stopped; if fracture healing after orthopedic stabilization is not evident in six to eight weeks, teriparatide (below) therapy should be considered<sup>17</sup>.

### Selective Estrogen Receptor Modulators

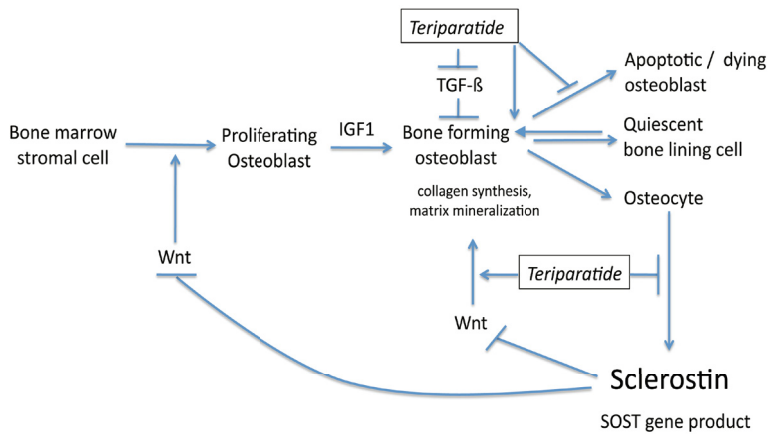
Selective Estrogen Receptor Modulators (SERM) are ligands for estrogen receptors that induce these receptors to adopt unique conformations that differentially recruit transcriptional modulators. SERMs can exert agonist activities in one target tissue, but antagonist activities in another<sup>18</sup>. Currently, raloxifene is the only SERM approved for treatment of osteoporosis<sup>3</sup>. Raloxifene inhibits the formation and activation of the bone-resorbing osteoclast by mimicking estrogen’s suppression of RANKL signaling within the osteoclast. By contrast, raloxifene inhibits estrogen’s actions in the breast, and significantly reduces the risk for breast cancer. It does not increase risk for uterine malignancy. Unlike estrogen/progestin combinations, raloxifene does not increase the risk of cardiovascular disease<sup>19</sup>. Like estrogen, raloxifene does increase risk for venous thromboembolism, including deep vein thrombosis and fatal stroke. Hot flashes and leg cramps can occur. Contraindications include a history of thromboembolism or pregnancy, and raloxifene should not be used in children or in men outside of a clinical trial. Like aminobisphosphonates, raloxifene decreases the risk for vertebral and non-vertebral fractures. For unclear reasons raloxifene has not been demonstrated to decrease the risk for hip fracture<sup>3</sup>. Nevertheless, in post-menopausal women with osteoporosis, particularly those with increased breast cancer risk, raloxifene represents an important therapeutic option for osteoporosis treatment<sup>19</sup>.

### Denosumab

The TNF superfamily member RANKL is absolutely essential for the development of osteoclasts from the monocyte lineage, and maintains osteoclast viability and bone-resorbing functions (See Figure 2). Denosumab is a humanized monoclonal antibody that binds to and inhibits RANKL function and is approved for treatment of

Figure 3

Targeting The Osteoblast in Osteoporosis



for treating osteoporosis is teriparatide<sup>22</sup>, a synthetic peptide that mimics the action of PTH to maintain osteoblast longevity and bone synthetic function<sup>23</sup>. The mechanisms of teriparatide anabolism involve polypeptide hormones known as Wnts that promote bone formation by signaling through receptors known as LRP5 and LRP6. Osteocytes, the mature form of osteoblasts, control osteoblast formation by producing sclerostin, an inhibitor of Wnt-LRP5/6 signaling. Teriparatide downregulates sclerostin, thus interrupting the negative feedback mechanism whereby osteocytes control the formation of less mature but more synthetically active osteoblasts<sup>23</sup>. These same actions likely contribute to recruitment / reactivation of previously quiescent bone lining cells to adopt the synthetic osteoblast fate. Furthermore,

osteoporosis. It reduces bone resorption, increases BMD, and reduces fracture risk – mimicking the role of an endogenous RANKL inhibitor called osteoprotegerin<sup>20</sup>. Denosumab can be dosed every six months, and is efficacious in men and women (See Table 2). Adjustment for renal insufficiency is not required. However, it should not be used indiscriminately in the setting of reduced renal function<sup>21</sup>. Because bone formation and bone resorption are generally very tightly coupled via osteoclast-mediated matrix turnover (See Figure 3), reductions in osteoclast formation with denosumab simultaneously decrease osteoblast-mediated bone formation. This effect was so significant that in 36% of patients, tetracycline labeling of bone surface, an index for bone formation, was completely absent<sup>21</sup>. Thus, the FDA indication for use of denosumab in osteoporosis is limited to those with severe disease and those that have failed other therapies. Back pain (30%), skin rashes (10%), lower extremity skin infections (0.4%) and pancreatitis (0.2%) may occur with denosumab therapy<sup>4</sup>.

As for any of the potent antiresorptive therapies, contraindications include hypocalcemia and drug hypersensitivity. Osteonecrosis of the jaw has been reported<sup>15</sup>. Safety has not been established for treatment of children, and the drug is currently listed as pregnancy category C. Because breast development requires RANKL signaling in utero, denosumab should not be administered to pregnant individuals without input from a bone expert.

**Teriparatide**

The only currently available anabolic agent in America

teriparatide inhibits osteoblast apoptosis, thus prolonging the synthetic life-span of this bone forming cell (See Figure 3)<sup>23</sup>. Novel neutralizing antibodies are being developed that target/inhibit sclerostin activity as anabolic agents<sup>23</sup>.

Teriparatide is administered as a 20 µg daily subcutaneous injection (See Table 2). Improvements as great as 15% have been observed in the vertebral column in response to teriparatide within a six-month period. Side effects are few, and include transient flushing, mild nausea, and transient hypercalcemia. The drug best administered at night just prior to bedtime, which minimizes perception of nausea and orthostasis. Teriparatide carries a “black box” label because lifetime dosing of rats from birth to death over a two-year period increases the risk for osteosarcoma<sup>22</sup>. This has not been observed in adult humans, and is thought to arise in part due to the continuously growing skeleton of the rat (epiphyses never close). Thus, children or young adults with open epiphyses indicative of skeletal growth should not be treated with teriparatide. Moreover, adult patients at risk for osteosarcoma – those with history of radiation therapy, Paget’s disease, a prior history of osteosarcoma, or an unexplained elevated serum alkaline phosphatase -- should not be treated with teriparatide. Therapy should be limited to a total of 24 months of exposure. Teriparatide use in pregnancy has not been well-studied, and this agent is pregnancy category C. Renal impairment (GFR < 30 cc/min) prolongs half-life by 75%, and may require dosing interval adjustment if hypercalcemia is noted > 12 hours after dosing once at steady state.

Glucocorticoid-induced osteoporosis (GIO) deserves

special but brief consideration. The skeleton is exquisitely sensitive to the negative impact of glucocorticoids. Chronic (> 3 month) daily doses as low as 2.5 – 5.0 mg prednisolone equivalents double the risk for fracture<sup>24</sup>. Because glucocorticoids inhibit collagen synthesis in the bone remodeling unit – a feature exacerbated by aminobisphosphonates -- teriparatide outperforms aminobisphosphonates in restoration of vertebral bone mass and vertebral fracture prevention<sup>25</sup>. With severe GIO, teriparatide is preferred as the initial therapy without contraindication. However, aminobisphosphonates clearly reduce fracture risk in GIO. An aminobisphosphonate should be implemented immediately after cessation of teriparatide for GIO treatment, or implemented very early on when it is known that long-term (> 3 month) glucocorticoid therapy will be needed<sup>24</sup>.

## Conclusions

Tremendous innovations in the treatment of osteoporosis have been achieved over the past two decades. However, with the advent of new therapies, new questions arise. While the benefits of therapy are clear – and far outweigh the risks for therapy for the vast majority of patients -- the accrual of rare, individual and time-dependent side effects are just now becoming evident. Although sequential anti-resorptive/anabolic pharmacotherapeutic cycles make biological sense, the role of any combination therapy in fracture reduction has not been established. Furthermore, treatment of osteoporosis in children and in the settings of malignancy, pregnancy, and chronic renal insufficiency present real concerns and vexing problems. Thankfully, novel therapies are on the horizon. The next decade holds even greater promise for delivering better care to our patients with osteoporosis.

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