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REVIEW

Management of severe osteoporosis

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ABSTRACT

Introduction: Severe osteoporosis represents a disease of high mortality and morbidity. Recognition of what constitutes and causes severe osteoporosis and aggressive intervention with pharmacological agents with evidence to reduce fracture risk are outlined in this review.

Areas Covered: This review is a blend of evidence obtained from literature searches from PubMed and The National Library of Medicine (USA), clinical experience and the author's opinions. The review covers the recognition of what constitutes severe osteoporosis, and provides up-to-date references on this sub-set of high risk patients.

Expert Opinion: Severe osteoporosis can be classified by using measurements of bone densitometry, identification of prevalent fractures, and, knowledge of what additional risk factors contribute to high fracture risk. Once recognized, the potential consequences of severe osteoporosis can be mitigated by appropriate selection of pharmacological therapies and modalities to reduce the risk for falling.

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1. Introduction

Osteoporosis is both an underdiagnosed and undertreated disease.[1,2] The annual costs in the US of caring for osteoporotic-related fractures parallel or exceed the annual costs of caring for myocardial infarction, breast cancer and/or cerebrovascular accident [3] (Figure 1). In a large Manitoba, Canada study, the ratio of the total annual costs of either prevalent or incident osteoporotic-related fractures exceeds the same ratio calculation for many other serious chronic diseases.[4] Furthermore, a study recently published by Oden and colleagues demonstrated that individuals with a high probability of osteoporotic fractures compromise a very significant disease burden to society and that this burden is set to increase markedly in the future.[5] Equally as disturbing is the data showing that the percent of patients receiving a registered therapy for osteoporosis, even after sustaining a hip fracture, has declined from 41% in 2001 to 21% in 2010 (Figure 2).[6] Finally, a major contributor to the loss of independence in subjects 70 years of age and older are falls at home and fragility fractures.[7]

There are many opinions regarding our decline in the awareness and treatment of osteoporosis. The international movement to develop Fracture Liaison Services (FLS), spearheaded internationally by the International Osteoporosis Foundation and in the US by the National Bone Health Alliance (NBHA), is a multidisciplinary effort to reduce the incidence of the second osteoporotic fracture.[8,9] The FLS relies on developing mechanisms and pathways to identify patients admitted to hospitals, emergency rooms or urgent care clinics with an osteoporotic fracture and direct those patients into a well-developed osteoporotic management and treatment plan.

The greatest risk factor for developing a second osteoporotic fracture is the occurrence of the first osteoporotic fracture.[10–14] There is broad international agreement that a low trauma fracture after the age of 50 years of age in postmenopausal women or men merits, first, an evaluation for secondary causes of osteoporosis; and, second, pharmacological therapy for osteoporosis in addition to adequate vitamin D and calcium.[15–18] Justifications for these recommendations are based on the population data previously cited showing the high risk of a second fracture following the first fracture in untreated subjects and the clinical trial data providing evidence that fracture reduction with pharmacological agents for osteoporosis reduces fractures above and beyond that reduction in fracture seen with vitamin D and calcium alone.[19–22] This article will define in the author's opinion what constitutes severe osteoporosis and what this author's opinion is regarding approaches to management of the high-risk patient. Literature searches were completed from PubMed, Medscape and National Institutes of Health reference databases.

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Article highlights

- Osteoporosis is largely underdiagnosed and undertreated.
- The annual costs of osteoporotic fractures exceed the annual costs of caring for myocardial infarction, cerebrovascular accidents and breast cancer.
- The underdiagnoses of osteoporosis are largely due to the declining utilization of bone mineral density, the underdetection of vertebral compression fractures and the underappreciation that a low-trauma fracture in women or men after the age of 50 years is a strong risk factor for future fragility fractures in untreated people.
- Severe osteoporosis constitutes a subgroup where the fracture risk is extraordinarily high.
- There are a number of registered pharmacological choices that can be considered in severe osteoporosis.
- New therapies in development will offer an even wider variety of therapies for severe osteoporosis with new mechanisms of action.

This box summarizes key points contained in the article.

2. Severe osteoporosis

The word severe in *Webster's* dictionary can mean 'critical or grave'. This term is appropriate for a certain magnitude of severity in bone strength, which is comprised of bone mineral density (BMD) and/or bone quality. While clinicians can measure BMD by dual-energy X-ray absorptiometry (DXA), we lack the clinical tools to quantitate bone quality. Bone quality can be measured at the current time by a number of research methods (high-resolution central or peripheral quantitative computerized tomography, micro-magnetic imaging resolution).[23,24] Recently, an office-based methodology that is based on a gray scale derived from the spine DXA imaging, trabecular bone score (TBS), has been approved by international registration agencies and offers a point-of-care means to quantitate

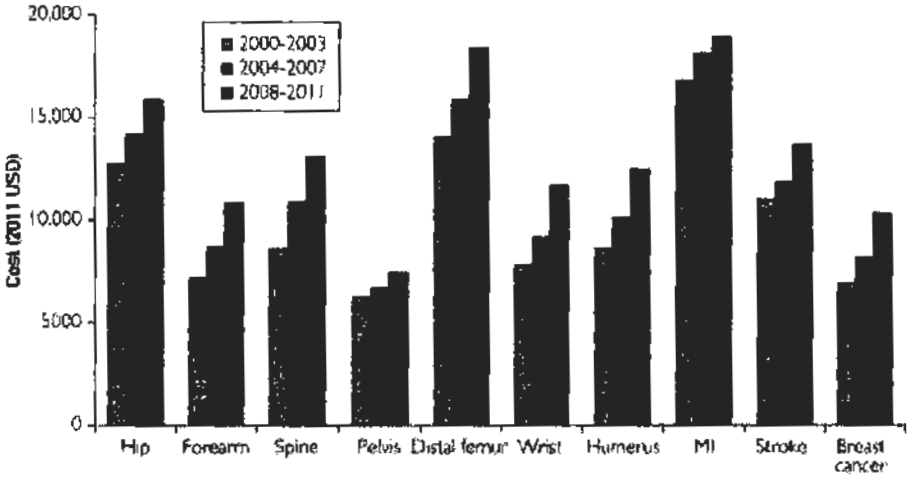

Figure 1. The annual costs of osteoporotic fractures as compared to the annual costs of three other major disease states. Reproduced with permission from [3].

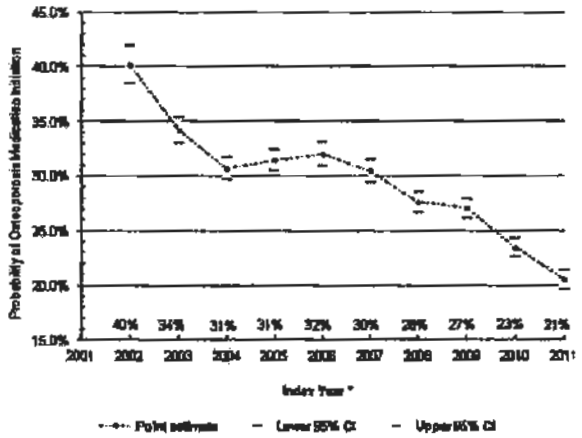

Figure 2. The declining annual probability of treatment with an osteoporosis agent after hospital discharge for hip fractures. Reproduced with permission from [6].

a portion of bone quality.[25–27] TBS values increase fracture risk prediction above and beyond that risk calculated by DXA alone and have been added to the World Health Organization's (WHO) risk calculator, Fracture Risk Assessment Model (FRAX™) (Figure 3). [28,29]

Severe osteoporosis constitutes a wide spectrum of skeletal disorders that all carry the common term, osteoporosis. The categories of severe osteoporosis should be made distinct from osteoporosis in general due to the very high risk for fracture high mortality and morbidity that accompanies severe osteoporosis.[30–32] There are a broad range of conditions that might be associated with severe osteoporosis:

(1) Severe postmenopausal osteoporosis (PMO) or severe male osteoporosis.[33,34]

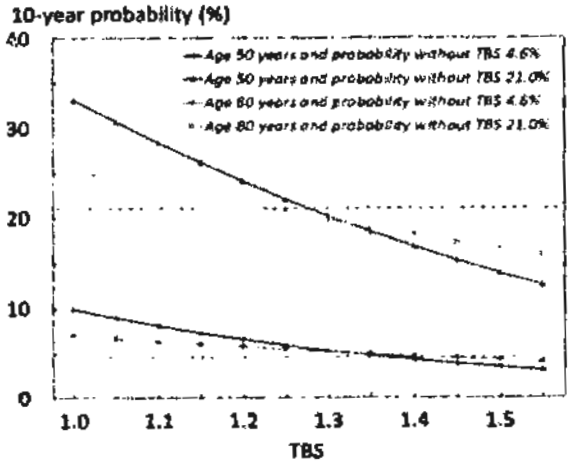

Figure 3. The predictive value of trabecular bone score (TBS) used in the FRAX™ calculator. Reproduced with permission from [28].

(2) Glucocorticoid-induced osteoporosis (GIOP).[35–38]
(3) Osteoporosis associated with systemic diseases that may also be associated with low bone formation and turnover such as diabetes mellitus. chronic kidney disease, multiple myeloma and monoclonal gammopathy of undetermined significance. Each of these conditions may have low bone formation associated with elevation in the serum of inhibitors of osteoblast function.[39–45] These diseases are also associated with poor bone quality.
(4) Osteoporosis associated with systemic diseases that are also associated with high bone turnover: for example, severe primary hyperparathyroidism; immobilization (e.g. quadriplegia).[46–50] Osteoporosis associated with systemic diseases associated with frailty and a high risk for fractures from falls: for example, Parkinson's disease, multiple sclerosis, polio, amyotrophic lateral sclerosis and diseases associated with marked sarcopenia (deficiency of muscle mass and strength), particularly malabsorption syndromes, age-related sarcopenia and myopathies of diffuse etiologies.[51–55]

3. Severe postmenopausal and male osteoporosis

There are certain risk factors that place a patient of either gender into the severe category regardless of underlying mechanisms of osteoporosis disease:

(1) A prior low trauma fracture after the age of 50 years
(2) Very low BMD (or T-scores) in older patients
(3) A very high FRAX™ score

The presence of a low trauma fracture in women or men past the age of 50 years is the greatest risk factor for a second fracture in untreated individuals.[10,56,57] Fractures of the hands, feet and skull are currently not considered osteoporotic fractures since they do not predict future fracture risk in untreated patients. One exception before discounting metatarsal fractures: metatarsal fractures may suggest the presence of adult hypophosphatasia (HPP), which is becoming increasingly diagnosed due to greater awareness of examining laboratory reports for low or low-normal serum total alkaline phosphatase.[58] The underlying pathophysiology of HPP is a decrease in osteoblast production of alkaline phosphatase and the adult patients can present with a singular skeletal manifestation (e.g. metatarsal fractures, lower extremity large bone (mid-shaft femur) fractures and/or poor dentation). The total serum alkaline phosphatase is often <40 IU/l in these patients, and, if suspected, can be followed up by looking for an elevated serum phosphorus and elevated pyridoxal phosphate (vitamin B6).

The most common and often unrecognized low trauma fracture that conveys a high risk for future fracture is vertebral compression fracture (VCF). The reality is that most VCFs are missed by clinicians.[59–61] The reasons behind this underdiagnosis and undertreatment of VCF include

(1) A lack of awareness that the majority of VCF are asymptomatic. Clinicians are looking for pain as the clue to the possible presence of a VCF.[62–64]
(2) The underappreciation that even morphometric (radiological detected) VCF conveys a high risk not only for more VCF but also for other further fractures at other skeletal sites.[65–69]
(3) That VCFs may exist even though the *T*-score is normal.[70–72]
(4) That simple height measurements are often not done in physician offices, or, rather, if done, are often done on inaccurate scales (e.g. the 'metal rod') rather than the wall-mounted and inexpensive stadiometer.[33,73]
(5) Height loss should be the alerting signal that a VCF may be present. Both the Canadian practice guidelines and the International Society for Clinical Densitometry have established specific prevalent or interval height loss values that have a high probability of detecting either a prevalent or incident VCF.[74,75]
(6) The underreporting of the presence of VCF by radiologists examining routine PA and lateral chest X-ray.[76–79]

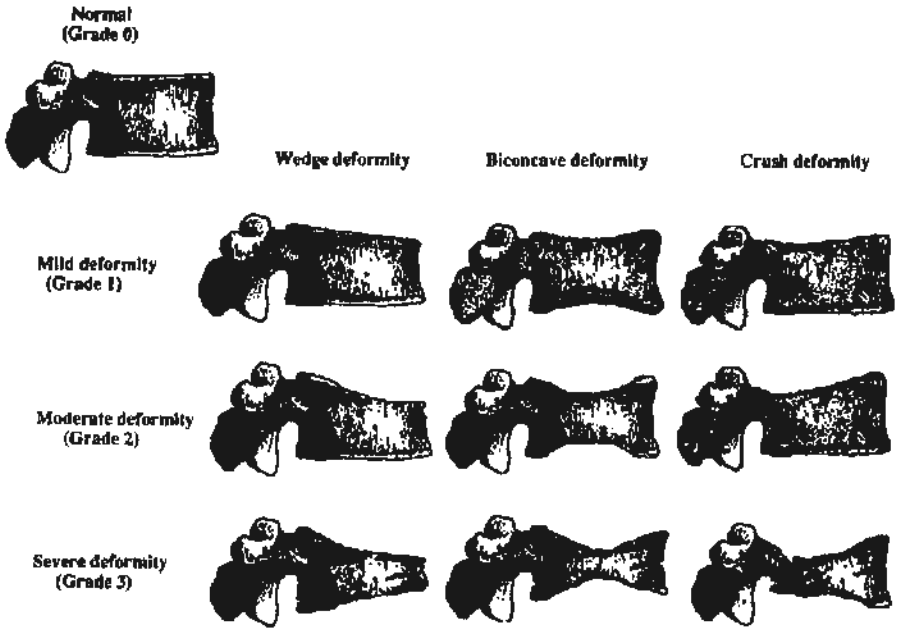

Figure 4. The semi-quantitative classification of morphometric vertebral compression fractures according to the Genant method. (Reproduced with permission from [82].

When an asymptomatic VCF is detected, even though the date of when the VCF occurred is unknown, there is a high risk for global fracture risk in untreated patients. Vertebral compression fractures are graded by severity according to the degree of vertebral compression [80–82] (Figure 4). The greater the severity of compression or the greater the number of prevalent VCF, the greater the risk for future fractures.[13,83–85]

While low BMD is a strong predictor for future fracture risk, fracture risk as a function of low BMD is highly age dependent [86] (Figure 5). For every decade above the age of 50 years, future fracture risk approximately doubles by decade at the same BMD. While more elderly patients may fall more, and this greater risk for falling is certainly a partial reason for the greater fracture risk as age increases, the relationship between increased age and fracture risk is also independent of falls. Bone strength, a composite of BMD and bone quality, is poorer in older patients as compared to younger patients. Practically, management recommendations for osteoporosis therapy should be different in a patient at 50 years of age with a *T*-score of −2.5 as compared to a patient of 80 years with the same *T*-score of −2.5. The fracture risk is ~6× greater in the 80 year old at the same BMD.

The WHO FRAX™ is a health-economic model to assess the risk for a major osteoporotic fracture or hip fracture over a 10-year period in untreated postmenopausal women and older men.[86] Based on a robust

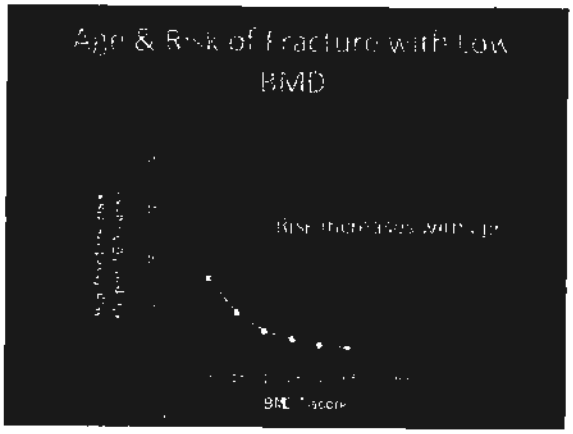

Figure 5. The effect of age on the risk of hip fractures. Reproduced with permission from [86]. BMD, bone mineral density.

data set, FRAX™ has provided a validated model to help guide clinicians as to which patients may need pharmacological therapy to reduce the risk of future fracture. While the provision of 20% for major fracture or 3% for hip fracture to consider treatment is based on a cost-effective analysis using the annual cost of alendronate at the time FRAX™ was developed, it is also known that broad clinical judgment must be incorporated along with FRAX™ to make treatment decisions.[87–89] For example, FRAX™ did not capture fall rates or doses of glucocorticoids into the model; nor a number of additional diseases that may contribute to greater skeletal fragility, such as chronic kidney failure or diabetes

mellitus. Hence, while prevalent fracture, low BMD and increased age constitute the most robust three risk factors for future fracture risk, clinicians must incorporate a wide range of risk factors, some captured and some not captured in FRAX™ to make treatment decisions. The National Osteoporosis Foundation's Clinician's Guide for the management of osteoporosis and the European guidance for the diagnosis and management of osteoporosis in postmenopausal women also provide evidence-based as well as opinion-based recommendations for initiating pharmacological therapy.[15,16,90] One of the hindrances to physician management and decisions to initiate therapy in today's changing health-economic environment are the restrictions imposed on physician judgment by insurance company 'phantom' physicians or administrators who have no accountability for the patient's health. Payers often base their decisions on simple economic numbers such as in the FRAX™ model without knowledge of the broad clinical issues that modulate individual patient management. Expanding the definition of osteoporosis by using the risk for fracture as a threshold and/or the expansion of diagnostic subcategories for the diagnosis by a new International Classification of Disease 10 has been suggested.[90] Whether or not these expanded criteria simplify diagnosis and management or make it more complex will be measured by quantitating whether these newer approached criteria increase the proportion of patients treated. The patient and her/his healthcare management lies in the hands of the physician who not only has medical, moral and legal accountability for their patient's care, but also the broad knowledge of the patient's clinical situations.

4. Glucocorticoid-induced osteoporosis

Glucocorticoids inhibit osteoblast activity.[36,91].In that regard, a major effect of glucocorticoids on fracture risk is a decrease in bone formation. The effect of glucocorticoids on bone strength is both dose and duration related. While not all patients on glucocorticoids have severe osteoporosis unless they have fractured, the severity increases with the dose and/or duration of glucocorticoid use. Low-dose prednisone, even at a dose of 2.5 mg/day, will convey a great risk for fractures than no dose and not as great as 5.0 mg/day. Even higher (>15 mg/day) sustained doses of glucocorticoids may induce fractures, particularly multiple VCF within a short (months) period of time.[91,92]

While low BMD is a strong predictor of fracture risk in PMO and male osteoporosis, BMD is not as strong a predictor for fracture in GIOP. In part, this is related to the fact that glucocorticoids inhibit osteoblast function and bone formation. Hence, impaired bone quality rather than low BMD is a major component of the fracture risk in GIOP. While patients who have already sustained a GIOP-related fracture or those with very low BMD (*T*-scores of −2.5 and lower) and older age certainly constitute a high-risk group, the challenge for clinicians is in deciding what patients may need pharmacological therapy who are younger, have not fractured and have higher BMD that are committed to chronic glucocorticoid therapy. Risk factors are not as predictive for future fracture risk in GIOP as they are in PMO.[93] Certainly the higher the dose of glucocorticoid and the longer the duration of use, the stronger are the considerations for the timing of the initiation of therapy for GIOP. Like all guidelines, both European US guidelines recognize the role that broad clinical judgment plays in ultimate management decisions.[94]

5. Other categories of severe osteoporosis

The other categories representing severe osteoporosis listed in Section 1 have been previously dealt with in individual peer-reviewed publications. The use of specific pharmacological agents for any specific condition will be included in the choices of pharmacological agents in the remainder of this paper.

6. Treatment of severe osteoporosis

The list of Food and Drug Administration (FDA) and European Medicine Agency-approved pharmacological agents for the treatment of PMO are shown in Table 1. In general, pharmacological agents are divided into drugs that inhibit bone resorption (antiresorptive) and drugs that stimulate bone formation (anabolic).[95–99] To date, there are no published data comparing the efficacy between or among these agents on the most important outcome-fracture risk reduction. While there are comparative studies examining important surrogate markers of bone strength (BMD and/or bone turnover

Table 1. The currently available pharmacological therapies for PMO.

Osteoporosis treatment options—2015
Antiremodeling agents (inhibit bone turnover)
• Bisphosphonates (oral and intravenous)
• Estrogen agonists/ antagonist (raloxifene)
• RANK-Ligand inhibitor (denosumab)
Bone activating agent (stimulates formation and resorption)
• Parathyroid hormone (1-34) (teriparatide)
• Parathyroid hormone (1–84) (not available in the US)
Other (no effect on bone turnover)
• Strontium ranelate (not available in the US)

markers (BTMs) between or among agents that have been published, suggesting differences between or among pharmacological agents), it is unknown whether these differences in BMD or BTM translate into differences in fracture risk as compared to placebo since the criteria for registration are fracture end point.[99–102].

Opinions about what is 'first-line' versus 'second-line' therapies, the terminology created by payers and/or professional organization practice guidelines, are based on a combination of efficacy/safety and costs. As pharmacological agents become 'generic' and costs for therapies decline, it is logical for payers to prefer a generic agent. Generic agents in the osteoporosis field do not require the same stringent evidence for efficacy for registration as is required for the initial registration of the branded drug (e.g. fracture risk reduction). The generics only have to show that as compared to the original registered agent the BMD increases in a noninferiority manner to the same degree as the branded formulation.[102] While this nonfracture end point seems acceptable, it is important to recognize that due to the nature of the very poor absorption of oral bisphosphonates [103,104] patients with gastrointestinal diseases that may affect bisphosphonate absorption such as celiac disease, malabsorption syndromes, small bowel resections and gastric bypass differ from the subjects in clinical trials. For this reason alone, monitoring the biological effect of oral bisphosphonates on bone metabolism is important.[44,105,106]

Measuring serial BMD and BTM is one way of gaining some assurance that the oral generic bisphosphonate, the most widely prescribed therapy for osteoporosis, is 'working'. Increases in BMD or declines in BTM with pharmacological therapy using antiresorptive agents are associated with reductions in fracture risk,[107–109] and increases in bone formation (osteoblast activity markers) with teriparatide are associated with improvements in BMD and bone microarchitecture.

The selective estrogen receptor modulators (SERMs) have evidence for reduction in vertebral fracture but not for nonvertebral fractures.[110] Certainly in patients with severe osteoporosis and a high risk for nonvertebral fractures a SERM should not be a viable treatment option.

While the oral bisphosphonates, alendronate, risedronate and ibandronate, are all effective and worthy, and have variable evidence for either reduction in vertebral, nonvertebral and/or hip fracture risk, they may have compliance issues as well as gastrointestinal tolerability issues that mitigate their effectiveness. Ibandronate is also not registered for the reduction in nonvertebral fractures.[111]

When the physician has concerns about compliance, absorption, tolerability or effectiveness, the administration of a parenteral therapy for osteoporosis is a viable option. Parenteral therapies guarantee that the delivery of the drug to the bone site includes intravenous bisphosphonates (zoledronic acid or ibandronate), subcutaneous administration of denosumab and the anabolic agent, teriparatide. Each agent has evidence for efficacy in reducing the risk of fractures and different mechanisms of action (MOA) for strengthening bone.[112–115] On examining individual clinical trial data, intravenous zoledronic acid and denosumab have the most robust evidence for reduction in all fractures: vertebral, nonvertebral including hip fractures.[116,117]

7. Pharmacological choices in severe osteoporosis

While all of the pharmacological agents have efficacy for fracture risk reduction, there are circumstances where the physician believes it is important to intervene in a severe situation where the risk is very high. These situations would include

(1) A recent (<12 months) fracture
(2) Fractures occurring while already receiving an osteoporotic agent
(3) Fractures that have a 'cascade' pattern, for example, recurrent VCFs
(4) Fractures occurring in the setting of high-dose glucocorticoid use

Recent fractures or cascade fracture events require immediate treatment. Both situations are very serious and can be life-threatening since they represent the extremes of risk. The terrible cascade vertebral fracture clinical situation is unusual but is associated with tremendous and rapid loss of height, pulmonary function, pain and a very high morbidity and mortality.[34,69,118,119] For any acute fracture, the risk for the second fracture is greatest in the first 12 months following a fracture.[120,121]

Fractures occurring while on a previous osteoporotic (usually an oral bisphosphonate) are common. In part, this observation is due to the fact that no pharmacological agent abolishes fracture risk—they reduce risk. Second, issues with compliance are prevalent, and there are situations where compliance and bioavailability of the bisphosphonate are insured yet the patient does not respond. While 'nonresponse' may be unusual, there are reversible factors that could mitigate a nonresponse such as vitamin D deficiency or celiac disease. Since oral bisphosphonate blood levels cannot be measured in clinical practice, the physician must use serial BMD and BTM to assess biological effects of the drug. While a decline in BMD beyond the least significant

change (LSC) of the precision of DXA is unacceptable, a stable or increasing BMD is acceptable since both are associated with fracture risk reduction. Likewise, for antiresorptive agents, a decline in BTMs beyond their LSC is also an indicator of response.[122] Though the bone resorption marker, serum collagen-crosslink, C-telopeptide (CTX), declines sooner than serum bone formation markers (bone-specific alkaline phosphatase, osteocalcin and pro-peptide type I collagen (PINP), all are indicators of response. Bone formation markers decline with antiresorptive therapies since the osteoclast–osteoblast cells are coupled in their activity, for example, a decline (or an increase) in the activity of one cell line will be followed by a directional change in the other cell line. The preferred marker by the American Association of Clinical Chemistry and the NBHA for bone resorption applications is the CTX, and the preferred formation marker is PINP.[123,124] While serum CTX must be drawn fasting before 10 AM, the PINP can be drawn at any time of the day.

8. Specific osteoporosis pharmacological agents for severe osteoporosis

All of the registered osteoporosis agents are effective to reduce the risk for fracture. Since there are no head-to-head comparative fracture studies to demonstrate superiority of any one agent over another, there are reasons that merit strong consideration for choosing the following agents as first-line therapies, not requiring that the patient 'fail' the most widely prescribed osteoporosis agent worldwide—oral bisphosphonates. These 'first-line' choices in my opinion are recommended according to the individual patient clinical situation, and the knowledge that achieving a rapid onset of action on bone may be a priority in severe osteoporosis.

9. Intravenous zoledronic acid and intravenous ibandronate

Assuring that a bisphosphonate is delivered to bone seems, clinically, to be a desirable goal in the patient population described as having severe osteoporosis. In these more severe patients, halting the cascade of vertebral fractures or reducing the risk of a second nonvertebral fracture in the immediate period following the first fracture is a desirable goal. Oral bisphosphonates have been shown to have a rapid onset of pharmacological effect to reduce VCF within 6 months.[125] If absorbability is uncertain and when a physician desires to guarantee that the bisphosphonate is being delivered to bone, an intravenous route of administration is the most confident means to guarantee this skeletal delivery. There are no head-to-head studies comparing the biological effects of oral as opposed to intravenous bisphosphonates. Yet with the knowledge that under the best circumstances of compliance and proper dosing instructions that 0.6% of an oral bisphosphonate is absorbed, achieving a secure and rapid delivery to the bone site is a desirable goal.[126–128]

Both intravenous zoledronic acid (5 mg/year) and intravenous ibandronate (3 mg every three months) achieve this end. While intravenous (as well as oral) bisphosphonates have either FDA contraindications or warnings not to administer for patients were more severe reductions in renal function (e.g. glomerular filtration rates (GFRs) < 35 ml/min), it seems ibandronate may have less of a risk for renal toxicity than zoledronic acid. It has been suggested from broad clinical experience that if one is concerned at all about renal function, slowing the infusion rate down with zoledronic acid to 30 or 60 min from the FDA label of 15 min may offer less renal toxicity.

In a prospective study, we did show that every 3-month intravenous ibandronate 'push' via a 5 min slower drip showed no differences in changes in GFR, even in diabetics with marginal GFR to begin with [129]. There is more robust fracture data with zoledronic acid than ibandronate from individual clinical trials and ibandronate is not registered for the reduction of nonvertebral fractures. In addition, extension data suggest that six annual doses of zoledronic acid may have additional morphometric vertebral fracture benefit in severe, specific osteoporotic populations (e.g. femoral neck *T*-score of −2.5 and with prevalent VCF).[130] In this regard, the extension of alendronate clinical trials, the Fosamax long-term extension (FLEX) trial, also showed some additional benefit, from the initial data analysis, for continuing oral alendronate beyond 5 years in subjects with a prevalent VCF or 'very low' BMD.[131] However, in the FLEX trial, interaction table (Table 4 in the FLEX manuscript) actually shows that the fracture risk reduction benefit of continuing alendronate beyond 5 years was independent of the baseline BMD (down to a femoral neck *T*-score of −2.0) or the presence of VCF. Both fracture intervention trials (FITs) either had randomized subjects with either a prevalent VCF (severe osteoporosis) or in FIT 2 without prevalent VFC but a *T*-score of ≤−2.0. Perhaps age is the risk factor that constitutes severe osteoporosis even with a non-osteoporotic (e.g. osteopenic) *T*-score since the FLEX population were between 66 and 91 years old when they entered FLEX.

10. Denosumab

Parenteral denosumab, 60 mg subcutaneous (SQ) every six months, is another first-line choice in severe osteoporosis or in situations where oral administrations of agents are unacceptable, or uncertainty of absorption is a clinical concern or poor compliance with oral medications is an issue.

Densoumab is a fully human monoclonal antibody to an activator of osteoclastic differentiation and activity, soluble Rank-Ligand (Rank-L). Rank-L is receptor activator (Rank being the receptor on osteoclasts, also called NF-□B). Rank-L, a glycoprotein produced in the osteoblast, is a member of the superfamily of ligands and is also known as TNF-activation-induced cytokine and osteoclast activator.[132]

Denosumab has robust fracture data with fracture risk reduction at all (vertebral, nonvertebral and hip) skeletal sites.[133] In addition, denosumab has robust extension BMD, safety and fracture data showing continual fracture efficacy up to 8 years, data that do not exist with any other osteoporosis pharmacological agent.[134,135]

Denosumab is metabolized by the reticuloendothelial system and the biological effect of increasing BMD or lowering bone turnover is nearly gone by the end of the sixth month of administration. Thus, every 6-month administration is needed to maintain efficacy.[135–139]

The FDA label for the PMO indication does not have any lower cutoff for renal function (Table 2). This is because denosumab is not cleared by the kidney but by the reticuloendothelial system, and may not have any adverse renal effects as may be seen, though rarely, with intravenous bisphosphonates. In a post hoc analysis of FREEDOM where the registration population had estimated GFR (eGFR) divided into quartiles (>90 ml/min to 15–29 ml/min), denosumab had evidence of reduction in incident vertebral fractures across these quartiles without any adverse renal effects (e.g. change in eGFR over 3 years).[140]

There are no data on changes in BMD or fractures in patients with GFR < 15 ml/min. In this latter population, the diagnosis of osteoporosis becomes far more difficult to establish, and there is concern that in patients with preexisting adynamic renal bone disease reducing bone turnover further may be associated with an increase in cardiovascular calcification.[140–145] This theoretical interaction is predicated on the knowledge that absorbed calcium and/or phosphorus cannot be adequately eliminated by renal clearance, and, if bone turnover is low, the capacity of bone to take up these ions is restricted, leaving vascular tissue exposed to calcium-phosphorus and risk for vascular calcification. One study has examined the effect of denosumab on vascular calcification in the FREEDOM trial and found that across the quartiles of eGFR there was no greater increase in vascular calcification with denosumab versus placebo, at least when assessed by lateral lumbar X-ray assessment of aortic calcification.[146] The FDA label cautions the physician concerning the possibility of hypocalcemia after denosumab administration. While all antiresorptive agents may induce a small and transient hypocalcemia after administration, clinically significant hypocalcemia (associated with tetany or paresthesias) is not observed in patients with adequate calcium and vitamin D intake, and with intact parathyroid hormone (PTH) responses to normalize the transient hypocalcemia. In that regard, hypocalcemia in the FREEDOM trial was no different between the treated versus placebo groups either in the registration (first 3 years) or the extension trial. It is important in patient management to ensure that an adequate amount of calcium and vitamin D is provided. Symptomatic hypocalcemia has been seen in patients on hemodialysis given denosumab.[147]

Denosumab, since FDA registration in June 2010 for the treatment of PMO, has had an impressive safety and efficacy track record.

Table 2. The emerging new therapies for PMO.

A new 'antiresorptive'
• Odanacatib
New anabolics
• Parathyroid-hormone-related peptide analogues (abaloparatide)
• Monoclonal antibody to sclerostin (romosozumab)

11. Teriparatide

Teriparatide (recombinant human 1–34 PTH) marketed under the brand name Forteo™ is the first anabolic agent registered for the treatment of osteoporosis.[112] Teriparatide has FDA registration for severe postmenopausal, male and GIOP.[148–150] In many restricted health plans, both in the US and in Europe, most patient have to have 'failed' a less-expensive oral bisphosphonate before approval of teriparatide.

This restrictive approach, based purely on health economics, is a hindrance to effective and humanistic patient care. Patients with severe osteoporosis and at extremely high risk for more fractures than they have already had deserve consideration, first line, to receive an anabolic agent. Many clinical bone specialists and bone biologists feel that first providing an anabolic agent to initially build new bone first in treatment-naive patients is the approach that should be taken.

Then after a new bone is formed, following anabolic therapy with an antiresorptive agent to maintain the newly formed bone in many patients with severe osteoporosis seems logical.

There remains a 'black box' warning on the FDA labels for the lifetime duration of teriparatide use to more than 24 months. This restriction, which is based on the life span of the rat model and the appearance of osteogenic sarcoma toward the end of the life span in the rat, should be removed now that teriparatide has been on the US market for 15 years. During this time period, osteogenic sarcoma has not been seen in four other animal models that remodel bone similar to human beings: dog, sheep, pig and monkey. In the human population, validated osteogenic sarcoma has only been reported in less than five cases with an exposure window of 15 years and >1.5 million patients.[151–154] The natural background incident rate of osteogenic sarcoma in adult human beings is 4/million/year, meaning that teriparatide does not increase the incident rate of this tumor. There is evidence that teriparatide continues to be effective beyond 2 years, and the GIOP data demonstrated this point in the clinical trials of teriparatide in GIOP. The biomarker data, especially the osteoblast activity marker, PINP, also demonstrates that osteoblast stimulation may continue to occur beyond 2 years such that the 'anabolic window', where bone formation and subsequent bone resorption biomarker lines cross, may be quite heterogeneous.[155–158] Modulating the anabolic window may allow for a longer period of bone formation before bone resorption 'catches up'. This can be done with combination therapy, an anabolic combined with an antiresorptive, perhaps by sequential therapy, or by drug development of agents that induce a less osteoblast stimulation of Rank-L.[159–164] While combination therapy has appeal, it is unlikely in today's more restrictive healthcare economy that payers will pay for combination therapies unless combination therapy shows greater fracture reduction than monotherapy.

12. New pharmacological agents

12.1 Abaloparatide

Abaloparatide (parathyroid-hormone-related peptide (PTHrP) analogue) is a PTHrP analogue with altered amino acid sequencing that conveys unique biological actions that differ from either PTH, PTHrP or teriparatide. Abaloparatide preferentially binds to the osteoblast parathyroid receptor, RO, more than the RG osteoblast receptor, where teriparatide or PTHrP preferentially bind.[165] Greater stimulation of the RO receptor may induce a less rise on osteoblast-derived Rank-L, leading to less bone resorption than teriparatide, yet similar increases in bone formation markers leading in this way to an expanded anabolic window.

In the pivotal registration clinical trial comparing abaloparatide to placebo to teriparatide, 80 µg SQ/day of abaloparatide significantly reduced the incidence of VCFs compared to placebo (the primary end point) and significantly reduced the incidence of nonvertebral and all clinical fractures as well (Miller PD et al., Endocrine Society 2015 abstract, submitted for publication). Fracture reduction between abaloparatide and teriparatide by Kaplan–Meier (time to first event), the reduction in nonvertebral and all clinical fractures occurred sooner with abaloparatide than teriparatide, and the increase in cortical bone site BMD was significantly greater with abaloparatide. Finally, there were significantly lower incident rates of hypercalcemia with abaloparatide than teriparatide. Thus, this novel PTHrP analogue may offer some distinct advantages as a new anabolic agent than teriparatide.

12.2 Romosozumab

The monoclonal antibody to sclerostin, romosozumab, has impressive data with regard to increases in BMD and bone formation with little increase in serum CTX or bone resorption.[166] Hence, even a wider anabolic window may be seen with romosozumab. Sclerostin, a product of the osteocyte, binds to the osteoblast and inhibits osteoblast activity. The discovery of sclerostin and the development of a monoclonal antibody to sclerostin represent an achievement in basic bone biology.[40,167] The phase III registration studies are currently ongoing.

12.3 Odanacatib

Cathepsin K is an enzyme that has ubiquitous presence throughout the human body, but its bone presence acts as a mediator of bone resorption. Cathepsin K works outside the osteoclast to induce bone resorption.[168,169] The discovery of cathepsin K inhibitors allowed targeting of bone resorption without altering the structural integrity of the osteoclast, resulting in maintenance of osteoclast cell membrane signaling back to the osteoblast. Hence, osteoblast bone formation is maintained with odanacatib administration, thus providing another mechanism whereby 'uncoupling' bone resorption to bone formation.[170] A number of well-designed phase II clinical trials have consistently

documented the large increases in BMD and other structural parameters of improvement in bone strength as well as safety over a long study period.[171–174] The phase III registration study given the acronym LOFT (long-term odanacatib fracture trial) in unpublished data shows that 50 mg/week of oral odanacatib provides significant incident fracture reduction at all skeletal sites as compared to placebo with a very favorable safety profile.

13. Conclusions

Severe osteoporosis is a devastating systemic disease with a high mortality, morbidity and economic cost. The important message to convey in this review is that fractures can be prevented by appropriate treatment and fall prevention strategies. Both current and emerging pharmacological treatments have evidence for efficacy and safety when used in the right population. As longer-term (extension) studies of newer osteoporosis therapies continue to provide reassurance of maintenance of efficacy and safety, the acceptance by patients of osteoporosis treatments should be attended by a reduction in the incidence of all fragility fractures.

14. Expert opinion

Severe osteoporosis remains a challenge in terms of recognition and treatment. The challenge is largely due to the underutilization of bone densitometry (DXA), the utilization of which is declining worldwide, and the underidentification of asymptomatic vertebral fractures that constitute a very high-risk population independent of that risk measured by BMD alone.

Populations are living longer, and associated with increased longevity is an increase in both the number and the severity of the consequences of all forms of low-trauma fractures. Osteoporotic fractures cost more than the costs of caring for myocardial infarction, breast cancer or cerebrovascular accidents.[3] The declining treatment of patients with pharmacological agents even with severe osteoporosis is disturbing.[6] The challenge to reverse these health-economic and undertreatment patterns is a great one and will only be resolved when governments and healthcare policy decision-makers focus enough resources into wider support for professional societies charged with increasing awareness and education about osteoporosis. The international movement to develop FLS throughout all communities offers a great opportunity to reduce the risk of the second osteoporotic fracture.

Existing and newer pharmacological agents for the treatment of osteoporosis offer great hope in reducing the burden of osteoporotic fractures and their consequences. The scientific limitations of these agents that show evidence to reduce fracture risk versus placebo are to provide evidence that one agent is superior to another by greater reduction in fracture risk. This may never be accomplished given the enormous costs of performing head-to-head fractures trials and should be the impetus for international drug registration agencies to accept solid surrogate markers of bone strength as sufficient evidence that fractures would be reduced. [103] The wider utilization of BTMs will provide physicians with the ability to measure early responses to therapies rather than wait 2 years until a BMD change occurs.

Newer emerging therapies (PTHrp analogue (abaloparatide), monoclonal antibody to sclerostin (romosozumab) and the cathepsin K inhibitor (odanacatib)) offer unique MOA on bone remodeling in that they may provide some uncoupling of remodeling for a period of time, resulting in a greater period of either bone formation or continual maintenance of bone formation as opposed to current pharmacological agents that have not been shown to uncouple the normal coupling patterns of bone remodeling.

In addition to emerging pharmacological therapies, the field of osteoporosis has been handed the opportunity to show the links between muscle and bone, and, by doing so, develop means to improve muscle strength and reduce the risk of falls. These advances will recognize the increasingly important challenge to quantitate muscle mass and strength in order to provide a consensus on the definition of sarcopenia and integrate physicians with other professional bodies in order to create a team dedicated to reducing falls.

The field of osteoporosis has to develop an office-based bone quality measurement tool that compliments BMD tests to enhance risk prediction. Since nearly 50% of bone strength is due to bone quality and not bone density and there is an increasing recognition that many diseases impair bone quality more than bone density, the capacity to measure bone quality as a point-of-care modality will be a great step forward.

Finally, this author has a large interest in improving the science and ultimately the acceptability of BTMs. BTMs have other potential utilization beyond enhancing fracture risk prediction, predicting rates of bone loss and response to therapies. They may be able to identify, to still an imperfect degree of positive predictive value, patients with low-bone turnover or even adynamic bone disease, an increasing form of bone

disease seen in diabetics and the growing population of chronic kidney disease. The 'gold standard' of identification of adynamic bone disease is quantitative bone histomorphometry, a field of great science but underutilized mostly related to fewer and fewer institutions providing quantitative histomorphometry reading. In the end, our field of osteoporosis will need the development of subspecialty boards in metabolic bone disease in order to train young physicians in this increasingly important and often complex field and provide professional/governmental licensing to support recognition of competence and proper reimbursement.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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