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REVIEW

Challenges in implementing and maintaining osteoporosis therapy

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Abstract: In the United States, an estimated 19% of older men and 30% of older women are at elevated risk of osteoporotic fracture and considered to be eligible for treatment. The burden of osteoporosis is similar in Europe and is projected to rise worldwide, with aging populations and increasing fracture rates accompanying urbanization. Notwithstanding its high prevalence, osteoporosis is often underdiagnosed and undertreated. Moreover, even when the diagnosis is made and the decision is taken to treat, there are remaining challenges in implementing therapy for osteoporosis. Several patient populations are particularly challenging for clinicians to treat and require further study with regard to osteoporosis therapy. These include the very elderly, who face challenges relating to adherence; men, in whom osteoporosis remains under-recognized; patients with glucocorticoid-induced osteoporosis or renal impairment, who are at increased risk of fracture; patients with preexisting gastrointestinal problems who cannot tolerate existing orally administered osteoporosis therapies; and high-risk patients who show inadequate response to therapy. Moreover, poor adherence and poor persistence with osteoporosis medications are common and result in an increased risk of fracture, higher medical costs, and increased hospitalizations. Once the decision to institute therapy is made, patient education about osteoporosis and fracture risk should be provided. This is particularly important for men, who may not be aware that osteoporosis can be a concern. Secondary prevention programs, including fracture liaison services and bone therapy groups, can help to improve adherence to therapy. Further study is needed to guide the treatment of men, the very elderly, patients with glucocorticoid-induced osteoporosis and renal impairment, high-risk patients not well-controlled despite therapy, and patients with preexisting gastrointestinal conditions. Moreover, therapies are needed that are viewed as effective and safe by both physicians and patients, and as convenient to take by patients.

Keywords: adherence, chronic kidney disease, glucocorticoid-induced osteoporosis, fracture

Introduction

An estimated 30% of women and 19% of men 50 years and older in the USA are at elevated risk of osteoporotic (fragility) fracture and are considered to be eligible for pharmacologic treatment.[1] The burden of osteoporosis is similar in Europe and is projected to rise around the globe, with aging populations and increasing fracture rates accompanying urbanization.[2,3] An estimated 9 million new osteoporotic fractures occurred worldwide in the year 2000 (Figure 1); these included 1.6 million hip fractures, 1.7 million forearm fractures, and 1.4 million clinical vertebral fractures, roughly half of which occurred in North America and Europe.[4] In Europe alone, the direct medical costs of osteoporotic fractures in 2005 were €31.7 billion, to which must be added the

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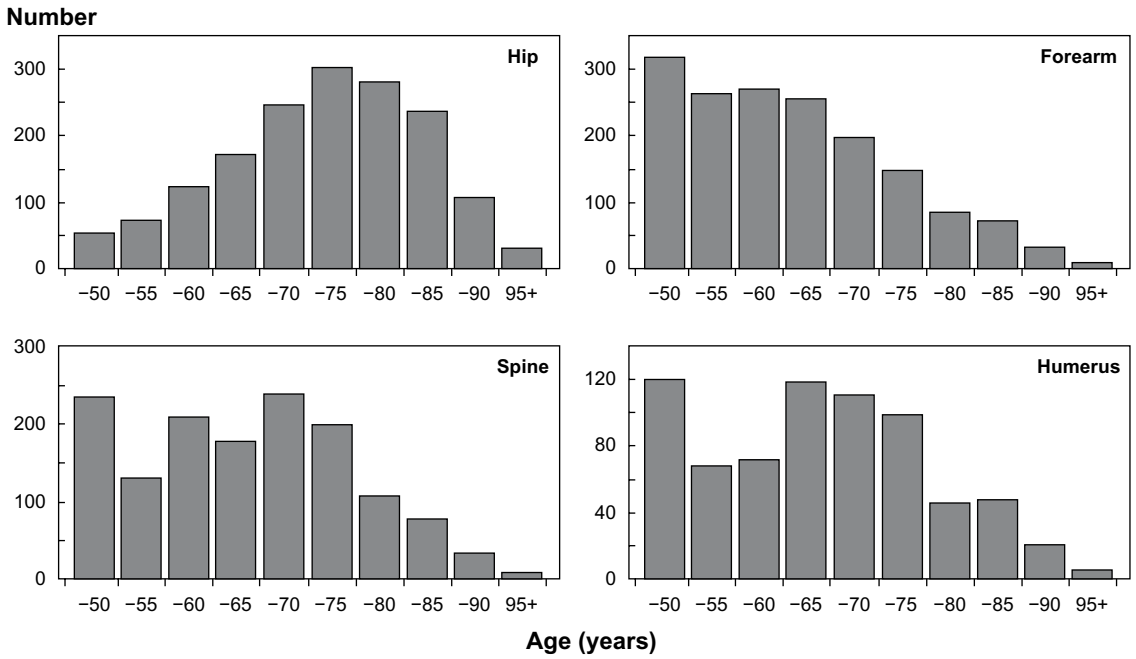

Figure 1 Number of common osteoporotic fractures by age worldwide in 2000.
Note: Reprinted from Springer and *Osteoporos Int*. 2006; 17(12):1726–1733, Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures.[4] © 2006. With kind permission from Springer Science and Business Media.

less easily quantifiable indirect costs of pain, disability, and reduced quality of life that accompany fracture.[4–6]

Notwithstanding its high prevalence, osteoporosis is often underdiagnosed and undertreated.[7–11] Moreover, even when the diagnosis is made and the decision is taken to treat, there are remaining challenges in implementing therapy for osteoporosis. Several patient populations are particularly challenging for clinicians to treat and are not as well studied as women with postmenopausal osteoporosis. These include men, the very elderly, disabled persons, patients with glucocorticoid-induced osteoporosis (GIOP) or renal impairment, patients after transplantation, high-risk patients who are not well-controlled despite therapy, and patients with preexisting gastrointestinal (GI) problems who cannot tolerate existing therapies. Indeed, the extent of under treatment tends to be greater for these patient populations than for postmenopausal women,[12–16] perhaps, in part, because physicians are reluctant to initiate therapy owing to doubts about efficacy or concerns about side effects. The objective of this review was to describe existing challenges to improving the treatment of osteoporosis.

General principles for diagnosing, preventing, and treating osteoporosis

Osteoporosis is defined by the World Health Organization (WHO) as a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Several national and regional guidelines for diagnosing and managing osteoporosis have been published for the USA, Canada, and Europe,[17–21] and a full list of guidelines worldwide is available on the International Osteoporosis Foundation website.[22] Lifestyle recommendations for reducing osteoporotic fracture risk include maintaining adequate calcium and vitamin D intake, regular weight-bearing and muscle-strengthening exercise, strategies to prevent falls, and avoiding tobacco and excessive alcohol consumption. Currently approved therapies to prevent or treat osteoporosis, summarized in Table 1, include the bisphosphonates (eg, alendronate, risedronate, ibandronate, and zoledronic acid), selective estrogen receptor modulators (SERMs) (eg, raloxifene), estrogen, calcitonin, parathyroid hormone (eg, teriparatide), the receptor activator of nuclear factor-kappa B ligand (RANKL) inhibitor, denosumab, and in some countries, strontium ranelate.[17,23,24]

The decision regarding when to initiate therapy to prevent osteoporotic fracture can be complex and must take into account the possible risk factors for the individual patient. The FRAX® tool has been developed by the WHO Collaborating Centre for Metabolic Bone Diseases to estimate the 10-year probability of major osteoporotic and hip fracture, using an individual's clinical risk factors, with or without the hip bone mineral density (BMD) measurement (Table 2).[25,26] There is great geographic heterogeneity in fracture risk,[27]

Table 1 Drugs approved for the prevention and treatment of osteoporosis

Pharmacologic category	United States	European Union
Bisphosphonate	Alendronate	Alendronate
	Risedronate	Risedronate
	Ibandronate	Ibandronate
	Zoledronic acid	Zoledronic acid
		Etidronate
		Clodronate[b]
RANK ligand inhibitor	Denosumab	Denosumab
SERM	Raloxifene	Raloxifene
		Bazedoxifene[a]
Parathyroid hormone and derivatives	Teriparatide	Teriparatide
		Parathyroid hormone
Other	Estrogen/HRT	HRT
	Calcitonin	Strontium ranelate
	Vitamin D	Calcitonin
		Vitamin D and derivatives

Notes: [a]Available only in Greece, Spain, and Germany; [b]approved for osteoporosis in only some countries Data from Kanis et al,[17] health.ny.gov,[23] and nof.gov.[24]
Abbreviations: HRT, hormone replacement therapy; RANK, receptor activator of nuclear factor-kappa B; SERM, selective estrogen receptor modulator.

and the appropriate FRAX tool is chosen according to the country and as needed, ethnicity and the patient population.[25] Further guidance for clinical decision-making when using FRAX has been published.[28]

Patient populations posing particular challenges for physicians

Patients with glucocorticoid-induced osteoporosis

The development of osteoporosis is a serious concern for patients who require long-term glucocorticoid therapy, such as for inflammatory joint disease or asthma. Glucocorticoids exert both direct and indirect effects on bone that contribute to increased fracture risk (Figure 2).[29] A decline in BMD begins within the first 3 months of glucocorticoid therapy; the rate of decline is most rapid during the first 6–12 months and slows thereafter.[30] However, the risk of fracture increases faster than can be explained by the loss of BMD alone; this is thought to be the result of disrupted architecture of the bone, particularly cancellous bone, and possibly other factors, including the rapidity of bone loss, myopathy, increased tendency to fall, and the condition for which the glucocorticoids were prescribed.[29,31] As many as 30%–50% of patients receiving long-term glucocorticoid therapy experience a fracture, often at higher BMD levels than in postmenopausal women, with fragility fracture and, most commonly, of the vertebrae or proximal femur.[29]

Table 2 Risk factors included in the WHO fracture risk assessment model (FRAX®)

- Current age
- Sex
- A prior osteoporotic fracture (including morphometric vertebral fracture)
- Femoral neck BMD
- Low body mass index (kg/m^2)
- Rheumatoid arthritis
- Secondary osteoporosis
- Parental history of hip fracture
- Current smoking
- Alcohol intake (3 or more drinks/day)
- Oral glucocorticoids ≥5 mg/day of prednisone for ≥3 months (forever)

Note: Fracture risk assessment model (FRAX®).[27]
Abbreviations: BMD, bone mineral density; WHO, World Health Organization.

Recommendations for preventing and treating GIOP have been published;[31–33] however, several areas of uncertainty remain, including the threshold glucocorticoid dose for initiating preventive therapy. The risk of GIOP has not been defined for lower doses of glucocorticoids (<5–7.5 mg/day prednisone) nor for intermittent rather than continuous administration. Moreover, with regard to treatment efficacy, the majority of clinical trials examine changes in BMD; few examine fracture endpoints for patients with GIOP.[34] Finally, patients with GIOP are at increased risk of fracture but are already receiving drugs (steroids) that can cause GI upset, adding to the difficulty of prescribing concomitant osteoporosis therapy.[35]

Patients with renal impairment

Patients with renal impairment are also at increased risk of fracture. For women 65 years and older, hip fracture risk increases as estimated glomerular filtration rate (eGFR) decreases below 60 mL/min,[36] while for both men and women, the hip fracture risk with an eGFR of <60 mL/min is double that with eGFR ≥60 mL/min.[37] As many as half of patients with renal impairment have experienced a fracture by the time they initiate dialysis,[38] and for patients on dialysis, the mortality rate during the year after hip fracture is 2.5 times higher than that in the general population.[39]

The etiology of fracture in patients with renal impairment is complex as renal impairment itself is characterized by abnormalities of bone and mineral metabolism, as well as an increased tendency to fall because of muscle weakness and impaired balance.[38] In the early stages of renal impairment (stages 1–3; GFR ≥30 mL/min/1.73 m^2), the association of lower BMD and higher fracture risk is present.[38] However, in patients with stage 4 (GFR 15–29 mL/min/1.73 m^2) and stage 5 (GFR <15 mL/min/1.73 m^2 or on dialysis), evidence is lacking for the associations among bone quality, bone turnover markers, neuromuscular function, and fractures; and BMD may no longer be reliable in predicting fracture

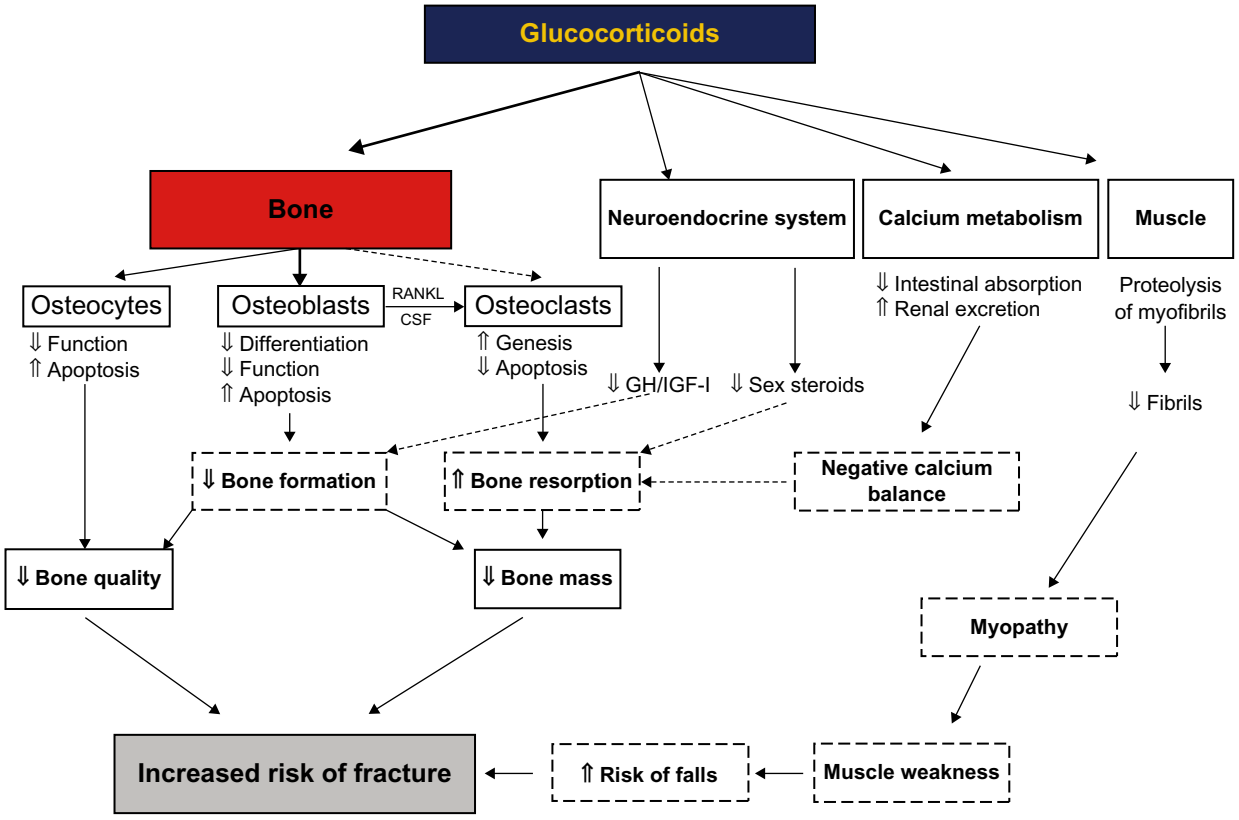

Figure 2 Diagram showing the direct and indirect effects of glucocorticoids on bone, leading to glucocorticoid-induced osteoporosis and fractures.
Notes: Reprinted from Springer and *Osteoporos Int*, 18; 2007, 1319-1328, Glucocorticoid-induced osteoporosis: pathophysiology and therapy, Canalis E, Mazziotti G, Giustina A, Bilezikian JP, Figure 1.[29] © 2007. With kind permission from Springer Science and Business Media.
Abbreviations: CSF, cerebrospinal fluid; GH, growth hormone; IGF, insulin-like growth factor; RANKL, receptor activator of nuclear factor-kappa B ligand.

risk. For these patients, it becomes increasingly difficult to differentiate between osteoporosis and chronic kidney disease–mineral and bone disorder (CKD–MBD) (defined in Table 3),[40,41] conditions for which the treatment differs.[38]

Physicians therefore face several challenges in treating patients with renal impairment and low BMD or fracture. Patients with renal impairment are often on multiple medications and may not tolerate additional therapy. Moreover, the bisphosphonates are excreted through the kidneys, a matter of concern if renal function is impaired.[42] The US Food and Drug Administration (FDA) and product manufacturers have defined a creatinine clearance (which runs slightly higher than GFR) of 35 mL/min as the threshold below which therapy with alendronate and zoledronic acid is not recommended; for ibandronate and risedronate, the threshold is 30 mL/min.[43–46] Nonetheless, while bisphosphonate therapy is approved for use in patients with stages 1–3 renal impairment, the cutoff point for initiating therapy is not defined for those patients who have not yet experienced fragility fracture. Moreover, for patients with GFR <30–35 mL/min, distinguishing between osteoporosis and CKD–MBD can be difficult.[42]

Table 3 Definition of chronic kidney disease-mineral and bone disorder, according to KDIGO

A systemic disorder of mineral and bone metabolism due to CKD and manifested by one or a combination of the following
1. Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
2. Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
3. Vascular or other soft tissue calcification

Note: Data from Moe et al[41] and Miller.[42]
Abbreviations: CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

Jamal et al[38] summarized the existing knowledge for determining fracture risk for patients with renal impairment. Published guidelines provide recommendations for working with these patients; however, the guidelines are admittedly weak or discretionary because of the lack of trials reporting clinical outcomes (fractures).[38,40,47] For patients with osteoporosis or at high risk of fracture who are at stages 1 and 2 or stage 3 with normal parathyroid hormone, the consensus guidelines recommend treatment as for the general population. Little evidence is available for the treatment of patients with stage 3 renal impairment with biochemical abnormalities and stages 4–5,[40,47]

although Miller[48] has published a practical opinion-based approach for these patients.

Men

Osteoporosis is often considered a "woman's disease;" however, worldwide, 39% of osteoporotic fractures occur in men,[4] and in the USA, the projections for 2005 attributed 29% of the fractures and 25% of the costs of osteoporosis to men.[2] Nonetheless, the preponderance of clinical trials has studied postmenopausal women, with men constituting a small proportion of enrolled patients. Most importantly, few trials have examined fracture endpoints for men[49–52]; thus, physicians have little basis for assuring their male patients of treatment efficacy.

Age-related bone loss develops more slowly and at older ages in men. The key risk factors for osteoporotic fracture in men identified in a recent meta-analysis[53] include increased age, low body weight, weight loss, physical inactivity, prolonged corticosteroid use, previous osteoporotic fracture, and androgen-deprivation therapy. The three most common causes of secondary osteoporosis in men are 1) glucocorticoid excess, usually secondary to chronic glucocorticoid therapy; 2) alcohol abuse; and 3) hypogonadism, increasingly common with the use of androgen-deprivation therapy for prostate cancer.[50,54] While there are sex-specific differences in osteoporosis pathophysiology,[50,51] the prevention and treatment of osteoporosis in men are as important as for women at risk of first or subsequent fracture. After a first fragility fracture, men, similar to women, are at higher risk of subsequent fracture,[55,56] and the increased mortality risk after fracture in men persists for 5–10 years and is similar to or higher, in some studies, than that for women.[56–58]

The number of osteoporosis therapies approved for men are fewer than for women, and not many clinical trials examine fracture endpoints for men; however, in trials using surrogate markers for fracture, such as BMD and markers of bone turnover, the effects of osteoporosis therapies have been similar for men and women, suggesting that treatment efficacy for preventing fracture is similar for the two sexes.[49-52] The current guidance thus recommends that men receive similar treatment to that for women with osteoporosis.[50] The importance of determining osteoporotic fracture risk, effective prevention, and optimal therapy specifically for men is increasingly recognized,[50] and recent studies have indeed focused on men.[59–61]

An important component of the treatment for male patients with osteoporosis is countering the common perception that osteoporosis is a concern only for women.[62] As reported by Solimeo et al,[62] men rarely consider osteoporosis to be a possible cause of their back pain or a result of aging or cancer treatment. The men they interviewed reported surprise at learning of the osteoporosis diagnosis; many believed that osteoporosis therapies have been insufficiently studied in men, were reluctant to take medications, and felt dissatisfied with side effects of therapy.

The very elderly

Advanced age is an important risk factor for osteoporosis and fracture for both men and women.[50,63–65] The prevalence of osteoporosis and risk of associated fracture increase with age, which is the criterion listed first in all geographic versions of the FRAX tool to estimate the 10-year probability of hip or other major osteoporotic fracture.[25] With advancing age, the balance between bone formation and bone resorption is altered, favoring resorption and thus, bone loss. The resultant bone fragility is coupled with an increased risk of falls among the elderly because of reduced muscle strength, poor balance, comorbidities, such as osteoarthritis, side effects of medications, or a combination of these.[64–66] The prevention of osteoporotic fracture for the very elderly thus requires dual strategies to prevent falls as well as to increase BMD.

The challenges are many in choosing and particularly, in maintaining pharmacological therapy for osteoporosis in very elderly patients. Patients over 80 years of age are not well-represented in clinical trials, and thus, this population has been insufficiently studied.[64] Moreover, many of these patients have comorbidities and are on multiple medications.[67] Polypharmacy increases the possibility of side effects and of falling and can reduce adherence to medications. An absence of perceived benefit, the occurrence of side effects, and the inability to comply with stringent administration protocols because of physical or mental disability are reported factors that can contribute to the potential for nonadherence.[17,67–69] Other common barriers to optimal adherence by elderly patients include dementia, Parkinson's disease, and lack of social support.[67,70,71] Moreover, GI intolerance to therapies, discussed further below, may be especially problematic for the very elderly.[72]

High-risk patients who are not well-controlled despite being on osteoporosis therapy

Therapy for osteoporosis reduces but does not eliminate the risk of fracture.[52,73] High-risk patients who are not well-controlled can be defined as those patients who experience fractures or decline in BMD, or whose BMD remains in

osteoporotic range, while receiving osteoporosis therapy. The risk factors identified for postmenopausal women who show inadequate response to therapy include a prior fragility fracture and low levels of 25-hydroxy vitamin D (<20 ng/mL).[74,75] A significant reduction in quality of life has been reported for these women.[75,76] Knowledge of the risk factors and an understanding of inadequate response are important for clinicians to identify patients who require close monitoring during treatment and to determine when a change in therapy is warranted. The identification of these patients will vary on a case-by-case basis according to physician opinion and individual patient circumstances.

The International Osteoporosis Foundation (IOF) has established a working group to study what constitutes an inadequate response to therapy.[77] The current IOF operational definition of "failure of treatment" is the occurrence of two or more incident fractures during treatment, a continuing decrease in BMD, and no suppression of bone remodeling markers by antiresorptive therapy.[78] These criteria assume that the patient has 1) good adherence to therapy, 2) adequate calcium and vitamin D supplementation, and 3) a treatment period of at least 1 year.

Issues that can affect patient adherence to therapy for osteoporosis

Suboptimal adherence to prescribed medication is a common and well-recognized problem with regard to long-term therapy for chronic diseases,[79,80] and adherence to treatment for osteoporosis is no exception.[81–87] The lack of adherence to osteoporosis therapy results in increased risk of fracture, higher medical costs, and increases in hospitalizations.[82,84,88–90] Conversely, better adherence to osteoporosis therapies is associated with greater reduction in fracture risk;[91–93] and a recent study reports reduced mortality risk in women and possibly men receiving osteoporosis therapy.[94]

Adherence, synonymous with compliance, is defined as the proportion of doses taken as prescribed, while persistence is used to describe the length of time for which the regimen is followed. Poor adherence and persistence can result from forgetfulness, inability to pay, or other nonintentional reasons. The degree of intentional adherence has been associated with the balance between patients' beliefs about the necessity of their medications and their concerns about medication side effects and safety.[95,96] For patients with osteoporosis, the failure to perceive their increased risk of fracture[97,98] or lack of satisfaction with treatment[99] has been associated with poor adherence. Fear of side effects, including GI side effects, is another important cause of suboptimal adherence or poor persistence with therapy.[68,69,100,101] Patients often have concerns even before initiating therapy as they may have heard about the side effects of osteoporosis therapy; therefore, the possible occurrence of side effects, whether real or perceived, is a problem.

A recent study has found that some physicians may not prescribe treatment for osteoporosis because of concerns about adverse effects.[102] Tolerability concerns are relevant for physicians, especially with regard to the patient populations described above, as well as for patients with preexisting GI problems. For example, patients with gastroesophageal reflux disease often do not tolerate the addition of oral bisphosphonate therapy. Indeed, GI intolerance has been a large enough barrier to treatment that less frequent dosing regimens and intravenous (IV) delivery routes have been developed.[103] Weekly regimens have indeed improved adherence and persistence levels over daily regimens;[104–106] nonetheless, these advances have not been enough to result in optimal adherence.[107,108] Moreover, while IV therapies have bypassed the problem of GI intolerance, persistence with IV regimens is also suboptimal, often because of adverse effects (postinfusion syndrome).[109,110] It has been previously reported that persistence with IV zoledronate is comparable with that of oral bisphosphonates after a year. Studies have shown that men are more likely to discontinue IV therapies; in addition, adverse effects, most commonly postinfusion syndrome, and a poor understanding of the benefits and risks of IV zoledronate are risk factors for discontinuation.

Bisphosphonates have been found to be generally well-tolerated in randomized controlled trials, with upper GI events and discontinuation rates similar to those of placebo.[111,112] However, patients with preexisting active GI conditions are usually excluded from these trials. A large prospective, observational US study found that GI side effects among women receiving osteoporosis therapy were common, with odds 1.5 times higher for women receiving bisphosphonates than other therapies; and GI side effects were associated with increased therapy discontinuation.[113] Moreover, data from real-world clinical practice suggest that GI side effects are an issue for patients, possibly because of improper drug administration.[114] Elderly patients in particular, may have difficulty complying with the requirement to take oral bisphosphonates early in the morning, with a full glass of water, while remaining upright and fasting for at least 30 minutes. Patients who experience GI side effects with bisphosphonates often have an underlying comorbidity or concomitant treatment, such as nonsteroidal anti-inflammatory drugs

or glucocorticoids, that would predispose them to these side effects.[35] These treatments themselves may cause GI side effects, leading to uncertainty around the drug that caused them. In addition, evidence suggests that GI problems are greater with generic bisphosphonates.[115,116]

Discussion

Substantial progress has been made over the past two decades in improving our understanding of osteoporosis and fracture risk in different patient populations. However, many therapeutic challenges remain. The challenges from the physician's perspective include the lack of information on how to treat specific patient populations and once treatment is initiated, how to allay patient concerns about side effects and how to encourage patient adherence to therapy. The challenges from the patient's perspective include reaching an understanding of the condition and maintaining adherence to chronic therapy, despite concerns about or the actual occurrence of side effects. Further study is needed to quantify and better characterize the specific patient populations at risk of osteoporotic fracture, including men, the very elderly, patients with GIOP and renal impairment, high-risk patients not well-controlled despite therapy, and patients who experience GI side effects.

Simple steps that can be taken for all patients at risk of fracture include instituting the measures recommended by the American College of Rheumatology for preventing and treating GIOP, namely, promoting general health awareness, ensuring that patients receive sufficient calcium and vitamin D, and for patients receiving glucocorticoids, reducing the glucocorticoid dose to a minimum.[31] The tendency to fall is an important fracture risk factor for the very elderly; thus, vitamin D supplementation and appropriate exercises are key components of osteoporosis therapy and fracture prevention.[64,65]

These measures are indicated for patients after fracture as well; however, the under diagnosis and under treatment of osteoporotic fracture, particularly among men, remain all too common.[9–11] Thus, the evaluation of all older patients with fracture is essential to close the postfracture care gap. In one study, an intervention program instituted by clinical pharmacy specialists to identify patients with atraumatic fracture was successful in improving osteoporosis treatment initiation rates among elderly patients, by ensuring they were screened for osteoporosis and then treated appropriately.[117]

Once the decision to institute therapy is made, patient education about osteoporosis and fracture risk should be provided. This is particularly important for men, who may not be aware that osteoporosis can be a concern. Patients' beliefs about fracture risk and need for therapy are influenced by the perceived attitudes and support of physicians and other health care providers.[69,118] Secondary prevention programs, including fracture liaison services, bone-therapy groups, telephone calls from a nurse or other health care provider, and scheduling regular follow-up visits, have been shown to improve patient adherence and persistence with therapy.[119,120] Newman et al reported success in improving adherence and BMD with a targeted program enrolling patients on chronic glucocorticoid therapy.[121]

Postmenopausal women constitute the largest population in need of effective strategies to promote adherence and persistence with osteoporosis therapy. With regard to postmenopausal osteoporosis, the results of economic modeling suggest that nonadherence and nonpersistence are costly and that behavioral interventions to improve adherence and persistence with therapy would be cost effective.[122,123] It is possible that these results could apply also to other patient groups with osteoporosis as well.

Conclusion

In conclusion, several patient populations are particularly challenging for clinicians to treat and require further study with regard to osteoporosis therapy. Clearly, more data are needed to guide the treatment of men, the very elderly, patients with GIOP and renal impairment, high-risk patients not well-controlled despite therapy, and patients who experience GI side effects. Therapies are needed that are viewed as effective and safe by both physicians and patients, and as convenient to take by patients.

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Disclosure

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