

## European osteoporosis pharmacological guidelines confirm current recommended treatment whilst answering important management questions

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One in 3 women and 1 in 5 men over the age of 50 will sustain an osteoporotic fracture.<sup>1</sup> These fractures are often associated with significant morbidity and increased mortality.<sup>1,2</sup> The economic burden of osteoporotic fractures is enormous.<sup>1</sup> Fracture risk is much higher in the elderly than in younger people.<sup>2</sup> With an ever increasing life expectancy, the prevalence of fragility fractures can be expected to rise exponentially.<sup>1</sup> It is estimated that by 2050 there will be in excess of 5 million hip fractures globally.<sup>3</sup> However, despite this high prevalence of osteoporosis, less than 20% of osteoporotic patients are assessed for fracture risk, screened for osteoporosis or initiated on appropriate secondary prevention including calcium or vitamin D supplementation.<sup>1,2</sup> A decline has been shown in both treatment initiation and adherence rates, especially in bisphosphonate treatment.<sup>2,4</sup> This has manifested in a higher incidence of hip fracture than what was projected in the United States, following a more than 10-year period of decline in hip fracture incidence.<sup>2</sup> Factors playing a role in sub-optimal treatment include a lack of disease awareness as well as uncertainty amongst treating physicians and patient fears. Physicians may be unsure regarding appropriate screening, identifying patients at high fracture risk, especially imminent fracture risk, appropriate treatment initiation and duration of treatment, as well as when to institute “drug holidays”. A further barrier to treatment initiation and adherence is patient concerns regarding route of administration, tolerability and fear of possible, although rare, side effects, such as osteonecrosis of the jaw (ONJ) and atypical femur fracture (AFF).<sup>2,5</sup>

The National Osteoporosis Foundation of South Africa (NOFSA) published clear guidelines in 2017 to help guide the treating physician. Recently, the European Society for Osteoporosis published their revised Pharmacological Management of Osteoporosis in Post-menopausal Women Clinical Practice Guideline. These guidelines explore drug efficacy but also importantly emphasise the importance of patient preferences, taking into account data on adherence and persistence whilst considering the risk and benefit profiles from both the patient's and healthcare providers' perspectives.

### Who to treat?

Benefits of pharmacologic therapies outweigh risks in post-menopausal women at high fracture risk, especially those who

have sustained recent fracture.<sup>5</sup> High fracture risk patients are defined as those with T-scores of  $-2.5$  or less at either the femoral neck, total hip or lumbar spine, or T-scores of  $-1.0$  to  $-2.5$  with a 10-year fracture risk probability of  $\geq 20\%$  for a major osteoporotic fracture or  $\geq 3\%$  for a hip fracture based on the FRAX<sup>®</sup> tool.<sup>5</sup> This definition is in keeping with our local definitions although it should be noted that the FRAX<sup>®</sup> tool is demographic specific and does not currently include South African demographics.<sup>6</sup>

Imminent fracture risk in fact refers to fractures sustained 12–24 months after the initial osteoporotic fracture.<sup>7</sup> A recent fracture doubles the risk for subsequent fracture within the next 24 months.<sup>7</sup> This is true for both vertebral fractures and non-vertebral fractures, such as distal radius and proximal humerus fractures. Treatment initiation should be prioritised and not delayed in these patients.<sup>5,7</sup>

The European guidelines recommend treatment for any patient 65 years and older who has sustained a major osteoporotic fracture irrespective of the bone mineral density or other associated fracture risks. Similarly, NOFSA have recommended treatment for those 60 years and older who have sustained an osteoporotic fracture. This is especially true for all hip fractures within this age group. Patients are not in need of a bone mineral density (BMD) assessment but should rather be treated without delay. In South Africa investigation costs are often a barrier and should not be a further barrier to accessing treatment in those who have already sustained an osteoporotic fracture.

### How long to treat?

The concept of “treat to target” can assist in treatment decisions that are based on achieving the target BMD (T-score  $> -2.5$  at the hip) or an acceptable reduced fracture risk. This allows for implementation of “drug holidays” but may require a change in therapy when the desired results are not being met.<sup>5,6</sup>

### Bisphosphonates

Bisphosphonates are recommended as initial therapy.<sup>5</sup> Bisphosphonate efficacy has been well established, with significant gains in BMD and fracture risk reduction.<sup>5,8</sup> NOFSA guidelines also recommend bisphosphonates as first line therapy for high risk post-menopausal women, in men, as well as for glucocorticoid induced secondary osteoporosis.<sup>6</sup>

The European guideline recommends the use of the currently available agents in South Africa – zoledronic acid, ibandronate, alendronate and risedronate. There is no preference in agent or route of administration.<sup>5</sup>

A meta-analysis comparison of alendronate vs. placebo showed a 44% (hazard ratio [HR], 0.56; 95% CI, 0.46 to 0.67) reduction in vertebral fracture risk, 40% (HR, 0.60; 95% CI, 0.39 to 0.92) reduction in hip fracture risk with a 17% (HR, 0.83; 95% CI, 0.74 to 0.93) reduction in non-vertebral fracture risk.<sup>5</sup>

A meta-analysis comparison of risedronate vs. placebo yielded a 36% (HR, 0.64; 95% CI, 0.53 to 0.77) reduction in vertebral fracture risk, 26% (HR, 0.74; 95% CI, 0.59 to 0.94) reduction in hip fracture risk and a 20% (HR, 0.80; 95% CI, 0.72 to 0.89) reduction in non-vertebral fracture risk, whilst the meta-analysis comparison of ibandronate vs placebo showed a 31% (HR, 0.69; 95% CI, 0.49 to 0.97) reduction in vertebral fracture risk.<sup>5</sup> It is noted that there is no evidence of a reduction in non-vertebral or hip fracture risk with ibandronate.<sup>5</sup>

A large trial of zoledronic acid conducted in both women and men after a hip fracture found a significant 35% (HR, 0.65; 95% CI, 0.50 to 0.84) reduction in all new clinical fractures.<sup>8</sup> This supports the current recommendations and value of bisphosphonate initiation after a hip fracture.

Bisphosphonates are distinct from other therapies in that their positive effects persist for years after treatment cessation; this is termed “the legacy effect”.<sup>5</sup> Fracture risk in patients on bisphosphonate therapy should be reassessed every 3 to 5 years.<sup>5</sup> Women who are no longer at high risk for fractures, should be considered for a drug holiday.<sup>5</sup> Drug holidays are generally recommended in these patients after 3 years of intravenous therapy or 5 years of oral therapy. This is made possible by the “legacy effect”, allowing for reduction in risk of rare long-term side effects. The rare risks of AFF and ONJ are associated with bisphosphonate use beyond 5 years.<sup>5</sup> However, in patients found to still be at high risk (total hip T-score persisting  $\leq -2.5$ ) “drug holidays” are NOT recommended as treatment benefits still far outweigh the risks.<sup>5</sup> An analysis involving 1 000 women treated with bisphosphonates for 3 years showed that approximately 100 new fragility fractures, including hip fractures, could be prevented for only 0.08 AFF events.<sup>5</sup> The decision to implement a drug holiday needs to be individualised and the patient counselled regarding the benefits of treatment continuation vs cessation. Patients on a “drug holiday” should be reassessed every 2 to 4 years.<sup>5</sup>

Compliance as with most other oral drugs was shown to be low. In such patients, intravenous therapy may be preferable.<sup>5</sup>

### Denosumab

Denosumab is another anti-resorptive agent widely used globally. Although it is not yet registered for use in South Africa, it is available under section 21 application with the South African Health Products Regulatory Authority.<sup>6</sup> It is recommended that denosumab be used in high risk post-menopausal women as an alternative initial therapy.<sup>5</sup> Denosumab may also be considered

as an alternative therapy for patients with chronic kidney disease with eGFR  $\leq 35$  ml/min/1.73m<sup>2</sup>, in whom bisphosphonates are contra-indicated.<sup>5</sup> Denosumab has been shown to effectively increase BMD and decrease fracture risk at all sites.<sup>5</sup> It is administered as a bi-annual subcutaneous injection.<sup>5</sup> Unlike bisphosphonates, the effects do not persist beyond 6 months and there is a rebound increase in bone turnover and increased fracture risk after this. Drug holidays or treatment interruption are therefore not recommended.<sup>4</sup> In the FREEDOM Extension study, there was evidence supporting ongoing stable fracture reduction up to 10 years.<sup>5</sup> Once the target is reached, either a BMD T-score above -2.5 or when the fracture risk is no longer high, the denosumab may be stopped, but should be followed up with a bisphosphonate.<sup>5</sup> Adherence rates and patient preference rates exceeded that of oral bisphosphonates, with up to an estimated 89% adherence at 12 months.

### Anabolic therapies

The use of anabolic agents teriparatide and abaloparatide is recommended to reduce both vertebral and non-vertebral fracture risk in patients at very high risk, such as those with severe or multiple vertebral fractures, for a treatment duration of up to 24 months.<sup>5</sup> Anabolic agents increase BMD by increasing bone formation, when administered intermittently.<sup>5</sup> Teriparatide is available in South Africa and is administered as a daily subcutaneous injection.<sup>6</sup> The antifracture effects of teriparatide are realised faster than those of the anti-resorptive agents and so may be a treatment option for those at high imminent fracture risk. NOFSA too recommends it for patients with very high fracture risk, including glucocorticoid induced secondary osteoporosis.<sup>6</sup> It may also be considered in cases where patients with good adherence on bisphosphonate therapy continue to lose BMD or sustain a fracture.<sup>6</sup>

In a meta-analysis compared to placebo there was a 74% (HR, 0.26; 95% CI, 0.18 to 0.39) vertebral fracture risk reduction and a 39% (HR, 0.61; 95% CI, 0.44 to 0.85) non-vertebral fracture risk reduction.<sup>5,9</sup> A black box warning was issued after it was associated with an increased associated risk of osteosarcoma in rats.<sup>5</sup> However, since its introduction in 2002, there has been no increased rate of osteosarcoma in patients using it, with only 1 case reported since 2016.<sup>5</sup> Maximum duration of therapy is limited to 24 months per lifetime.<sup>5</sup>

There has been concern that prior bisphosphonate therapy use may blunt the efficacy of teriparatide.<sup>5</sup> Studies, however, suggest that it retains its anabolic effect.<sup>5</sup> In a sub-analysis group of the severe osteoporosis VERO trial, similar fracture reduction rates for vertebral and clinical fractures were found in prior bisphosphonate users compared to treatment naïve patients.<sup>5</sup>

Once again, if not followed up with bisphosphonate therapy, the gains obtained with this drug are rapidly lost within the first year post-therapy.<sup>5</sup> Limitations include the high cost and the acceptability of a daily injection as the route of administration.<sup>5</sup>

### Selective estrogen receptor modulators (SERMS)

The European guideline recommends the use of selective oestrogen receptor modulators raloxifene and bazedoxifene in post-menopausal women with high fracture risk in whom bisphosphonate or denosumab are not appropriate, in whom there is a low risk of deep venous thromboses (DVT), or a high risk of breast cancer.<sup>5</sup> Raloxifene is registered in South Africa for the prevention and treatment of osteoporosis.<sup>6</sup> Importantly, it has only been shown to reduce vertebral fracture risk by 40% and not hip or non-vertebral fracture risk.<sup>5</sup> Raloxifene has the added benefit of a reduced incidence of oestrogen receptor-positive breast cancer during treatment and for at least 5 years following treatment.<sup>5</sup> Raloxifene is best suited to younger women with osteoporosis and no vasomotor symptoms.<sup>5</sup>

### Hormone replacement therapy (HRT)

Menopausal hormone replacement therapy is recommended by the European guideline in post-menopausal women at high fracture risk who are younger than 60 years, or less than 10 years post menopause, with a low DVT risk and without contra-indications, and in whom bisphosphonates or denosumab are not appropriate.<sup>5</sup> As recommended by NOFSA guidelines, these patients should not be initiated on hormone replacement therapy (HRT) for osteoporosis indications alone, but for concomitant significant menopausal symptoms.<sup>5,6</sup> If HRT prescribed for osteoporosis is stopped, alternative therapy should be initiated,<sup>5</sup> as a decline in BMD similar to that of natural menopause can be expected.

HRT, as compared to placebo in the meta-analysis, reduced vertebral fracture risk by 34% (HR, 0.66; 95% CI, 0.49 to 0.80), hip fracture risk by 29% (HR, 0.71; 95% CI 0.52 to 0.98) and non-vertebral fracture risk by 21% (HR, 0.79; 95% CI, 0.70 to 0.90).<sup>5</sup> Fracture risk benefits were not limited to patients at high fracture risk but were also present in women at lower fracture risks.<sup>5</sup>

### Calcium and vitamin D

It is suggested that calcium and vitamin D be used as adjunct therapy in post-menopausal women at high fracture risk.<sup>5</sup> Importantly, most of the major osteoporotic drug trials proving antifracture efficacy include the adjunct use of calcium and vitamin D with the drug.<sup>5</sup> Recommended dosages are similar to those recommended by NOFSA; 1 000 mg of calcium daily,

including dietary contributions, and vitamin D up to 800 iu where deficient.<sup>5,6</sup>

### Non-pharmacological management

It should be noted that the scope of these guidelines only addressed the pharmacological management of osteoporosis, which is only one aspect of disease management. It is not within the scope of this review, however it remains important that all osteoporosis patients undergo a comprehensive fracture risk assessment. This should include factors such as nutrition, lifestyle habits, exercise and a falls risk assessment. A falls risk assessment would include a review of chronic medication with the possible elimination of sedatives, balance assessment, review of eyesight and aids. This is pertinent in South Africa where resources are limited, and appropriate intervention is generally low cost but can be effective.

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