

## Therapy of Osteoporosis

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**Received:** April 04, 2018; **Published:** May 22, 2018

### Abstract

Osteoporosis leads to high risk of preventable fractures. This article describes guideline recommendations for the therapy of this condition which are relevant for the primary care level. Since we have highly effective therapeutic options we should be more aware of these risks and treat them consequently. Basic measurements should be encouraged for all people: regular weight bearing movement, intake of at least 1000mg calcium daily and sufficient supply with vitamin D and avoiding underweight as well as smoking or high alcohol consumption. The following drugs lead to increased risk of falls or bone loss so that their use and dosage should be reviewed critically: glucocorticoids, Thyroxin, proton pump inhibitors, glitazones, antidepressants, sedatives, neuroleptic drugs and antihypertensives (avoid orthostatic effects). Several endocrine diseases foster osteoporosis and should be treated adequately. Specific therapy is only indicated in persons with high fracture risk. This can be calculated by different tools like Frax (evaluated in many countries), Q-risk (especially in UK) or DVO-recommendations (German speaking countries). Also the recommended thresholds are slightly different. In case of risk for major fractures >10% within the next 10 years and bone mineral density  $\leq -2,5$  T-value according to DXA-measurement therapy with oral bisphosphonates is cost-effective. With BMD  $>-2,0$  (with high-dose glucocorticoids  $>-1,5$ ) and in men beneficial effect of specific therapy is less well proven. Several other drugs given orally or parenteral have good evidence base of effectiveness. The article describes strengths and limitations of different drug classes. During and after specific therapy basic measurements should be realized consequently. After fractures usually supportive therapy is necessary. These are especially pain therapy with drugs or orthosis or surgery and physiotherapy. Fracture liaison services and psychosocial support can improve adherence to therapy. Controls: 3 to 6 months after introduction of new drugs adherence and subjective effects should be evaluated. After 3 to 5 years of specific therapy or after cessation of high risk status the continuation of therapy should be critically reassessed. Especially Alendronat and Zoledronat have long persistence in bone and hence effects after cessation.

**Keywords:** Fracture; Guideline; Osteoporosis; Therapy

### Background

Osteoporosis is a systemic skeletal condition characterized by low bone mass and microarchitectural deterioration of bone tissue that increases bone fragility and risk for fractures. Estimates indicate that as many as 50 percent of Americans age > 50 years will be at risk for osteoporotic fractures during their lifetimes [1]. The World Health Organization (WHO) has defined osteoporosis to exist in postmenopausal women or men when axial bone density T-score (measured by dual-energy X-ray absorptiometry (DXA)) at the femoral neck falls 2.5 standard deviations (SD) or more below the average value in young healthy women (T-score  $\leq -2.5$  SD). Severe osteoporosis (established osteoporosis) is defined by bone mineral density (BMD) that is 2.5 SD or more below the young female adult mean in the presence of one or more fragility fractures [2,3]. Despite the fact that we have a bundle of effective preventive and therapeutic interventions in order to reduce the risk of osteoporotic fractures [4,5] these measures are not consequently used in routine care [6].

### Basic measurements

There are a lot of known risk factors for osteoporotic fractures and many of them can be mitigated [7]. Primary care has a special responsibility to keep these aspects in mind and thus being effective in primary and secondary prevention and we should act here also on the public health level.

Weight-bearing movement: we should advise all persons to be physically active regularly according to their functional status, especially improving muscle strength and coordination.

Sufficient supply with Calcium: the daily intake should be 1000-1500 mg. There are calcium calculators by which patients can see whether their intake is according to this. If this cannot be achieved, supplements are recommended.

Sufficient supply with Vitamin D: if there is not enough exposition to UV-light or endogene transformation is inhibited this leads to secondary hyperparathyroidism and loss of bone mass. In case of signs of lacking Vitamin D this should be supplemented with 800 - 1000 IU daily.

Sufficient supply with Vitamin B12, folic acid, no smoking or high alcohol consumption, no underweight is recommended. Glucocorticoids including high dosage of inhalatives, Thyroxin especially when TSH is suppressed, antiepileptics, long-term use of proton pump inhibitors and glitazones increase fracture risk.

All factors which increase risk of falls also increase risk of fractures. So we should assess risk of falls and try to influence risk factors. These are among others medications with central effects like antidepressants, sedatives, neuroleptic drugs, antihypertensives (due to orthostatic effects).

Drug review with critical evaluation of indication and dosage should lead to reduce these risks.

Other risk factors which can be treated are hyperthyroidism, Cushing's Syndrome, primary or secondary hypogonadism, lack of growth hormone.

### Specific therapy

There are several approved medications with proven reduction of fracture risk in high-risk patients. Approximately they reduce typical osteoporotic fractures by 50% and peripheral fractures by one third in patients with osteoporosis. When should they be used? The guidelines mentioned above give different recommendations. Internationally, Frax is the most used tool with adaptation to several countries [8]. Q-Fracture risk tool is very well evaluated in Great Britain but does not integrate bone density measurement [9]. The German DVO-Score will be re-calculated by the end of this year. Until then, the calculation from the recent guideline can be used [7]. Oral Bisphosphonates are cost effective at least from a risk for major fractures >10% and DXA T-Score  $\leq -2,5$  [5]. German speaking countries recommend specific therapy with a risk for vertebral (including those which are only radiologically confirmed) and hip fractures  $\geq 30\%$  for the next 10 years and T-Score  $\leq 2,0$  (with high dose Glucocorticoids  $\leq -1,5$ ). There are some more remarks which are of interest for special situations and hence specialists. In case of renal insufficiency (GFR < 30l/min) nephrologists should recommend the drugs to be used. Evidence for risks and effects in men is much less than for women.

The following table shows the most used and approved drugs with good evidence for fracture reduction (adapted from [7]).

Substance	Less vertebral fractures	Less peripheral fractures	Less hip fractures
Alendronat	A	A	A
Risedronat	A	A	A
Ibandronat+	A	B	-
Zoledronat	A	A	A
Denosumab	A	A	A
Raloxifen+	A	-	-
Teriparatid*	A	B	-
Estrogens +**	A	A	A

Table

A: Good evidence (SIGN 1) B: Evidence-level less sure (SIGN 2). \*: Has to be stopped after 48 months \*\*: Only, if indicated by other reasons or other drugs not possible/effective +not approved for men.

For differential use contraindications, costs, risks, additional effects, mode of application and patient's preferences shall be taken into account. In general, oral Alendronat and Risedronat once weekly have the best cost-benefit ratio. Alendronat [10] and Zoledronat [11] have a long persistence in bone tissue, so that the therapeutic effects last longer after interruption of treatment than in most other drugs. Typical side-effects (see official informations about these drugs) are: esophagitis in oral bisphosphonates, acute phase reactions in parenteral bisphosphonates, and rarely: osteonecrosis and atypical femoral fractures in bisphosphonates and denosumab, thromboembolic events in estrogens and Raloxifen. In Denosumab which is given twice yearly subcutaneously and parenteral bisphosphonates dangerous hypocalcemia can occur so that sufficient supplementation in these phases are strongly recommended. Before and during application of bisphosphonates and Denosumab teeth should be treated carefully. Basic measurements shall be followed continuously and consequently.

### Supportive therapy

In case of pain due to fractures or persistent deformity adequate pain management is important. These include physiotherapy and rehabilitation, self help groups, pain medication and orthoses. Kyphoplastie/Vertebroplastie is only indicated if pain after acute fracture cannot be alleviated adequately and an interprofessional conference recommends such an operation [7]. Psychosocial support increases adherence to therapy and patient satisfaction [12]. Fracture liaison services are also helpful in this respect [6].

### Controls

After 3 to 6 months subjective treatment effects and adherence should be evaluated. Specific treatment can be stopped, if there is no longer a high fracture risk. If more than one fracture occurs during 3 years of treatment change of therapeutic concept should be considered. Generally, after 3 to 5 years of treatment risks and benefits of continuing or stopping the drug should be reassessed. But there is no clear evidence about the preferable duration of specific therapy. It is also unclear whether controlling of DXA-measurement is generally beneficial.

### Conclusion

Guidelines for osteoporosis give clear recommendations for proven effective measurements in order to treat osteoporosis and prevent many fractures in our ageing population. In practice, this is not consequently put into reality and we can do better.

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**Volume 9 Issue 6 June 2018**

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