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# Side effects of drugs for osteoporosis and metastatic bone disease

Michael Kriegbaum Skjødt, MD<sup>1,2</sup> Morten Frost, MD PhD<sup>3,4</sup> Bo Abrahamsen, MD PhD<sup>1,5</sup>

1 Department of Medicine, Holbæk Hospital, DK-4300 Holbæk, Denmark

2 Department of Medicine, Slagelse Hospital, DK-4200 Slagelse, Denmark

3 Department of Endocrinology M, Odense University Hospital, DK-5000 Odense C, Denmark

4 Steno Diabetes Centre Odense, DK-5000 Odense C, Denmark

5 Odense Patient Data Explorative Network, Institute of Clinical Research University of Southern Denmark and Odense University Hospital, DK-5000 Odense C, Denmark,

## Corresponding author

Bo Abrahamsen: [b.abrahamsen@physician.dk](mailto:b.abrahamsen@physician.dk)

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## Abstract

Osteoporosis is a common condition that leads to substantial morbidity and mortality and affects an increasing number of persons worldwide. Several pharmacological therapies that inhibit bone resorption, promote bone formation, or both, are available for the treatment of osteoporosis. The osteoanabolic treatment spectrum was recently expanded by the introduction of a novel bone-forming agent in the United States, and clinical trials indicate that a new class of bone anabolic therapy may become available. Both antiresorptive and bone anabolic therapies are associated with common and rare adverse effects, which are particularly important to address as these drugs are used for long-term treatment in numerous patients with a large proportion being elderly and/or having multimorbidity. In addition, antiresorptive drugs are used to inhibit bone resorption in patients with malignant hypercalcaemia or to prevent skeletal events in cancer patients, and bisphosphonates have been repurposed as a cancer preventive therapy. However, therapeutic doses are generally higher when antiresorptive drugs are used in the oncological setting, which influence the prevalence of adverse effects significantly. This review highlights key issues and controversies regarding adverse effects of currently available and emerging drugs used for osteoporosis and metastatic bone disease.

## Introduction

With increasing longevity, conditions commonly occurring in the elderly including osteoporosis and cancer affect an increasing number of patients[1]. Bone loss with impairment of bone microarchitecture and strength develops with advancing age. Patients undergoing cancer treatments commonly require sex hormone depleting therapies, which may cause osteoporosis and increase fracture risk[2]. Additionally, bone metastases themselves are a common cause of fractures.

Insight into bone remodelling has paved the way for developments of treatments that exercise antiresorptive effects through inhibition of osteoclast activity or increase bone formation by promoting remodelling, effectively increasing bone matrix volume and reducing the incidence of osteoporotic fractures. The antiresorptive treatments comprise selective oestrogen receptor modulators[3], bisphosphonates[4, 5], and denosumab[6], and used to include strontium[7], which has been discontinued due to side effects, and oestrogen replacement[8], generally considered unfavourable due to concerns regarding the balance in risks and benefits in older women. However, strong case remains for oestrogen replacement to preserve skeletal health in the setting of premature or early menopause. Prevailing bone forming therapies include teriparatide[9] and abaloparatide[10], while romosozumab[11] is emerging as a promising osteoporosis therapy that reduces fracture risk in osteoporotic patients. Bisphosphonates and denosumab prevent skeletal-related events in cancer patients[12], and bisphosphonates counteract development of bone metastases in postmenopausal women[13]. Moreover, bisphosphonates and denosumab are effective treatments of hypercalcaemia caused by bone metastases or secretion of parathyroid hormone related peptide (PTHrP) by tumours[14].

Although osteoporosis is a chronic condition, duration of osteoporosis treatment generally depends on fracture risk. For this reason, osteoporosis patients at high risk of fragility fractures may require long-term treatment, stressing the importance of long term safety, generally exceeding the length of randomized clinical trials (RCTs). By comparison, the antiresorptive drugs are generally used for a shorter period (albeit at a higher dose) in cancer treatment. Short-term safety is often uncovered in clinical trials, but long-term side effects are rarely assessable in clinical trials, however, register-based studies have disclosed rare and dose-dependent adverse effects.

This review focuses on the short- and long-term safety in clinical use of currently available and emerging therapies of osteoporosis and skeletal-related events in cancer. The length of the sections below do not in themselves indicate whether one class of pharmaceuticals is safer than another but

merely the availability of more safety observations for the older compounds due to their longer time on the market and larger utilisation (Fig 1).

## Anti-resorptives

### Bisphosphonates

First introduced as a novel class of bone drugs almost fifty years ago[15], the bisphosphonates have been the mainstay of anti-resorptive therapy for the past thirty years and continue to be the most widely used class of specific skeletal agents. Bisphosphonates have large therapeutic areas within metabolic bone diseases including osteoporosis and in the prevention and treatment of skeletal metastases, skeletal adverse events related to cancer therapy and hypercalcaemia within the broad theme of oncology. Adverse effects of bisphosphonates fall into two distinct categories. One category is thought to follow directly from the desired mechanism of action and includes Atypical Femur Fractures and Osteonecrosis of the Jaw. These are not specific to bisphosphonates but can also be seen with other potent antiresorptives such as denosumab, which is addressed below. The other category covers adverse effects that are not skeletal in nature and which may differ between different agents within the group, such as between intravenous and oral bisphosphonates or between nitrogen-containing and non-nitrogen containing bisphosphonates[16].

Atypical femur fractures (AFF) are fractures of the subtrochanteric femur or the femoral shaft that satisfy specific clinical and chiefly radiological criteria[17]. In brief, these fractures are believed to arise from over-hardening and loss of flexibility at the areas of maximum tensile loading at the lateral aspect of the femur. A national radiology review in Sweden revealed a total of 172 such fractures over a three year period, during which 43,000 hip fractures occurred in the same population[18]. An exponential increase in risk with increasing duration of use has been inferred from observational cohorts and the current preventive strategy consists in shortening the duration of treatment to 3 to 5 years in patients at lower or moderate risk but continued treatment for ten years or longer in those who remain at high risk of osteoporotic fractures[19]. The role of drug holidays remains controversial though reports of increased or high fracture risk in this setting is based on small case series[20, 21]. By contrast, the judicious use of drug holidays was associated with a low relative risk of fractures in a large observational study using health data from four Kaiser Permanente health regions[22]. Here the risk of osteoporotic fractures remained as low - or lower - during drug holidays in excess of 12 months as the risk in those who continued on treatment after having been established on bisphosphonates for three years. It stands to reason that drug holidays

would have been targeted to patients who were clinically deemed to be at relatively low risk of fractures and that these results will be unlikely to extend to patients at high risk of fractures.

Osteonecrosis of the jaw (ONJ) is a slowly healing or non-healing lesion of the oral mucosa with exposure and potentially necrosis of the underlying bone, which may require surgical intervention though many milder lesions heal on conservative treatment. Though the mechanism remains to be fully elucidated, the condition is most commonly seen in patients who have received several courses of intravenous bisphosphonates or other potent antiresorptive agents, usually in an oncology setting - e.g. multiple myeloma or breast cancer - and often in conjunction with other anti-cancer agents such as anti-angiogenesis agents and/or systemic glucocorticoids. In multiple myeloma, a meta-analysis of 24 studies found that about 1:1000 patients in bisphosphonate myeloma studies developed ONJ[23]. Though the incidence rates of ONJ in the dosing regimens used for osteoporosis has varied substantially between different observational studies, it has generally been found to be ten fold lower than for the cancer regimes[24]. Specifically, using nationwide hospital and prescription data, the risk of ONJ severe enough to require surgical treatment has been estimated to be 2.5 per 10,000 patient years in Danish patients treated with oral bisphosphonates[25].

Upper gastrointestinal adverse effects are very common with oral bisphosphonates, especially in patients with pre-existing gastroesophageal reflux[26]. Because sodium alendronate only dissolves at low pH, damage to the oesophageal mucosa is more likely when the mucosa is exposed to a bisphosphonate that is returned from the ventricle. Correct instruction to the patient is very important and physicians should not try to treat GI side effects by adding a proton pump inhibitor, which have been linked to added fracture risk. It is unclear if there is an increased risk of oesophageal cancer attributable directly to oral bisphosphonate use[27–29]. Interestingly, there is no excess oesophageal cancer mortality in oral bisphosphonate users though the prognosis of oesophageal cancer is known to be poor[27]. As a group, osteoporosis patients may have an increased oesophageal cancer risk due to a higher prevalence of smoking and alcohol consumption, both being risk factors for osteoporotic fractures. Because a nominal reduction in gastric cancer risk has been reported in oral bisphosphonate users it is possible that oral bisphosphonate users and the background population do not differ in the combined incidence of oesophageal and gastric cancer but that the higher frequency of endoscopy in oral bisphosphonate users may allow earlier detection of adenocarcinomas at a stage where their origin can still be established as being the lower oesophagus as opposed to the ventricle[27, 29]. Though gastrointestinal AEs are also occasionally seen with intravenous BPs, in clinical practice most patients who stop oral bisphosphonate due to GI issues can be successfully switched to parenteral treatment.

Musculoskeletal pain is not uncommon, especially after intravenous bisphosphonate therapy where pain may occur in isolation or accompanying flu-like pyrexia symptoms. In the initial trial of Zoledronic acid, for example, 31.6% of those receiving active treatment experienced some type of post-dose pain or febrile symptom. Pyrexia was experienced by 16%, myalgia by 9.5% and arthralgia by 6.3%[5]. Subsequent doses are less likely to elicit flu-like symptoms. Musculoskeletal pain is less common with oral bisphosphonates, where the prevalence has been reported to be 5.6%[30].

Bisphosphonates are cleared rapidly from the circulation by renal filtration and all bisphosphonates come with the caveat that they should be avoided in patients with a creatinine clearance below 30 to 35 ml, depending on the drug in question. The absolute risk of causing renal function impairment depends strongly on the clinical circumstances. Hence for zoledronic acid, the HORIZON primary prevention trial in postmenopausal women found that 1.2% of patients experienced transient increases in serum creatinine of 0.5 mg/dl or over, compared with 0.4% in the placebo group[5]. By contrast, in multiple myeloma, which in itself carries a risk of renal function impairment, acute renal failure events has been reported to occur in 5 to 6% of patients treated with intravenous bisphosphonates[31]. With oral bisphosphonates used for osteoporosis in the elderly, a register based study in Ontario comprising 18,000 alendronate users in a secondary prevention scenario found no increased risk of acute kidney injury compared to matched untreated control subjects[32].

Cardiovascular harms or benefits with bisphosphonates remain controversial and it will not be possible to do justice to the full scientific discussion given the space available here. RCT data support an increased risk of episodes of atrial fibrillation after zoledronic acid in postmenopausal women[5] though this was not the case in a more fragile study population of hip fracture patients[33]. An increased incidence of heart failure with bisphosphonates has been reported in observational studies from Denmark[34] and Taiwan[35]. In the Danish study, oral bisphosphonate use was linked to increased occurrence of heart failure. However, the risk decreased with increased adherence and was present even if only one prescription had been filled, suggesting that allocation bias plays a role. In the Taiwanese study, nitrogen-containing bisphosphonates were linked to a higher incidence of heart failure (adjusted hazard ratio 1.65, 95% CI 1.36-1.99). A pathophysiological pathway for such an effect is not known. Effects on the risk of myocardial infarction are controversial with no excess or reduced risk suggested in published RCTs. However, preliminary RCT results[36] (and Reid, personal correspondence) for zoledronic acid given every 18 months for 6 years in women with osteopenia found a fairly substantial lowering of myocardial infarction risk with this treatment (rate ratio 0.6, 95% CI 0.3-0.9) and a reduced mortality (rate ratio 0.7, 95% CI 0.4-1.1), the latter suggesting that the reduced mortality reported in observational studies[37] should perhaps not be attributed to allocation bias as has been the matter of some controversy in the past[16].

## Denosumab

Denosumab, a biological therapeutic that interferes with the main signalling pathway for osteoclast activation, differs radically from other drugs for osteoporosis and bone metastatic disease by being nominally not contraindicated in patients with impaired renal function. However, though elimination of denosumab is not by any renal route, lowering bone turnover in persons with CKD accompanied by low turnover CKD-MBD could lead to development of adynamic bone disease with added bone fragility. Also, it is important for clinicians to be aware that severe hypocalcaemia requiring acute hospitalisation[38–40] can develop in CKD patients as the requirement for  $1\alpha$ -25(OH)<sub>2</sub>-vitamin D may increase to meet the demands of an increased flux of calcium and phosphate into the skeleton with denosumab, a condition akin to hungry bone syndrome. Similarly, denosumab and other strong anti-resorptive agents should be avoided in patients with hypoparathyroidism as the normal increase in PTH to offset the drop in serum calcium will be absent or insufficient in these patients. In the oncology setting, denosumab has a clinical profile that is fairly comparable to that of zoledronic acid though with a lower occurrence of renal adverse events. Hence, a recent RCT in multiple myeloma[41] reported renal AEs in 17% of patients treated with zoledronic acid against 10% in the denosumab arm. Though skin and urinary infections are seen with denosumab in the osteoporosis setting, there appeared to be no difference between the two drugs regarding infections in the myeloma trial. A US register-based study comparing adverse events in patients treated with denosumab for osteoporosis, using zoledronic acid as the comparator, revealed no significant differences in serious infections (26 per 1000 person years with denosumab and 31 per 1000 person years with zoledronic acid) or any differences regarding CVD outcomes. Denosumab shares the risk of ONJ and AFF with other potent antiresorptive agents, both within the osteoporosis area and within oncology. Commonly reported adverse events in the primary RCT for postmenopausal osteoporosis were flatulence and skeletal pain.

## Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) is a class of drugs with varying agonistic and antagonistic effects on estrogen receptors, and thus different indications[42]. In osteoporosis, two SERMs are available, namely raloxifene and bazedoxifene. The key concern related to these drugs is venous thromboembolism (VTE), while other common adverse events include hot flashes, leg cramps, and peripheral edema[42].



The safety of raloxifene in postmenopausal women has been evaluated in several, large-scale, long-term clinical trials against placebo and active comparators (alendronate and tamoxifen, respectively)[43–49]. These trials have demonstrated the cardiovascular (CV) safety of raloxifene, with no significant overall differences between treatment groups in terms of CV, coronary, or cerebrovascular events[43–46]. However, in the RUTH trial (10,101 postmenopausal women with high CV risk or established coronary heart disease, randomized to raloxifene 60 mg once daily or placebo, and followed for a median of 5.56 years), a higher risk of fatal stroke was noted with raloxifene vs placebo (HR 1.49; 95% CI 1.00-2.24)[43, 50]. This was attributable to ischemic and undetermined stroke[50]. There was no difference in the total incidence of stroke between groups nor in the incidence of atrial fibrillation, and this finding has not been observed in the other large-scale clinical trials with raloxifene[43–46, 50].

In RCTs, the risk of VTE, including deep vein thrombosis and pulmonary embolism, has been found to be increased with the use of raloxifene. The risk was approximately 1.4 to 3.1 fold higher than with placebo, and tended to decrease over time[3, 43, 51]. When compared to tamoxifen, the risk of VTE was 30% lower with raloxifene (RR 0.70; 95% CI 0.54-0.91)[48]. Both raloxifene and bazedoxifene are contraindicated in patients with a history of VTE, while treatment should be paused during planned or persisting immobilization[42, 52–56].

Raloxifene reduces the risk of breast cancers, driven by a reduction in invasive, estrogen-receptor (ER) positive breast cancers[43, 47, 49]. In RUTH, the hazard ratio of invasive ER-positive breast cancer with raloxifene vs placebo was 0.45 (95% CI 0.28-0.72)[43]. There seem to be no effect on non-invasive and invasive ER-negative breast cancers[43, 47, 49]. Also, there appears to be no effect of Raloxifene on the risk of endometrial cancer vs placebo, while a non-significant risk reduction for uterine cancers was observed when compared to tamoxifen, which is known to increase the risk of uterine cancer[43, 47–49, 57].

Bazedoxifene is a more recent SERM for osteoporosis, and is less extensively studied. The safety profile appear to be comparable to raloxifene in a head-to-head study as well as in a recent meta-analysis[58, 59]. Bazedoxifene is noted to increase the risk of somnolence, visual disturbances, and increased levels of triglycerides, alanine aminotransferase and aspartate aminotransferase[56].

## Bone anabolics

### Teriparatide

Osteoanabolic treatments are characterised by their ability to stimulate bone formation and improve cortical and trabecular bone microarchitecture[60]. Parathyroid hormone (PTH) exerts effects on calcium metabolism and bone cell activity by binding to the parathyroid hormone type 1 receptor (PTHr1). Contrary to continuous stimulation, temporary stimuli of PTHr1 promote bone formation, but both types of stimuli may lead to hypercalcaemia.

Recombinant human parathyroid hormone teriparatide (rhPTH 1-34) was the first osteoanabolic drug to be approved for the treatment of postmenopausal osteoporosis. The pivotal fracture trial that included 1,637 postmenopausal women showed similar rates of serious adverse events in teriparatide and placebo groups. Compared to the latter, dizziness and leg cramps were more common in the teriparatide group, who were also more likely (11% vs. 2% on placebo) to develop post-dose hypercalcaemia[9], but the proportion of participants that withdrew from the study was similar in those treated with placebo and the usual dose of teriparatide. The trial was stopped after 21 months due to emergence of osteosarcoma in rats treated life-long with teriparatide[61], however, neither of the participants developed osteosarcoma[9], and carcinogenic effects of teriparatide in humans have not been corroborated by subsequent post-marketing, register-based studies[62, 63].

The overall incidence of adverse events in patients treated with teriparatide or placebo or active comparators such as alendronate and risedronate is generally comparable. However, teriparatide may cause nausea, arthralgia, dizziness, headache, muscle, leg cramps as well as hypercalcaemia[64–72]. In contrast to what was observed in subjects with osteoporosis[69, 70], hypercalcaemia was not observed in patients treated with teriparatide for osteogenesis imperfecta[71]. In general, teriparatide-induced hypercalcaemia is asymptomatic and transient, and wanes with reduction in dose or by reducing calcium supplements.

### Abaloparatide

The PTHrP analogue abaloparatide binds with greater affinity to a PTHr1 receptor conformation that associates with temporary signalling than teriparatide, indicating a more pronounced effect on bone formation and lower risk of hypercalcaemia than with teriparatide[73]. Like teriparatide, chronic exposure to abaloparatide may cause osteosarcoma in rats[74], limiting the acceptable treatment duration in humans.

Abaloparatide recently emerged as an osteoanabolic therapy[75]. Therefore, information on adverse effects of abaloparatide is derived from clinical trials with participants followed for up to 43 months. Similar rates of adverse events were observed in a 24-weeks dose-finding study that compared the effects of placebo, teriparatide or abaloparatide in 164 postmenopausal women with osteoporosis[76]. However, the incidence of post-dose hypercalcaemia was higher with teriparatide (40%) than abaloparatide (7%-14%) or placebo. The effect of treatment for 18 months with abaloparatide, teriparatide, or placebo on new morphometric vertebral fractures in 2,463 postmenopausal women with osteoporosis showed similar incidence of serious adverse events in all groups[10]. The proportion of adverse events that lead to early discontinuation was higher in those treated with abaloparatide than in participants on placebo or teriparatide, primarily due to nausea, dizziness, and palpitations. Abaloparatide treatment associated with lower incidence of hypercalcaemia than teriparatide treatment (3.4% vs. 6.4%)[10]. Among the 1,139 participants of the 24-months extension trial, similar rates of adverse events were observed in those previously treated with placebo or abaloparatide. Neither atypical femoral fractures nor osteonecrosis of the jaw was reported in the clinical trials [10, 77].

Although the dropout-rate was higher and hypercalcaemia less frequent on abaloparatide than teriparatide treatment in the fracture trial, data indicates that the safety profiles of these drugs are comparable. Future studies may provide further evidence of long-term safety of abaloparatide treatment.

### Romsozumab

In osteoporosis, the efficacy and safety of Romsozumab (a pre-marketing, sclerostin inhibitor antibody) has been evaluated in phase 2 and 3 clinical trials enrolling a total of more than 12,000 postmenopausal women[11, 78–84]. These trials evaluated Romsozumab against alendronate, teriparatide, and/or placebo, and some included extensions where Romsozumab groups were transitioned to anti-remodeling therapy[11, 80–84]. Here we shall focus on the safety profile during Romsozumab therapy.

In general, Romsozumab was well tolerated. Across the trials, rates of adverse and serious adverse events were comparable between Romsozumab and comparator groups[11, 80–84]. With Romsozumab, injection site reactions occurred in 3.2-15.3% as compared to 1.6-4% in the comparator groups[11, 80–84]. Romsozumab antibodies were detected in 15.3-32.1%, with in vitro neutralizing activity in 0-7.9%, but with no effect on efficacy and safety[11, 80–84]. Few cases of atypical femoral fracture and osteonecrosis of the jaw were observed, and they were generally balanced between Romsozumab and comparator groups[11, 80–84].

In the ARCH-trial, an imbalance in adjudicated serious cardiovascular (CV) events was observed with Romosozumab (2.5%) vs alendronate (1.9%)[odds ratio (OR) 1.31; 95% CI 0.85-2.0][11]. Sixteen patients on Romosozumab (0.8%) vs 6 (0.3%) on alendronate reported coronary ischaemic events (OR 2.65; 95% CI 1.03-6.77), while 16 (0.8%) and 7 (0.3%) reported cerebrovascular events, respectively (OR 2.27; 95% CI 0.93-5.22)[11]. It has been speculated that sclerostin may play a down-regulating role in vascular calcification, although patients with hereditary sclerostin deficiency have not in fact been observed to be at an increased CV risk[11, 85, 86].

In contrast, a CV outcomes imbalance has not been reported in other romosozumab trials[80–84]. There are at least two possible explanations why romosozumab can have a placebo level CV disease signal, yet show a risk increase in the active comparator trial against alendronate. First, ARCH recruited older women with more advanced stages of osteoporosis and it is possible that cardiovascular effects may differ in older subjects who already have more established atherosclerosis. Second, the comparator drug in ARCH, alendronate, has - albeit controversially - been associated with a reduction in cardiovascular risk[87]. Animal studies have not demonstrated an increased vascular mineralization due to sclerostin inhibition[11]. Further evidence is awaited, including results from a study in Korean women with postmenopausal osteoporosis[79].

The BRIDGE trial evaluated Romosozumab in men aged 55-90 years old with osteoporosis[88]. The safety of Romosozumab was generally comparable to that observed in postmenopausal women, while a non-significant imbalance in cardiovascular events was observed with Romosozumab (8 [4.9%]) as compared with placebo (2 [2.5%])[88]. This may be attributed to more patients in the Romosozumab group having a history of cardiovascular disease at baseline, and among those with such history, fewer patients in the Romosozumab group used any CV-related medication at baseline[88].

### **Nomenclature of Targets and Ligands**

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [appropriate reference number], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [appropriate reference number(s)].

## Conclusion

In this paper we have reviewed the safety of currently available treatments for osteoporosis and bone metastasis, as well as one emerging, pre-marketing treatment. While these treatments can be classified as anti-resorptive or osteoanabolic, respectively inhibiting osteoclast resorptive activity or stimulating osteoblast remodeling activity, they exercise their effects by different modes of action, thus constituting very different safety profiles[4–6, 9, 10, 42, 84].

In cancer, several chemotherapeutics, amongst others aromatase inhibitors and gonadotropin-releasing hormone agonists, induces bone loss, while bone metastases may cause fractures[2, 89]. Bisphosphonates and denosumab may prevent aromatase inhibitor induced bone loss as well as skeletal related events in cancer patients with bone metastases, while bisphosphonates may be used to treat androgen-deprivation therapy induced bone loss and limit the recurrence of bone metastases in postmenopausal women with breast cancer[12, 13, 89, 90].

In general, there seems to be no increased risk of cancer with osteoporosis treatments. Bisphosphonates have been statistically associated with oesophageal cancer incidence, yet it is unclear if this is a true treatment effect or rather due to confounding factors in the osteoporosis population[27–29]. The latter is more likely since no excess oesophageal cancer mortality has been found. Abaloparatide and teriparatide have been associated with osteosarcoma in rats, although such adverse effects have not been observed in humans[9, 61–63, 74]. Raloxifene is associated with a significant risk reduction for invasive ER-positive breast cancer[43, 47–49].

While this review has provided an overview of the safety profiles of osteoporosis treatments, there are reported adverse events that we did not include in order to conserve space. Indeed, this narrative review includes the safety concerns judged most relevant by the authors of this paper. The prescribing information of the medication in question should be consulted for more detailed safety information prior to prescribing. Another limitation is that clinical trials may not be ideal for identifying rare or slowly developing adverse effects and many real world users differ from the RCT participants on key parameters[91]. Hence observational studies and post-marketing safety surveillance is needed, and for the more recent medications in osteoporosis, particularly abaloparatide and romosozumab, awaited.

In conclusion, this review has highlighted the clinically most important or most controversial safety concerns of available and emerging osteoporosis treatments. In addition we have reviewed how these drugs perform when used in the oncology area where doses are generally higher and treatment duration often shorter. In our clinical work we recognize that the available therapeutics in this area differ more in their adverse event profiles and administration form than in the absolute risk reductions that they achieve, yet the final choice of therapy should always depend on an assessment of the pros and cons of the treatment as well as the individual medical history, personal preferences and concerns of the patient in question.

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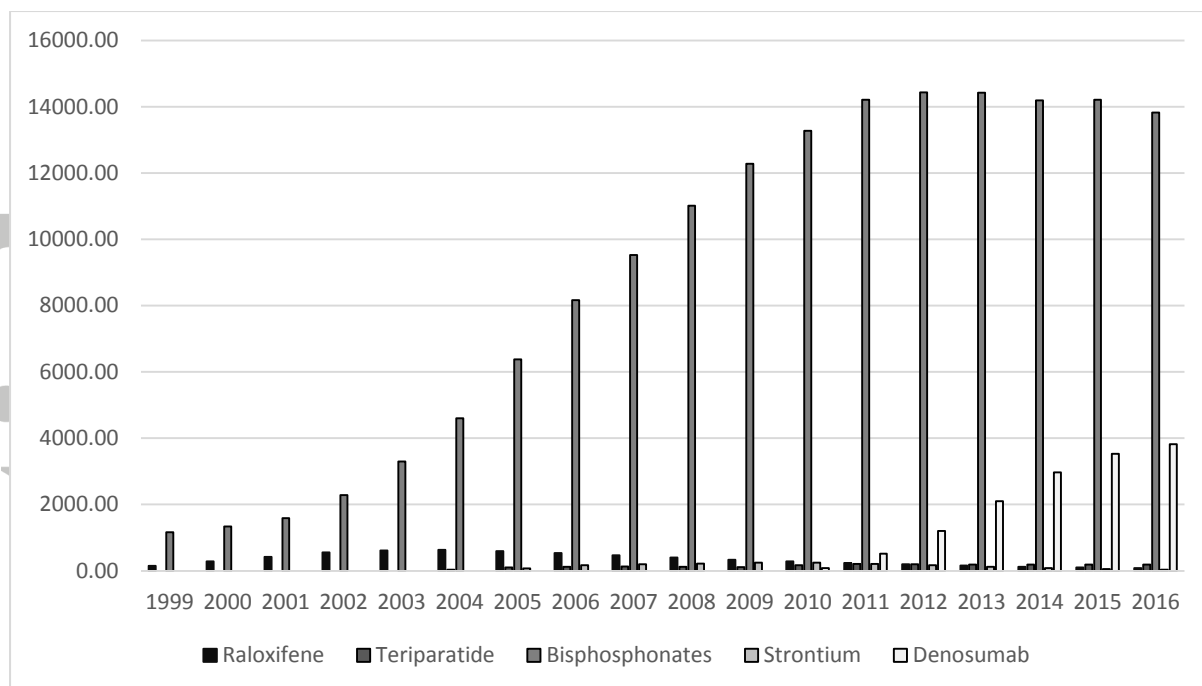
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**Figure 1: Total sale (DDD) of osteoporosis medications in Denmark per year per 1,000 persons aged 50 years or older from 1999 to 2016.** Bisphosphonates remains the most commonly used osteoporosis medication. Denosumab use has been steadily increasing since its market introduction. As compared to bisphosphonates and denosumab, raloxifene and teriparatide is less frequently used, while strontium is scarcely used. Abaloparatide is not licensed in Europe. Source: [www.medstat.dk](http://www.medstat.dk) (an open-access, online database of all prescription based and over-the-counter sales of medications in Denmark) and Statistics Denmark ([www.dst.dk](http://www.dst.dk)). DDD, Defined Daily Dose.

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