Review Article

A narrative review of the pharmaceutical management of osteoporosis

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Background and Objective: Osteoporosis is a skeletal disorder classified by the loss of bone density in older adults leading to compromised bone strength and an increased risk of fracture. It can be divided into categories based on its etiology: senile, post-menopausal, and secondary osteoporosis. Specific prevention measures and treatments exist for targeting bone loss. Here we review and summarize the literature regarding the presentation of osteoporosis and discuss pharmaceutical therapies.

Methods: PubMed and Google Scholar were searched for articles published in English between 1980 and 2021. Search terms combined "senile osteoporosis", "osteoporosis treatment", "osteoporosis", "bisphosphonates", "denosumab", types of hormone therapy, and other relevant keywords used in various combinations.

Key Content and Findings: Osteoporosis affects millions but often goes undiagnosed until a pathologic fracture. Dual-energy X-ray absorptiometry (DEXA) scans evaluate bone mineral density (BMD) and are a diagnostic tool for osteoporosis. Adults over the age of 65, post-menopausal women, and those with risk factors such as previous fractures are recommended to receive DEXA scans every one to two years. Bisphosphonates, denosumab, and hormonal therapies are among the most common pharmacologic treatments for osteoporosis.

Conclusions: Daily, orally administered bisphosphonates are the first-line therapy for osteoporosis given their efficacy in decreasing fracture risk and favorable safety profile. Denosumab is an alternative that is administered subcutaneously every six months and may be given as initial therapy to select patients. Hormonal therapies are used if patients cannot tolerate bisphosphonates or denosumab or are refractory to these medications. Preventative measures for osteoporosis include tailored exercise and sufficient intake of calcium and vitamin D via diet or supplementation.

Keywords: Osteoporosis; pharmacology; bisphosphonates; denosumab

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Introduction

Background

A 2014 study reported a 10.3% prevalence of osteoporosis among Americans 50 years or older, equating to 10.2 million people, with an additional 43.4 million experiencing low bone mass (1). Additionally, the annual healthcare cost of osteoporosis and related fractures was estimated to be $16 billion in 2008 (2). These costs are predicted to increase to $25.3 billion by 2025, with approximately 3 million fractures caused by the disorder (3). Deformities including kyphosis and related height loss often accompany senile osteoporosis (4). These financial and physical burdens are likely to grow along with the aging population in the coming years.

Rationale and knowledge gap

Current treatments for osteoporosis include lifestyle modification, pharmacological management, minimally invasive procedures, and extensive surgical treatments. However, only pharmacological management is recognized as treatment for the cause. There is limited literature that provides the efficacy of various medications for osteoporosis and other relevant pharmacological data in a single compiled manuscript.

Objective

The aim of this review is to focus on the pharmacological management of osteoporosis to provide a succinct source of data for practitioners. This review begins with an overview of osteoporosis and its diagnosis, then we discuss the specific medications that can be used to treat osteoporosis, starting with the first-line treatment of bisphosphonates and denosumab and then hormonal therapy. The efficacy of the various medications will also be discussed, along with comparisons between first- and second-line treatments. Finally, we present lifestyle modifications and nutrient supplementations that can influence the pathogenesis of osteoporosis. We present this article in accordance with the Narrative Review reporting checklist (available at https://aoj.amegroups.org/article/view/10.21037/aoj-23-2/rc).

Methods

A comprehensive search of PubMed and Google Scholar was conducted for articles published between 1980 and 2021 in English (*Table 1* and Table S1). Search terms included “osteoporosis”, “senile osteoporosis”, “osteoporosis pharmacology”, and “treatment”. Other relevant keywords were included in various combinations for searches. Articles were also collected by critically examining the reference lists of publications found in the database search. Exclusion criteria included cadaveric studies.

Discussion

Pathophysiology

Osteoporosis may be of a primary or secondary origin, with primary osteoporosis arising more frequently in post-menopausal women but affecting both sexes in old age as bone density and estrogen levels naturally decline (5). Secondary osteoporosis results when the decreased bone density is due to another conduction, such as hypogonadism or celiac disease, or medications, such as glucocorticoids (6).

Osteoporosis reduces bone volume and integrity, rendering patients vulnerable to fracture and deformity. This can be attributed to an imbalance of osteoblast and osteoclast activity, which results in unequal bone formation and bone reabsorption, respectively (7). Estrogen deficiency may also lead to osteoporosis as estrogen plays an important role in increasing the storage pool of pre-osteoclasts, as well as upregulating transforming growth factor beta (TGF-β), a cytokine that decreases osteoclast activity. Calcium and vitamin D deficiencies also increase the risk of developing osteoporosis because when less calcium is absorbed from the intestinal tract, there is an increased release of stored calcium via osteoclasts in bones to increase serum calcium. The increased osteoclastic activity causes further bone loss and an increased risk of fractures (5).

It is estimated that 1 in 2 women along with up to 1 in 4 men 50 years old and older living with osteoporosis will break a bone due to the disorder. Since osteoporosis weakens bone strength, bone fractures are typically the first sign of the disorder, as one is not able to feel their bones weakening. These fractures are mostly seen in the hip, distal radius, and spine. While these are the frequently seen fractures, there has been an increase in the number of fractures and the types of fractures that should be considered osteoporotic (4). Those who experience a fracture are at an increased risk of subsequent fractures in the future: 10% within one year, 18% within two years, and 31% within 5 years (8). Kyphosis is another sign seen in those with osteoporosis, which can lead to visible height loss (4).

Table 1 The search strategy summary

Items	Specification
Date of search	March 30, 2022
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Osteoporosis, Osteoporosis treatment, Senile osteoporosis, Osteoporosis pharmacology, Osteoporosis medication, Bisphosphonate, Alendronate, Ibandronate, Risedronate, Zoledronate, Denosumab, Raloxifene, Teriparatide, Abaloparatide, Calcitonin
Timeframe	1980–2021
Inclusion and exclusion criteria	Inclusion criteria: (I) written in English; (II) reporting various outcome measurements of different medications; (III) peer-reviewed
	Exclusion criteria: (I) articles not written in English; (II) studies only reporting drug-induced osteoporosis; (III) posters or abstracts at annual meetings; (IV) graduate theses without peer-reviewed publication of an article
Selection process	Three authors independently reviewed the title and abstracts of each article identified in the search. If the articles were appropriate and additional information was necessary, full-text articles were retrieved and data were extracted. If three authors differed on whether to include an article, the fourth author was consulted to achieve consensus

Table 2 National Osteoporosis Foundation DEXA scan recommendations

Women	Men
Age 65 and older	Age 70 and older
Age below 65 and post-menopausal	Age 50–69 with risk factors
Age 50 and older with history of fracture in adulthood	

DEXA, dual-energy X-ray absorptiometry.

Diagnosis

Fractures are typically the first indicator of osteoporosis, as age-related loss of bone density is otherwise difficult to perceive. Estimates of bone mineral density (BMD) can be made using noninvasive dual-energy X-ray absorptiometry (DEXA). The National Osteoporosis Foundation (NOF) recommends BMD testing via DEXA based on age, sex, and risk factors (9) (*Table 2*). After diagnosis and initiation of therapy, BMD testing should be repeated every two years, and more often in the case of recurring fractures (10). The time between scans can also be increased to 15 years in patients with normal BMD or mild osteopenia or five years in patients with moderate osteopenia (11). Osteopenia can be distinguished from osteoporosis by the T-score of BMD testing, with a T-score between –1.01 and –2.49 indicating osteopenia and –2.50 or lower being osteoporosis (11). While it is important to note that BMD test results do not always correlate with fracture probability, early identification of low BMD can inform preventative clinical decision-making (12).

Pharmacological management

First line—bisphosphonates

Mechanism of action and efficacy

Bisphosphonates are Food and Drug Administration (FDA)-approved for the prevention and treatment of osteoporosis. Due to their high affinity for bone mineral and ability to bind to hydroxyapatite crystals, these drugs work well to inhibit osteoclast activation and decrease bone resorption, thereby decreasing bone loss (13-15). The mechanism of action for bisphosphonates varies by generation due to the difference in structure. First-generation non-nitrogen-containing bisphosphonates are incorporated into nonhydrolyzable adenosine triphosphate (ATP) once taken up by osteoclasts on the bone surface. These nonhydrolyzable ATP accumulate, inhibiting numerous ATP-dependent cellular processes, which leads to osteoclast apoptosis. Examples of first-generation bisphosphonates include etidronate, clodronate, and tiludronate. Second- and third-generation bisphosphonates, also called aminobisphosphonates, contain a nitrogen side chain, which allows the drug to inhibit the continuation of the mevalonic acid pathway by binding to and inactivating farnesyl

pyrophosphate synthase. This disruption further causes inhibition of posttranslational modifications of proteins, causing osteoclast apoptosis. Alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid are a few of the second- and third-generation bisphosphonates. Another differentiation between the classes of drugs is what cells they target. Non-nitrogen-containing bisphosphonates can affect mammalian cells expressing farnesyl pyrophosphate synthase, whereas nitrogen-containing-bisphosphonates only cause apoptosis in osteoclasts due to their selective affinity to bone mineral (15). This differentiation could be a contributing factor to why nitrogen-containing bisphosphonates are the favorable choice for the treatment of osteoporosis.

Bisphosphonates can be administered orally after a prolonged fast with water and nothing by mouth for 30–60 minutes after or given intravenously (16). The most common side effects are gastrointestinal, including reflux and esophagitis (17). Some rare adverse complications of bisphosphonates include osteonecrosis of the jaw and atypical fractures (16). The use of bisphosphonates and osteonecrosis of the jaw appear to be more prevalent in patients with cancer, but a causal linkage has not been established due to the small number of cases. Similarly, more conclusive data are needed to associate atypical fractures and bisphosphonates as some reports make it difficult to distinguish if the cause of these fractures is due to the medication use or osteoporosis. Despite having a short plasma half-life, bisphosphonates can remain in bone for years (16,18).

Alendronate, an aminobisphosphonate, is one of the most popular prescribed medications for osteoporosis treatment, with approximately 2.01 million US patients estimated to be taking the drug in 2020, according to the Medical Expenditure Panel Survey (MEPS) administered by the Agency for Healthcare Research and Quality (AHRQ) (19). Specifically, for postmenopausal osteoporosis, alendronate has been the most popular anti-osteoporosis drug since 1996 (20). Alendronate decreases the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women when compared to calcium and vitamin D supplementation (21). Over two years, daily administration of alendronate, 10 mg, increased BMD in the lumbar spine and total hip by 7.4% and 4.3%, respectively (*Table 3*). This was a slightly higher increase when compared to a once-weekly administration of alendronate, 70 mg, with lumbar spine and total hip results of 6.8% and 4.1%, respectively. Because these two administration frequencies are therapeutically equivalent, it is suggested to prescribe the once-weekly regimen as it is more convenient and can enhance compliance (40,41).

In terms of fracture risk for postmenopausal women, daily alendronate for one year provided a 47% risk reduction in nonvertebral fractures relative to a placebo (42). Daily alendronate can be tolerable for an extended period, with some treatments lasting up to 10 years. During a 10-year treatment of 10 mg daily alendronate, an increase in BMD was seen, with the greatest in the lumbar spine (13.7%), followed by the trochanter (10.3%), total proximal femur (6.7%), and femoral neck (5.4%) (22).

In men with osteoporosis, alendronate significantly increases the BMD of the spine, hip, and total body, along with decreasing the incidence of vertebral fractures over nonvertebral fractures (23,24).

Another aminobisphosphonate that can be used in osteoporosis treatment is ibandronate. Ibandronate can significantly increase BMD after 12 months of treatment. Administration of ibandronate in postmenopausal women after a cementless total hip arthroplasty can decrease the amount of bone loss within six months (43). Of note, ibandronate has been shown to only prevent spinal fractures and not hip or non-vertebral fractures, despite increasing BMD (21,44).

Risedronate is a third-generation aminobisphosphonate that is suggested to be one of the first bisphosphonates prescribed when treating osteoporosis. Over three years, risedronate has been shown to reduce the rate of vertebral fractures by 41% and nonvertebral fractures by 39% (25). In terms of BMD, when compared to placebo, risedronate had a greater effect on increasing the BMD of the lumbar spine, femoral neck, femoral trochanter, and midshaft of the radius (25). For women with osteoporosis, between the ages of 70–79, the incidence of hip fractures when treated with risedronate is notably lower than the placebo group, 1.9% and 3.2% respectively (45). Risedronate is more potent than alendronate, but overall leads to less of an increase in BMD; however, it remains a viable treatment, especially when considering patients who cannot tolerate the gastrointestinal side effects of alendronate (21,46,47).

Zoledronate is an intravenous aminobisphosphonate that can be administered once yearly and has the highest potency in its class. In postmenopausal women, it considerably decreased the risk of morphometric vertebral fracture by 70% and hip fractures by 41%. Zoledronate was also shown to decrease the risk of nonvertebral and clinical vertebral fractures by 25% and 77%, respectively. Additionally, it markedly increased the BMD of the total hip (6.02%),

Table 3 Commonly prescribed anti-osteoporosis medications and their clinical outcomes (16,22-39)

Drug	Mean effect on BMD				Mean effect on fracture risk/incidence		
	Lumbar spine	Total hip	Femur	Radius	Vertebral	Nonvertebral	Hip
Bisphosphonate							
Alendronate (Fosamax)	↑ 7.1–7.4% Over 2 years[†a] ↑ 13.7% Over 10 years[†a] ↑ 7.1% Over 2 years[‡a]	↑ 4.3% Over 2 years[†a]	Trochanter: ↑ 2.5% Over 2 years[†a] ↑ 13.7% Over 10 years[†a] Proximal: ↑ 6.7% Over 10 years[†a] Neck: ↑ 5.4% Over 10 years[†a] ↑ 2.5% Over 2 years[‡a]	–	RR =0.41 ↓ 59% RR =0.33[‡]	–	–
Ibandronate (Boniva)	–	–	–	–	RR =0.28 (non-significant)	–	–
Risedronate (Actonel)	↑ 5.4% Over 3 years[†a]	–	Trochanter: ↑ 3.3% Over 3 years[†a] Neck: ↑ 1.6% Over 3 years[†a]	↑ 0.2% Over 3 years[†a]	↓ 41% Over 3 years[†a] ↓ 65% Over 1 year[†a]	↓ 39% Over 3 years[†a]	–
Zoledronate (Reclast)	↑ 6.71% Over 3 years[†b]	↑ 6.02% Over 3 years[†b]	Neck: ↑ 5.06% Over 3 years[†b]	–	Morphometric: ↓ 70% Over 3 years[†b] Clinical: ↓ 77% Over 3 years[†b]	↓ 25% Over 3 years[†b]	↓ 40% Over 3 years[†b]
RANKL inhibitor							
Denosumab (Prolia)	–	–	–	–	Radiographic: ↓ 68% Over 3 years[†c]	↓ 20% Over 3 years[†c]	↓ 40% Over 3 years[†c]

Table 3 (*continued*)

Table 3 (*continued*)

Drug	Mean effect on BMD				Mean effect on fracture risk/incidence		
	Lumbar spine	Total hip	Femur	Radius	Vertebral	Nonvertebral	Hip
Hormones							
Raloxifene (Evista)	60 mg: ↑ 2.5–2.6% Over 4 years[†a] 120 mg: ↑ 2.6–2.7% Over 3 years[†a]	–	60 mg: neck: ↑ 2.1% Over 4 years[†a] 120 mg: neck: ↑ 2.3–2.4% Over 3 years[†a]	–	–	–	–
Teriparatide (Forteo)	20 microg: ↑ 9% Over 21 months (average)[†a] ↑ 7.2% Over 18 months[§a] 40 microg: ↑ 13% Over 21 months (average)[†a] ↑ 17.8% Over 30 months[†a]	20 microg: ↑ 3.8% Over 18 months[§a] 40 microg: ↑ 8.1% Over 30 months[†a]	20 microg: neck: ↑ 3% Over 21 months (average)[†a] 40 microg: neck: ↑ 6% Over 21 months (average)[†a] ↑ 10.8% Over 30 months[†a]	40 microg: ↓ 7.1% Over 30 months[†a]	RR =0.40 (not significant)	RR =0.52 (not significant)	–
Calcitonin (Miacalcin)	–	–	–	–	200 IU: ↓ 33%[a]	RR =0.80 (not significant)	–

[a], indicates daily administration; [b], indicates yearly administration; [c], indicates biannual administration. [†], indicates in postmenopausal women; [‡], indicates in men; [§], indicates in men and women glucocorticoid-induced osteoporosis. ↑, indicates an increase; ↓, indicates a decrease. BMD, bone mineral density; RR, risk ratio.

lumbar spine (6.71%), and femoral neck (5.06%) (26). When comparing three and six years of zoledronate infusions, there were no significant differences in the incidence of clinical fractures; meanwhile, there were increases, albeit non-significant, in serious atrial fibrillation events and stroke in the group receiving six years of treatment, showing zoledronate is preferred in a three-year regimen (48). Interestingly, a single infusion has been shown to have a similar reduction in fracture rate compared to three infusions, 32% and 34%, respectively (49). Further studies are needed to directly compare the efficacy of zoledronate and oral bisphosphonates.

Depending on the patient's risk of fractures, a bisphosphonate drug holiday could be warranted. Because bisphosphonates accumulate in bone and continue to have effects after discontinuation of treatment, it is not necessary for low-risk patients to continue the regimen. For these patients, treatment can be stopped after approximately five years and does not need to continue if bone density is stable and there are no fractures. For higher-risk patients, bisphosphonate therapy can be initiated for 10 years followed by a holiday of one or two years, maximum. Non-bisphosphonate therapy could be indicated for higher-risk patients during their drug holiday (16). The length of the drug holiday depends on the specific bisphosphonate. For example, discontinuation from risedronate would have a

shorter drug holiday (1–2 years) compared to zoledronate (3–6 years) (50). During the drug holiday, the patient's bone density and relevant markers should be monitored (16). For all patients, if there is a fracture or other factors arise that increase fracture risk, then bisphosphonate or other osteoporosis therapy should be initiated.

Second line—denosumab and hormonal therapy

Denosumab: mechanism of action and efficacy

Denosumab is a human monoclonal antibody that decreases bone resorption by inhibiting receptor activator of nuclear factor kappa-B ligand (RANKL), which is involved in the formation and activation of osteoclasts. It is administered every six months subcutaneously by a healthcare professional, benefiting those patients who cannot use oral therapy or are at high risk for fractures (27,51,52). Fatigue and weakness are some adverse effects associated with denosumab (53). It has been shown to decrease hip, vertebral, and non-vertebral fractures when compared to calcium and vitamin D supplementation (52). In postmenopausal women, denosumab reduced the risk of radiographic vertebral fractures by 68%, hip fractures by 40%, and non-vertebral fractures by 20% (28). After discontinuation of denosumab, or other anabolic treatments, patients should transition to oral bisphosphonates to prevent bone loss (51).

Hormonal therapy: mechanism of action and efficacy

Hormonal therapy can also be implemented for the prevention and treatment of postmenopausal osteoporosis. However, the use of hormone replacement therapy has declined due to increasing the risk of cardiovascular complications, including stroke and coronary heart disease, and breast cancer (21,52,54,55). One class of hormone therapy is selective estrogen receptor modulators (SERMs), such as raloxifene. Depending on the target tissue, SERMs act as estrogen receptor agonists or antagonists (56). Raloxifene is the only drug of its class to be approved for the prevention and treatment of osteoporosis (16). It is administered daily by mouth and decreases the risk of vertebral fractures only (29,30). Before prescribing, the benefits of raloxifene should be weighed against the potential adverse effects, such as venous thromboembolism. Combination therapy, such as estrogen-plus-progestin, has been shown to reduce the risk of hip, vertebral, and wrist fractures (54). Even so, the risks of cardiovascular disease and breast cancer do not outweigh the benefits, so it is recommended that these therapies be limited in their usage and not used for long-term treatment (54,57).

Another class of hormones that has been evaluated for the prevention and treatment of osteoporosis is parathyroid hormone analogs, such as teriparatide and abaloparatide. Teriparatide is an anabolic agent that has been shown to increase bone mass by stimulating osteoblasts (31,58). It increases vertebral and hip BMD more than alendronate (32,33,59). Abaloparatide has also been implicated in better reducing the risk of vertebral fracture than alendronate, but additional studies are needed to strengthen this finding (60).

Calcitonin, a thyroid hormone, is indicated for the treatment of osteoporosis in women who have been postmenopausal for at least five years (16). Calcitonin inhibits bone resorption by disrupting the ruffled border of osteoclasts, which causes the cells to move away from bone and thus decreases resorption (61). These morphological changes are observed as soon as 15 minutes after treatment and reach maximal effect within 1 hour (61). Calcitonin is primarily administered intranasally, whereas in the past it was parenterally administered. The efficacy of calcitonin has been variable due to several limitations in multiple studies. However, a meta-analysis by Cranney *et al.* [2002] suggested that calcitonin can increase bone density in postmenopausal women and potentially decrease the risk of vertebral fracture (62). Future studies need to address the potential publication bias surrounding calcitonin's efficacy in treating osteoporosis. An interesting clinical application of calcitonin would be its use as an analgesic to relieve osteoporotic bone pain, but more studies are needed to understand this mechanism since it is independent of calcitonin's metabolic effect (63).

Comparison of first and second line

Even though bisphosphonates are typically the first-line treatment for osteoporosis, denosumab and other effective medications contribute to the controversy around osteoporosis treatment. Multiple meta-analyses have demonstrated denosumab increases BMD of the distal radius, femoral neck, lumbar spine, and total hip, more so than bisphosphonates, but does not decrease the fracture risk relative to bisphosphonates (64-66). Therefore, denosumab and bisphosphonates may be indicated for two different populations: denosumab for patients at low-risk for fracture with low BMD and bisphosphonates for patients at high-risk for fracture regardless of BMD. Additionally, denosumab and other non-oral medications are indicated for patients who cannot take oral medications or who have not responded to bisphosphonates (52). The American College of Physicians (ACP) strongly recommends

treatment with alendronate, risedronate, zoledronate, or denosumab for women with known osteoporosis to reduce the risk for hip and vertebral fractures (67). However, there are fewer studies involving men with osteoporosis, so the ACP weakly recommends bisphosphonates to decrease the risk of vertebral fractures in men with clinically recognized osteoporosis (67). It is also important for practitioners to consider patients' access to healthcare and the feasibility of a medication regimen. For example, elderly patients, who are typically affected by osteoporosis, may have difficulty traveling to receive treatment that needs to be administered by a healthcare professional, such as zoledronate or denosumab. In these instances, an oral pill that could be taken at home would be preferable. However, a medication only administered once a year could be preferred over a pill that needs to be taken daily. Because of the various treatment methods, it is important to discuss the different regimens with the patients to ensure compliance with the regimen.

Lifestyle and supplement prevention methods

Osteoporosis may be prevented by altering modifiable risk factors such as inadequate exercise and nutrition (68). Walking and low-impact aerobic exercise can prevent a decrease in BMD, while high-impact aerobic exercise and weight training can increase BMD in the hips and lumbar spine (69). As BMD naturally declines with age, effective prevention can begin early to ensure healthy development before BMD peaks in the third and fourth decades of life (70). High-impact exercise such as jumping leads to increased bone mass in children that can be maintained for several years (71). However, these benefits are diminished in post-menopausal women, emphasizing the importance of early prevention (72). In cases of senile osteoporosis, exercise regimens must also be designed to diminish the potential for falls and fractures. Although there is no standardized exercise regimen for elderly patients, most focus on improving muscle strength and balance through resistance training, weight-bearing impact exercise, and functionally challenging mobility activities (68,73).

Certain nutrients, such as vitamin D and calcium, are essential for bone strength. However, there have been multiple observations of low vitamin D and calcium intake in the elderly (68,74). The NOF recommends postmenopausal women and men over 65 years old should consume at least 1,200 mg of elemental calcium daily; anyone over the age of 50 should consume at least 800–1,000 IU of vitamin D daily (75,76). Vitamin D-fortified foods have also been shown to significantly increase BMD, but adequate intake is uncommon in geographical areas with lesser annual sun exposure, suggesting many could benefit from supplementation (77,78). A meta-analysis conducted by the NOF found a 30% reduction in the risk of hip fractures and a 15% reduction in the risk of total fractures in adults with calcium plus vitamin D supplementation (79). While dietary modifications or supplementation can be highly beneficial to older adults at risk for osteoporosis, longitudinal optimization of intake beginning as early as childhood is ideal.

Strengths and limitations

This review summarizes the current literature on the pharmacology of osteoporosis and relevant clinical information, including physiology and effectiveness. By compiling this information in a single review, clinicians will have quicker access to relevant information and the original sources for further investigation. Despite these strengths, there are some limitations to this narrative review. There were only two databases searched and they were not exhaustively explored; the search was limited to the most relevant articles using select keywords. The quality of the studies referenced was not assessed using a standardized methodology, although the authors preferentially chose meta-analyses and systematic reviews. Another limitation is the relative lack of literature in certain osteoporotic populations, such as men or drug-induced; much of the studies focus on post-menopausal women. Future studies should address these other populations and include them in comparison studies between different classes of medications for osteoporosis.

Conclusions

Osteoporosis is a highly prevalent condition that is growing along with aging and expanding populations. It carries a large financial burden, and its related fractures can significantly decrease quality of life. Despite the availability of DEXA, many cases of osteoporosis are not diagnosed until a fracture occurs. These often include vertebral compression fractures, hip fractures, and distal radius fractures, which can cause significant pain and functional impairment. First-line treatment for osteoporosis includes bisphosphonates, which can increase lumbar spine BMD between 5.4% (risedronate over three years) and 13.7% (alendronate over 10 years) and femur BMD between

1.6% (femoral neck, risedronate over three years) and 13.7% (femoral trochanter, alendronate over 10 years). Bisphosphonates also decrease the incidence/risk of fracture, ranging from a 25% decrease (nonvertebral fracture, zoledronate over three years) to a 77% decrease (vertebral fracture, zoledronate over three years). Denosumab is a RANKL inhibitor that can decrease the risk of radiographic vertebral fractures by 68% when used over three years. Hormone therapy can also be used to manage osteoporosis if the first-line treatments are not possible or patients are refractory to them. Raloxifene, a SERM, can increase lumbar spine and femoral neck BMD by approximately 2.6% and 2.3%, depending on the dosage. Teriparatide, a parathyroid hormone analog, can increase lumbar spine BMD between 7.2% and 17.8%, depending on time and dosage. Prevention measures include BMD-promoting exercise and dietary adjustment in earlier life, which may also slow BMD decline in older adults. Educating young patients about osteoporosis may prompt them to adopt lifestyle changes that can prevent exacerbation of the condition in old age. Adoption of BMD screening can help identify early cases of osteoporosis that could benefit from medical intervention. Future development of medical devices, surgical techniques, and medications could minimize complications and burdens of living with osteoporosis. Similarly, additional research may identify previously unrecognized preventative measures.

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Footnote

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References

1. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res 2014;29:2520-6.
2. Blume SW, Curtis JR. Medical costs of osteoporosis in the elderly Medicare population. Osteoporos Int 2011;22:1835-44.
3. Dempster DW. Osteoporosis and the burden of osteoporosis-related fractures. Am J Manag Care 2011;17 Suppl 6:S164-9.
4. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. Injury 2006;37:691-7.
5. Becker C. Pathophysiology and clinical manifestations of osteoporosis. Clin Cornerstone 2006;8:19-27.
6. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285:785-95.
7. Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. N Engl J Med 1995;332:305-11.
8. Balasubramanian A, Zhang J, Chen L, et al. Risk of subsequent fracture after prior fracture among older women. Osteoporos Int 2019;30:79-92.
9. Foundation NO. Osteoporosis 2021. Available online: https://www.nof.org/
10. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int 2014;25:2359-81.
11. Gourlay ML, Fine JP, Preisser JS, et al. Bone-density testing interval and transition to osteoporosis in older

women. N Engl J Med 2012;366:225-33.
12. Berry SD, McLean RR, Hannan MT, et al. Changes in bone mineral density may predict the risk of fracture differently in older adults according to fall history. J Am Geriatr Soc 2014;62:2345-9.
13. Russell LA. Osteoporosis and orthopedic surgery: effect of bone health on total joint arthroplasty outcome. Curr Rheumatol Rep 2013;15:371.
14. Rodan GA, Fleisch HA. Bisphosphonates: mechanisms of action. J Clin Invest 1996;97:2692-6.
15. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008;83:1032-45.
16. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010;95:1555-65.
17. Genev IK, Tobin MK, Zaidi SP, et al. Spinal Compression Fracture Management: A Review of Current Treatment Strategies and Possible Future Avenues. Global Spine J 2017;7:71-82.
18. Whitaker M, Guo J, Kehoe T, et al. Bisphosphonates for osteoporosis--where do we go from here? N Engl J Med 2012;366:2048-51.
19. Alendronate, ClinCalc DrugStats Database [Internet]. 2022 [cited September 25, 2022]. Available online: https://clincalc.com/DrugStats/Drugs/Alendronate
20. Kataoka Y, Luo Y, Chaimani A, et al. Cumulative network meta-analyses, practice guidelines, and actual prescriptions for postmenopausal osteoporosis: a meta-epidemiological study. Arch Osteoporos 2020;15:21.
21. Ralston S. Bisphosphonates for Osteoporosis. In: Harrison-Woolrych M. editor. Medicines For Women. Cham: Springer International Publishing; 2015:345-71.
22. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189-99.
23. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343:604-10.
24. Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. J Am Geriatr Soc 2017;65:490-5.
25. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-52.
26. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
27. Tu KN, Lie JD, Wan CKV, et al. Osteoporosis: A Review of Treatment Options. P T 2018;43:92-104.
28. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756-65.
29. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab 2002;87:3609-17.
30. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637-45.
31. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
32. Finkelstein JS, Wyland JJ, Lee H, et al. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. J Clin Endocrinol Metab 2010;95:1838-45.
33. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med 2007;357:2028-39.
34. Hildebrand GK, Kasi A. Denosumab. StatPearls. Treasure Island (FL); 2022.
35. Das S, Crockett JC. Osteoporosis - a current view of pharmacological prevention and treatment. Drug Des Devel Ther 2013;7:435-48.
36. McLaughlin MB, Jialal I. Calcitonin. StatPearls. Treasure Island (FL); 2022.
37. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet 2011;377:1276-87.
38. Muñoz-Torres M, Alonso G, Raya MP. Calcitonin therapy in osteoporosis. Treat Endocrinol 2004;3:117-32.
39. Zeng LF, Pan BQ, Liang GH, et al. Does Routine Anti-Osteoporosis Medication Lower the Risk of Fractures in Male Subjects? An Updated Systematic Review With Meta-Analysis of Clinical Trials. Front Pharmacol 2019;10:882.
40. Rizzoli R, Greenspan SL, Bone G 3rd, et al. Two-year results of once-weekly administration of alendronate 70

mg for the treatment of postmenopausal osteoporosis. J Bone Miner Res 2002;17:1988-96.
41. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. Aging (Milano) 2000;12:1-12.
42. Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999;9:461-8.
43. Muratore M, Quarta E, Quarta L, et al. Ibandronate and cementless total hip arthroplasty: densitometric measurement of periprosthetic bone mass and new therapeutic approach to the prevention of aseptic loosening. Clin Cases Miner Bone Metab 2012;9:50-5.
44. Tella SH, Gallagher JC. Prevention and treatment of postmenopausal osteoporosis. J Steroid Biochem Mol Biol 2014;142:155-70.
45. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40.
46. Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone 2006;38:617-27.
47. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res 2005;20:141-51.
48. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2012;27:243-54.
49. Reid IR, Black DM, Eastell R, et al. Reduction in the risk of clinical fractures after a single dose of zoledronic Acid 5 milligrams. J Clin Endocrinol Metab 2013;98:557-63.
50. Anagnostis P, Paschou SA, Mintziori G, et al. Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. Maturitas 2017;101:23-30.
51. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment Of Postmenopausal Osteoporosis-2020 Update. Endocr Pract 2020;26:1-46.
52. Jeremiah MP, Unwin BK, Greenawald MH, et al. Diagnosis and Management of Osteoporosis. Am Fam Physician 2015;92:261-8.
53. Patel D, Liu J, Ebraheim NA. Managements of osteoporotic vertebral compression fractures: A narrative review. World J Orthop 2022;13:564-73.
54. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290:1729-38.
55. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
56. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Prz Menopauzalny 2014;13:213-20.
57. Fink HA, MacDonald R, Forte ML, et al. Long-Term Drug Therapy and Drug Discontinuations and Holidays for Osteoporosis Fracture Prevention: A Systematic Review. Ann Intern Med 2019;171:37-50.
58. Gass M, Dawson-Hughes B. Preventing osteoporosis-related fractures: an overview. Am J Med 2006;119:S3-S11.
59. Yamamoto T, Tsujimoto M, Hamaya E, et al. Assessing the effect of baseline status of serum bone turnover markers and vitamin D levels on efficacy of teriparatide 20 μg/day administered subcutaneously in Japanese patients with osteoporosis. J Bone Miner Metab 2013;31:199-205.
60. Leder BZ, Mitlak B, Hu MY, et al. Effect of Abaloparatide vs Alendronate on Fracture Risk Reduction in Postmenopausal Women With Osteoporosis. J Clin Endocrinol Metab 2020;105:938-43.
61. Kallio DM, Garant PR, Minkin C. Ultrastructural effects of calcitonin on osteoclasts in tissue culture. J Ultrastruct Res 1972;39:205-16.
62. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:540-51.
63. Gennari C. Analgesic effect of calcitonin in osteoporosis. Bone 2002;30:67S-70S.
64. Beaudoin C, Jean S, Bessette L, et al. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. Osteoporos Int 2016;27:2835-44.
65. Lin T, Wang C, Cai XZ, et al. Comparison of clinical

efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis. Int J Clin Pract 2012;66:399-408.
66. Wu J, Zhang Q, Yan G, et al. Denosumab compared to bisphosphonates to treat postmenopausal osteoporosis: a meta-analysis. J Orthop Surg Res 2018;13:194.
67. Qaseem A, Forciea MA, McLean RM, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med 2017;166:818-39.
68. Srivastava M, Deal C. Osteoporosis in elderly: prevention and treatment. Clin Geriatr Med 2002;18:529-55.
69. Todd JA, Robinson RJ. Osteoporosis and exercise. Postgrad Med J 2003;79:320-3.
70. Sezer A, Altan L, Özdemir Ö. Multiple Comparison of Age Groups in Bone Mineral Density under Heteroscedasticity. Biomed Res Int 2015;2015:426847.
71. Gómez-Bruton A, Matute-Llorente Á, González-Agüero A, et al. Plyometric exercise and bone health in children and adolescents: a systematic review. World J Pediatr 2017;13:112-21.
72. Nelson K, Kouvelioti R, Theocharidis A, et al. Osteokines and Bone Markers at Rest and following Plyometric Exercise in Pre- and Postmenopausal Women. Biomed Res Int 2020;2020:7917309.
73. Daly RM, Dalla Via J, Duckham RL, et al. Exercise for the prevention of osteoporosis in postmenopausal women: an evidence-based guide to the optimal prescription. Braz J Phys Ther 2019;23:170-80.
74. Muñoz-Garach A, García-Fontana B, Muñoz-Torres M. Nutrients and Dietary Patterns Related to Osteoporosis. Nutrients 2020;12:1986.
75. Chen LR, Ko NY, Chen KH. Medical Treatment for Osteoporosis: From Molecular to Clinical Opinions. Int J Mol Sci 2019;20:2213.
76. Hanley DA, Cranney A, Jones G, et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. CMAJ 2010;182:E610-8.
77. Tangestani H, Djafarian K, Emamat H, et al. Efficacy of vitamin D fortified foods on bone mineral density and serum bone biomarkers: A systematic review and meta-analysis of interventional studies. Crit Rev Food Sci Nutr 2020;60:1094-103.
78. Coughlan T, Dockery F. Osteoporosis and fracture risk in older people. Clin Med (Lond) 2014;14:187-91.
79. Weaver CM, Alexander DD, Boushey CJ, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int 2016;27:367-76.

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Supplementary

Table S1 Search strategy

Databases	PubMed, Google Scholar
Search Term (MeSH terms)	Osteoporosis Osteoporosis treatment Senile osteoporosis Osteoporosis pharmacology Osteoporosis medication Bisphosphonate Alendronate Ibandronate Risedronate Zoledronate Denosumab Raloxifene Teriparatide Abaloparatide Calcitonin
Search Query	((((“osteoporosis”[All Fields] OR “senile osteoporosis”[All Fields]) AND “osteoporosis treatment”[All Fields]) OR ((“osteoporosis”[MeSH Terms] OR “osteoporosis”[All Fields] OR “osteoporoses”[All Fields] OR “osteoporosis, postmenopausal”[MeSH Terms] OR (“osteoporosis”[All Fields] AND “postmenopausal”[All Fields]) OR “postmenopausal osteoporosis”[All Fields]) AND (“pharmacology”[MeSH Terms] OR “pharmacology”[All Fields] OR “pharmacologies”[All Fields] OR “pharmacology”[MeSH Subheading])) OR “osteoporosis medication”[All Fields]) AND (“bisphosphonate”[All Fields] OR “alendronate”[All Fields] OR “ibandronate”[All Fields] OR “risedronate”[All Fields] OR “zoledronate”[All Fields] OR “denosumab”[All Fields] OR (“raloxifene”[All Fields] OR “teriparatide”[All Fields] OR “abaloparatide”[All Fields] OR “calcitonin”[All Fields]))) AND ((1980:2021[pdat]) AND (english[Filter]))

Each part was translated for searching other databases.

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