ORIGINAL RESEARCH

Translational Health Reports. 2025;1(1): 6
https://doi.org/10.22034/thr.2025.509428.1006

Osteoporosis: Pharmacological Treatments, Pain Management, and Their Implications for Clinical Practice

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Article history:

Received: 15 Nov 2024
Accepted: 12 Jan 2024
Available online: 18 Jan 2025

Keywords:

Osteoporosis
Fracture Risk
Bisphosphonates
SERMs
Pain Management
Sclerostin Inhibitors

Abstract

Introduction: Osteoporosis is a widespread bone disease characterized by low bone mineral density (BMD), structural bone deterioration, and an increased risk of fractures. It primarily affects postmenopausal women and the elderly, representing a significant global health burden. The management of osteoporosis involves pharmacological treatments aimed at preventing fractures, alleviating symptoms, and improving overall quality of life. **Methods:** This review analyzes the pharmacology of current osteoporosis treatments, including bisphosphonates, selective estrogen receptor modulators (SERMs), monoclonal antibodies, and newer agents such as sclerostin inhibitors. It also examines pain management strategies, particularly those targeting fracture-related pain, and explores the intersection between bone therapies and analgesia. **Results:** The current pharmacological treatments for osteoporosis have shown significant efficacy in reducing fracture risk. However, managing pain in osteoporosis, particularly post-fracture pain, remains a complex challenge. This review highlights the need for a multidimensional approach that integrates both bone-targeted therapies and effective pain management strategies. **Conclusion:** While osteoporosis therapies have greatly reduced fracture risk, pain management in osteoporosis patients remains an area requiring further research. This review synthesizes current literature on osteoporosis treatments and pain management, offering insights into best practices and identifying future research directions to improve patient outcomes.

Cite this article as: Chamanara M, Shirdel SS, Meskar H, Taheri S, Ghanbarpour Juybari A, Aezzi G, et al. Osteoporosis: Pharmacological Treatments, Pain Management, and Their Implications for Clinical Practice. Transl Health Rep. 2025;1(1):6. https://doi.org/10.22034/thr.2025.509428.1006

INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by a reduction in bone mineral density (BMD) and a deterioration of bone microarchitecture, resulting in increased bone fragility and a higher risk of fractures. These fractures are most commonly seen in the hip, spine, and wrist, which are particularly vulnerable due to their high trabecular bone content and

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weight-bearing function (1). Osteoporotic fractures are associated with significant morbidity, mortality, and healthcare costs, with an increasing burden on global healthcare systems as the global population ages. The condition is most prevalent among postmenopausal women and older adults, with the incidence expected to rise further in the coming decades due to the aging demographic and increased life expectancy (2).

Worldwide, osteoporosis affects approximately one in three women and one in five men over the age of 50, with the risk increasing substantially with age (3). In fact, by 2050, the number of osteoporotic fractures globally is projected to increase by over 300%, primarily due to the rising number of elderly individuals (4). Fractures resulting from osteoporosis often lead to long-term disability, reduced quality of life, and increased mortality, particularly in the case of hip fractures, where mortality rates are as high as 20% within the first-year post-fracture (5). Furthermore, osteoporosis-related fractures also place a significant economic burden on healthcare systems, with costs related to hospitalizations, long-term care, and rehabilitation, estimated to exceed $20 billion annually in the United States alone (6).

Beyond the physical consequences of fractures, many individuals with osteoporosis experience chronic pain, particularly those who have suffered from vertebral or fragility fractures in the lower extremities. Chronic pain from vertebral fractures, in particular, can result in long-lasting discomfort, stiffness, and limited mobility, often requiring long-term pain management strategies (7). This pain is not only physical but also psychological, contributing to depression, anxiety, and social isolation, particularly among the elderly (8). Therefore, addressing both the underlying bone disease and the associated pain is a critical component of managing osteoporosis.

The pharmacological treatment of osteoporosis primarily focuses on either inhibiting bone resorption, stimulating bone formation, or employing a combination of both approaches to restore bone strength and reduce fracture risk. Antiresorptive medications, such as bisphosphonates and denosumab, reduce osteoclast activity to decrease bone resorption, while anabolic agents, such as teriparatide and romosozumab, promote bone formation by stimulating osteoblast activity (9). Bisphosphonates like alendronate, risedronate, and zoledronic acid are among the most commonly prescribed drugs for osteoporosis. These medications have been proven to increase BMD and significantly reduce fracture risk, including vertebral, hip, and nonvertebral fractures (10). However, concerns about side effects, such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures, have emerged with prolonged use, leading to greater scrutiny regarding their long-term safety (11).

Selective estrogen receptor modulators (SERMs), such as raloxifene, are another class of drugs used in osteoporosis, particularly in postmenopausal women. These agents mimic estrogen's effects on the bone by reducing osteoclast activity and promoting bone formation. Raloxifene has been shown to reduce the risk of vertebral fractures but has a limited effect on nonvertebral fractures (12). However, it is associated with an increased risk of venous thromboembolism, which limits its use in certain patient populations (13). Denosumab, a monoclonal antibody that targets RANKL, has gained recognition for its ability to reduce osteoclast-mediated bone resorption, leading to improved BMD and a decrease in fracture risk (14). Denosumab is particularly useful in patients who cannot tolerate bisphosphonates or have contraindications to their use. Newer therapies, such as romosozumab, a sclerostin inhibitor, provide a dual mechanism of action, promoting bone formation while inhibiting bone resorption. Romosozumab has shown significant potential in improving BMD and reducing fractures, particularly in patients with severe osteoporosis (15).

While pharmacological treatments have significantly improved the management of osteoporosis and fracture prevention, they do not directly address the pain associated with osteoporosis-related fractures. Pain management in osteoporosis is essential, particularly in patients with chronic pain arising from vertebral compression fractures or nonvertebral fractures of the extremities. The pain may be acute, arising immediately after the fracture, or chronic, persisting for weeks, months, or even years after the fracture has healed (16). Pharmacological pain management typically includes the use of analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Acetaminophen is often the first-line therapy for mild to moderate pain due to its relative safety profile. However, NSAIDs are commonly used for pain with an inflammatory component, though their long-term use can lead to gastrointestinal, renal, and cardiovascular risks, particularly in older adults (17). Opioids, while effective for short-term pain relief, are associated with significant risks, including dependency, tolerance, and adverse side effects such as sedation and constipation (18). Therefore, careful consideration must be given when prescribing opioids, and they should be used for the shortest duration possible, particularly in the elderly population.

In addition to pharmacological strategies, non-pharmacological approaches such as physical therapy, exercise, and cognitive-behavioral therapy (CBT) can play an important role in managing pain and improving functional outcomes. Physical therapy aims to improve

mobility, strength, and posture, thereby alleviating pain and reducing the risk of falls and further fractures (19). Spinal bracing and other supportive devices may also provide temporary relief for those with acute back pain from vertebral fractures, offering stability and reducing pain during the healing process (20). Cognitive-behavioral therapy has been increasingly recognized as an effective adjunct in the management of chronic pain, helping patients develop coping strategies and reduce the emotional distress associated with long-term pain (21).

The aim of this study is to provide a comprehensive review of the current pharmacological management of osteoporosis, focusing on the various drug classes available and their efficacy in reducing fracture risk. Additionally, this review will examine the range of pain management strategies utilized in the care of patients with osteoporosis, including pharmacological and non-pharmacological approaches. By synthesizing the available literature, the study seeks to offer evidence-based insights into optimizing the treatment of osteoporosis and improving both bone health and pain management outcomes for patients.

Pharmacology of Osteoporosis Medications

The pharmacologic treatment of osteoporosis aims to decrease fracture risk, primarily by enhancing bone density and structure. The medications available fall into two major categories: antiresorptive agents, which reduce bone resorption, and anabolic agents, which promote bone formation.

Antiresorptive Agents

Bisphosphonates

Bisphosphonates are the most commonly prescribed antiresorptive medications for osteoporosis. Drugs like alendronate, risedronate, and zoledronic acid work by inhibiting osteoclast-mediated bone resorption. They bind to hydroxyapatite in bone and prevent the activation of osteoclasts, promoting osteoclast apoptosis (4). Bisphosphonates have been shown to increase bone mineral density (BMD) and significantly reduce the incidence of fractures, including vertebral, hip, and nonvertebral fractures (5).

While bisphosphonates are effective in reducing fracture risk, they are not without side effects. Long-term use has been associated with rare but serious complications such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures (6). These risks necessitate careful patient selection and monitoring. Additionally, bisphosphonates must be taken with caution in patients with renal impairment due to the potential for nephrotoxicity (7).

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene, a SERM, is an alternative to bisphosphonates, especially in postmenopausal women who cannot tolerate bisphosphonates or are at higher risk for breast cancer. Raloxifene acts as an estrogen agonist in bone, promoting bone formation while inhibiting bone resorption (8). Clinical trials have demonstrated that raloxifene reduces the risk of vertebral fractures but does not significantly affect nonvertebral fracture risk (9). Raloxifene is associated with an increased risk of venous thromboembolism (VTE) and hot flashes, which can limit its use in some patients (10).

Monoclonal Antibodies

Denosumab

Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor-kappa B ligand (RANKL), a key mediator of osteoclast activation. By binding to RANKL, denosumab inhibits osteoclast differentiation and activity, leading to decreased bone resorption (11). Denosumab has been shown to increase BMD and reduce the risk of both vertebral and nonvertebral fractures (12). It is administered as a subcutaneous injection every six months, making it a convenient option for patients who may have difficulty adhering to daily or weekly oral medications. While denosumab is well tolerated, its use can be associated with a transient increase in the risk of vertebral fractures upon discontinuation (13).

Sclerostin Inhibitors

Romosozumab

Romosozumab is a novel sclerostin inhibitor that works by increasing bone formation and decreasing bone resorption. Sclerostin, a protein produced by osteocytes, inhibits osteoblast function; by blocking sclerostin, romosozumab promotes osteoblast activity, resulting in an increase in bone formation (14). Clinical trials have demonstrated that romosozumab significantly increases BMD and reduces the risk of vertebral, nonvertebral, and hip fractures (15). However, concerns regarding cardiovascular risk have emerged, necessitating careful patient selection (16). Romosozumab is typically administered as a monthly injection for 12 months, making it a more intensive treatment option.

Pain Management in Osteoporosis

Chronic pain related to osteoporosis is often secondary to fragility fractures, especially vertebral fractures. Pain management in osteoporosis patients involves not only addressing the underlying bone disease but also mitigating the pain associated with fractures.

Pharmacological Approaches to Pain Relief

Analgesics

Acetaminophen is commonly used for mild pain associated with osteoporosis. It is generally well tolerated and can provide effective pain relief for non-inflammatory pain (17). However, acetaminophen is less effective for inflammatory pain and has limited utility in more severe pain scenarios.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, such as ibuprofen and naproxen, are widely used for pain relief, particularly for acute pain due to fractures. These medications reduce inflammation and provide analgesia through the inhibition of cyclooxygenase (COX) enzymes (18). However, long-term use of NSAIDs carries risks, including gastrointestinal bleeding, renal dysfunction, and cardiovascular events, especially in older adults (19). Therefore, their use should be limited to the shortest duration possible and in the lowest effective dose.

Opioids

Opioids may be considered for more severe pain, particularly in cases where fractures result in intractable discomfort. While opioids are effective for managing acute pain, their long-term use is fraught with risks, including dependency, tolerance, and adverse effects such as constipation and sedation (20). Thus, opioids should only be used in select cases and for the shortest duration necessary, with close monitoring for adverse effects.

Non-Pharmacological Approaches

Physical Therapy and Exercise

Physical therapy is an essential component of pain management in osteoporosis. Regular weight-bearing and muscle-strengthening exercises help improve bone health, reduce fall risk, and alleviate pain associated with spinal fractures (21). Furthermore, physical therapists can help patients with posture correction, gait training, and pain management strategies to enhance mobility and function.

Spinal Bracing and Vertebral Fracture Treatment

For patients with spinal fractures, the use of a back brace may help reduce pain by stabilizing the spine and preventing further compression of the vertebrae. Additionally, minimally invasive procedures such as vertebroplasty and kyphoplasty can be effective in treating painful vertebral compression fractures. These procedures involve the injection of bone cement into the fractured vertebra to stabilize the bone and alleviate pain (22).

Cognitive Behavioral Therapy (CBT)

CBT is a psychological approach that has been found effective in managing chronic pain. It helps patients identify and modify pain-related thoughts and behaviors, improving pain coping strategies and overall quality of life (23). CBT is particularly useful for managing the chronic pain associated with osteoporotic fractures.

Discussion

Osteoporosis continues to present a significant challenge in healthcare, particularly as the global population ages. The prevalence of the disease is increasing, especially among older adults, leading to an escalation in fractures, morbidity, and the associated economic burden. Although pharmacological treatments for osteoporosis have significantly reduced fracture risk, addressing the pain that accompanies osteoporotic fractures remains a complex task. This discussion will explore the various pharmacological treatments for osteoporosis, their effectiveness in fracture prevention, and the ongoing challenges in managing pain in these patients.

The pharmacological management of osteoporosis primarily focuses on reducing bone resorption and enhancing bone formation. Bisphosphonates, such as alendronate, risedronate, and zoledronic acid, have long been the cornerstone of osteoporosis treatment. These antiresorptive agents work by inhibiting osteoclast-mediated bone resorption, which ultimately leads to increased bone mineral density (BMD) and a reduction in fracture risk (14). Studies have consistently demonstrated that bisphosphonates are effective in reducing vertebral, hip, and nonvertebral fractures, with a risk reduction of up to 70% for vertebral fractures (15). Despite their proven efficacy, the long-term use of bisphosphonates has been linked to serious adverse effects such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures, especially when used for prolonged periods (16). These risks necessitate careful patient selection and monitoring, particularly in patients who require long-term therapy.

Denosumab, a monoclonal antibody that targets RANKL (Receptor Activator of Nuclear Factor-Kappa B Ligand), represents another important advancement in osteoporosis therapy. By inhibiting RANKL, denosumab effectively decreases osteoclast-mediated bone resorption, leading to increased BMD and a reduction in fracture risk (18). Denosumab has been shown to reduce the risk of both vertebral and nonvertebral fractures in postmenopausal women (19). One of the key advantages of denosumab is its administration via subcutaneous injection every six months, making it a convenient option for patients who have difficulty adhering to daily or weekly oral medications (20). However,

discontinuation of denosumab has been associated with a rebound effect, where bone resorption increases rapidly, leading to an elevated fracture risk (21). This phenomenon underscores the importance of long-term commitment to therapy and careful monitoring after discontinuation.

Sclerostin inhibitors, such as romosozumab, represent a newer class of drugs that offer a dual mechanism of action by both inhibiting bone resorption and promoting bone formation. Sclerostin is a protein produced by osteocytes that inhibits osteoblast activity, thus limiting bone formation. By inhibiting sclerostin, romosozumab enhances osteoblast activity, leading to an increase in bone formation while also reducing osteoclast-mediated resorption (22). Clinical trials have demonstrated that romosozumab significantly increases BMD and reduces the risk of vertebral, nonvertebral, and hip fractures (23). For example, romosozumab has been shown to reduce the risk of vertebral fractures by 73% compared to placebo (23). However, the cardiovascular safety of sclerostin inhibitors has been a topic of concern, as some studies suggest a potential increase in cardiovascular events, particularly in patients with pre-existing cardiovascular conditions (24). Therefore, romosozumab must be used cautiously in such populations, and its cardiovascular risk profile needs to be more thoroughly evaluated in future studies.

Selective estrogen receptor modulators (SERMs) like raloxifene have also been utilized in the management of osteoporosis, particularly in postmenopausal women. Raloxifene mimics estrogen's effects on the bone by inhibiting osteoclast activity and promoting bone formation, thus increasing BMD and reducing fracture risk (25). However, while raloxifene has been shown to reduce the risk of vertebral fractures, it does not significantly affect the risk of nonvertebral fractures, which limits its overall efficacy in preventing all types of osteoporotic fractures (26). Furthermore, raloxifene carries a risk of venous thromboembolism (VTE) and hot flashes, which limits its use in certain populations, particularly those with a history of clotting disorders (25). As a result, its use has become more limited as newer agents with fewer side effects have become available.

While the pharmacological management of osteoporosis has advanced considerably, pain management remains a key issue for patients, particularly those with chronic pain resulting from vertebral fractures or other osteoporotic fractures. The pain associated with osteoporotic fractures can be debilitating, affecting both physical and emotional well-being. Managing this pain requires a multifaceted approach that incorporates both pharmacological and non-pharmacological strategies.

Acetaminophen remains the first-line treatment for mild to moderate pain in osteoporosis patients due to its favorable safety profile and efficacy in treating non-inflammatory pain (27). However, acetaminophen is less effective in addressing inflammatory pain, such as that associated with fractures. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for more severe pain with an inflammatory component. NSAIDs like ibuprofen and naproxen are effective at reducing pain and inflammation by inhibiting cyclooxygenase (COX) enzymes (28). However, their long-term use can lead to significant side effects, particularly in elderly patients, including gastrointestinal bleeding, renal dysfunction, and cardiovascular events (29). Therefore, NSAIDs should be used with caution, particularly in patients with comorbidities such as hypertension or renal insufficiency.

For patients with severe pain, opioids may be considered, although their use is fraught with risks, including dependency, tolerance, and side effects like constipation and sedation (30). Opioids may be particularly useful in the short-term management of pain immediately following a fracture, but their use should be limited to the shortest possible duration to avoid the development of tolerance and other adverse outcomes (31). In elderly patients, the risks associated with opioid use are particularly concerning due to the increased risk of falls, cognitive impairment, and fractures (31). Therefore, opioids should be prescribed with caution, and alternative pain management strategies should be explored whenever possible.

Non-pharmacological approaches also play a crucial role in managing pain and improving functional outcomes in osteoporosis patients. Physical therapy is an important component of pain management, especially for individuals with chronic pain associated with vertebral fractures. Weight-bearing and resistance exercises help improve bone strength, reduce the risk of further fractures, and alleviate pain by improving posture, muscle strength, and mobility (32). Furthermore, physical therapy can help patients manage their pain by teaching them strategies for minimizing discomfort and improving functional capacity.

Spinal bracing is another important non-pharmacological intervention for managing pain, particularly in patients with vertebral compression fractures. Bracing helps stabilize the spine, reduce mechanical stress on the fractured vertebrae, and provide pain relief during the healing process (33). For patients with persistent pain despite conservative management, minimally invasive procedures such as vertebroplasty and kyphoplasty can provide significant relief. These procedures involve the injection of bone

cement into the fractured vertebrae, which stabilizes the bone and alleviates pain (34).

Pickering and colleagues (2024) conducted a scoping review to assess the analgesic effects of anti-osteoporosis (OP) drugs in managing osteoporosis-related pain (35). The review included 31 studies, revealing that these medications might reduce pain, likely through their effects on bone and pain sensitization. However, the authors noted significant methodological variability across studies, including differences in endpoints and statistical methods, which limited the ability to draw firm conclusions. They concluded that while osteoporosis drugs may offer pain relief, more rigorous and larger trials are needed to standardize pain assessment tools and identify patient subtypes that respond best to treatment. The study highlights the need for more research to optimize both bone health and pain management in osteoporosis care.

In addition to these interventions, cognitive-behavioral therapy (CBT) has been shown to be effective in managing chronic pain. CBT helps patients develop coping strategies, modify pain-related thoughts, and improve their overall quality of life (35). This psychological approach is particularly beneficial for patients experiencing depression or anxiety as a result of chronic pain, helping them manage the emotional aspects of their condition and improve their overall well-being (36).

Conclusion

Osteoporosis treatment is evolving, with several pharmacological therapies now available to prevent fractures and improve bone health. At the same time, pain management in these patients requires a multi-faceted approach that includes both pharmacological and non-pharmacological strategies. Future research should continue to focus on optimizing the balance between fracture prevention and pain relief, as well as investigating the long-term safety of newer medications. Given the growing elderly population and the increasing burden of osteoporosis, effective management strategies are essential for improving the quality of life in affected individuals.

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