Drug holiday effect on osteoporosis: a narrative review of the current literature

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Received: 09-Nov-2023
Revised: 26-Jan-2024
Accepted: 01-Feb-2024
Published: 03-Apr-2024

The Egyptian Orthopaedic Journal 2024, 59:1–5

Bisphosphonates are most common drugs used in the treatment of osteoporosis being effective in reducing fracture risk. Although these drugs are quite safe and tolerable drugs, there has been an association with severe adverse effects after a prolonged period of use. The idea of 'drug holiday' is becoming a trend, because of the way these drugs work, absorbed by the bone and continuing the exertion of an antiresorptive effect even after discontinuation, meaning that the patient continues to benefit from anti-fracture efficacy, while the risk of side effects is reduced. Discontinuation of bisphosphonates should be considered in patients who have been treated for more than 5 years with alendronate or more than 3 years with risedronate or zoledronic acid, and reassessment should be done every 1 to 3 years if there is no new adverse event in the meantime.

Keywords:
bisphosphonates, denosumab, drug holiday, osteoporosis

Egypt Orthop J 2024, 59:1–5

1110-1148

Introduction and Background

Osteoporosis is a chronic systemic skeletal disease characterized by progressive loss of bone mass and disruption of the microarchitecture of bone tissue, and as a result in reduced mechanical strength of bones and increased risk of fractures [1]. It affects hundreds of thousands of people worldwide, mainly postmenopausal women, and it is estimated that 1 in 3 women and 1 in 5 men over 50 years of age will suffer an osteoporotic fracture at some point in their lives [2,3]. The aim of the treatment is to achieve an optimal therapeutic outcome so that there are benefits at the individual level due to the deterioration in quality of life and at the social level due to the high economic burden. The clinical significance of osteoporosis is the presence of fragility fractures. The calculation of patients' fracture risk should take into account as many risk factors affecting bone strength as possible, aiming at a more accurate and reliable assessment for the possible occurrence of osteoporotic fractures in the future [4]. The most important risk factors for osteoporosis regardless of bone mass and apart from ethnicity are female gender, age over 65 years, presence or history of low-force fracture and family history of fracture. Additional factors include low body mass index, long-term corticosteroid administration, smoking, excessive alcohol use, rheumatoid arthritis as well as secondary osteoporosis. Secondary osteoporosis refers to all conditions that cause secondary bone loss and includes a) untreated hypogonadism b) inflammatory bowel diseases c) prolonged immobilization d) organ transplantation and e) endocrinological diseases [5]. The FRAX algorithm, a widely used tool, calculates the 10-year probability of hip and major osteoporotic fractures based on multiple risk factors [6,7].

Drugs that are used for the treatment of osteoporosis affect bone remodeling and are divided into a) Anti-catabolic drugs that inhibit bone resorption, such as aminodiphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) and denosumab, and b) Osteoanabolic drugs that induce bone formation such as teriparatide, romosumab, and ampaloparatide. To provide a clear overview, a table with drug names and concise descriptions will replace detailed drug paragraphs.

Anti-catabolic drugs, such as bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) and denosumab, target bone resorption by influencing osteoclast function. Bisphosphonates, synthetic analogues of inorganic pyrophosphate, are administered orally or intravenously and remain in bone after discontinuation [8-10] Table 1.

Selective Estrogen Receptor Modulators (SERMs), including raloxifene and bazedoxifene, act as co-agonists and antagonists of estrogen receptors. Raloxifene is indicated for postmenopausal osteoporosis prevention and treatment, while

 DOI: 10.4103/eoj.eoj_141_23

Table 1 Overview of Anti-Catabolic Drugs

Drug	Approved Indications	Administration	Common Adverse Effects
Alendronate	Postmenopausal osteoporosis, male osteoporosis, corticosteroid-induced osteoporosis	Oral, IV	Headache, dizziness, musculoskeletal pain
Risedronate	Postmenopausal osteoporosis, established osteoporosis	Oral (daily, weekly, monthly)	Dyspepsia, constipation, diarrhea, musculoskeletal pain
Ibandronate	Postmenopausal osteoporosis	Oral (daily, monthly), IV	Hot flashes, muscle cramps, thromboembolic events
Zoledronic Acid	Postmenopausal osteoporosis (prevention, treatment), prevention of new fractures post low-force hip fracture	IV (annual or every 2 years)	Headache, dizziness, musculoskeletal pain
Denosumab	Postmenopausal osteoporosis, fracture risk under aromatase inhibitors, male osteoporosis under androgen blockade	Subcutaneous (every 6 months)	Hypocalcaemia, rash, pain in extremities, constipation

bazedoxifene is approved for postmenopausal osteoporosis treatment [11].

Denosumab, a human monoclonal antibody inhibiting RANKL, is administered subcutaneously every 6 months and is effective in treating osteoporosis and preventing fractures [12,13].

Teriparatide, a recombinant form of parathyroid hormone (PTH), directly acts on osteoblasts, promoting bone formation. Administered daily by subcutaneous injection, it is indicated for high-fracture risk osteoporosis and glucocorticoid-induced osteoporosis [14].

Romosozumab, a monoclonal antibody against sclerostin, has a dual mode of action, increasing bone formation and reducing resorption. It is used in severe osteoporosis postmenopausal women at high fracture risk, with precautions due to cardiovascular risks (EMA reassessment in 2019) [15].

Ampaloparatide, a synthetic PTHrP [1-33] analog, is indicated for postmenopausal osteoporosis treatment, with studies showing significant bone density increases and fracture risk reduction. Subcutaneously administered daily, it is recommended for a duration not exceeding 2 years [15] Table 2.

This review aims to clarify the meaning, importance, and dangers of pausing the long-term treatment of osteoporosis and also, to make a synopsis of the bibliography regarding the drug holiday effect on osteoporosis.

Table 2 Effect of antiosteoporotic drugs for postmenopausal osteoporosis

Pharmaceutical substance	Effect against fractures		
	Vertebral	Hip	Nonvertebral
Alendronate	√	√	√
Rizendronate	√	√	√
Ibandronate	√		√
Zolendronic Acid	√	√	√
Denosumab	√	√	√
Teriparatide	√		√
Abaloparatide	√		√
Romosozumab	√	√	√
Raloxifene	√		
Bazedoxifene	√		

Understanding drug holiday

The concept of drug holiday for osteoporosis was introduced in 2008 and became more popular as the time passed. Drug holiday period is defined as the planned temporary cessation of effective treatment for osteoporosis after a period of continuous use. The concept of a 'drug holiday' in osteoporosis treatment has emerged as a strategic pause in the administration of bisphosphonates, the primary class of drugs used for managing osteoporosis. The rationale behind this approach is multifaceted. Firstly, there is a belief that beyond a certain duration of bisphosphonate treatment, no additional benefits are observed. Secondly, concerns about potential adverse events associated with prolonged bisphosphonate use have prompted the consideration of temporary discontinuation. The risk of rare but severe side effects, such as atypical fractures and osteonecrosis of the jaw, has steered the medical community towards exploring the feasibility and effectiveness of drug holidays. Moreover, the persistence of bisphosphonates in the skeletal system and their residual efficacy against fractures post-discontinuation adds complexity to the decision-making process [16]. To address the concern about atypical fractures, a study involving 59 cases demonstrated a 72% reduction in the risk of such fractures within the first year after discontinuing bisphosphonates [17]. Several scientific organizations have issued guidelines supporting the discontinuation of drugs, including the American Society of Bone and Mineral Research [18], the International Osteoporosis Foundation [19], the American Association of Clinical Endocrinology [20], the Endocrine Society [15], and the European Menopause and Andropause Society [21]. The recommended durations for bisphosphonates,

Table 3 Main findings of randomized controlled trials

Drug	Study	Result noted	Conclusions
Alendronate [24]	FLEX	BMD; fracture	2–2.5% difference in BMD in the groups that received 5 or 8 years of treatment; Y higher incidence rate of clinical vertebral fractures in the 5-year group
Risendronate [25]	VERT	BTM; BMD	Difference between 2 and 7 years of treatment
Risendronate [26]	VERT-NA	BTM; BMD; fracture	One year after discontinuation of 3-year treatment with risedronate, did BMD decrease at the lumbar spine and hip and did bone metabolism indices return to pre-treatment levels? The risk of new morphometric vertebral fractures remained lower in patients on risedronate compared with patients in the control group
Zolendronic Acid [27]	HORIZON	BTM; BMD; fracture	In patients treated for 3 years versus 6 years, differences were observed in bone turnover markers (starting to return to normal but remaining lower than baseline in the 3-year group); Does BMD at the femoral neck tend to decrease in the 3-year group? Morphometric vertebral fractures higher in the 3-year treated group?
Zolendronic Acid [28]	HORIZON	BTM; BMD; fracture	Small nonsignificant differences in BMD, bone turnover markers and fractures between the two groups
Ibandronate [29]		BTM; BMD	Discontinuation of treatment led to a decrease in hip BMD and an increase in BTM
Denosumab [30-32]	FREEDOM	BMD; fracture	10-year treatment associated with lower vertebral and nonvertebral fractures compared with the placebo group; if not followed by bisphosphonate therapy, discontinuation of denosumab is associated with bone loss and new multiple vertebral fractures

BMD = bone mineral density; BTM = bone turnover markers

a common class of osteoporosis drugs, vary by type: 10 years for alendronate, 7 years for risedronate, 9 years for zoledronic acid, 8 years for raloxifene, 7 years for bazedoxifene, 2 years for teriparatide, and 10 years for denosumab [22]. However, the critical question remains: can a 'drug discontinuation' strategy balance the increase in bone density and the reduction in fracture risk achieved by long-term bisphosphonate use?

Clinical studies and trial outcomes

Placebo-controlled studies have provided substantial data supporting the anti-fracture benefits of both oral and intravenous bisphosphonates administered for 3–5 years. Generally, a 40–50% reduction in vertebral fractures and a 20–30% reduction in nonvertebral fractures is associated with bisphosphonate use. Specific trials, such as the Fracture Intervention Trial and the Horizon trial, demonstrated significant reductions in vertebral fractures with alendronate and zoledronic acid, respectively [23]. However, studies like FLEX and the Horizon extension study revealed that discontinuing bisphosphonate treatment led to approximately 50% higher vertebral fracture rates compared with those who continued treatment. Notably, these results might not be universally applicable to all bisphosphonates. An analysis of Medicare data also indicated increased fracture risks for patients discontinuing bisphosphonates after 3 years of continuous administration. The results of the most notable studies for bisphosphonates and denosumab are depicted in Table 3.

Current status of drug holiday

The current guidelines suggest periodic reviews of bisphosphonate therapy after 5 years for alendronate, risedronate, or ibandronate, and after 3 years for zoledronic acid. High-risk patients, such as those with a history of hip or spinal fractures, low T-scores, or those sustaining low-force fractures during treatment, are recommended to continue bisphosphonates for 6–10 years. Moderate-risk patients can consider discontinuation after 5 years, while low-risk patients may opt for a drug holiday after 3–5 years. Denosumab, on the other hand, is not recommended for discontinuation.

Various factors influence the duration of a drug holiday, including the specific bisphosphonate used, patient compliance, and individualized assessments by physicians. The binding affinity to bone mineral salts and the antagonistic effects of each bisphosphonate also contribute to the persistence of their action after discontinuation. Zoledronic acid, alendronate, and risedronate show differing durations of action postdiscontinuation Table 4.

Conclusion

In conclusion, the concept of a drug holiday in osteoporosis treatment is rooted in addressing potential adverse effects and optimizing therapeutic benefits. While clinical studies highlight the efficacy of bisphosphonates, particularly in reducing fracture risks, the decision to embark on a drug holiday should be individualized. Key factors include the type of bisphosphonate, patient risk profile, and ongoing assessments during the discontinuation period. Discontinuation of bisphosphonates should be considered in patients who have been treated for more than 5 years with alendronate or more than 3 years with risedronate or zoledronic acid. The strategy

Table 4 Recommended approach for bisphosphonates' drug holiday [33]

Completion of 3–5 years of bisphosphonate therapy	During a planned 5-year drug holiday	After the completion of 5-year drug holiday
Continuation of the drug holiday with re-evaluation every year	Continuation of the drug holiday with re-evaluation every year	Continuation of the drug holiday with re-evaluation every year
Age <65-75 years No recent fracture (<2years) No vertebral or hip fracture T-score of femoral neck >-2,5 Evaluation of possible positive and negative effects	No new fractures No new or worsening risk factors for fracture# Compliance with non-pharmacological treatment	Revision of femoral neck T-score after 5 years if value remains>-2,5 No new fractures No new or worsening risk factors for fracture# Compliance with non-pharmacological treatment
Continue bisphosphonate up until 10 years without any drug holiday:	Stop of drug holiday and resumption of bisphosphonate or other therapy:	Resumption of bisphosphonate or other therapy:
None of the above Understanding the potential benefits and risks of continuing treatment	New fractures New or worsening risk factors for fracture # Revision of femoral neck T-score if <2,5 AND >5% bone loss after ≥3 years of drug holiday	Revision of femoral neck BMD after 5 years if <2,5 AND >5% of bone loss New fracture after discontinuation New or worsening risk factors for fracture #

of temporarily stopping anti-osteoporotic treatment recommended with the use of bisphosphonates cannot be safely applied to other drugs, such as denosumab, selective estrogen receptor modulators or teriparatide. Discontinuation of denosumab has been associated with an increased risk of multiple fractures (rebound effect). The decision to initiate temporary discontinuation should be individualized, considering the long-term efficacy and safety of the bisphosphonate used, as well as the individual patient's risk of fracture. Studies emphasize the importance of patient compliance and suggest that well-monitored drug holidays can be safe, but vigilant monitoring and case-by-case evaluation remain paramount. The patient's overall picture should be reassessed after 1–3 years of discontinuing the bisphosphonate. The decision to restart treatment depends on the occurrence of new fractures, the patient's risk factors, and possibly bone mineral density. As research continues, the landscape of osteoporosis management may evolve, refining the understanding of drug holidays and their implications.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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