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Atypical Femur Fractures in Post-Menopausal Patients Taking Bisphosphonates and Their Indication When to Start after Holiday Period of 5 Years and Its Effects

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ABSTRACT

Postmenopausal women are at risk of fractures owing to osteoporosis, which is worsened by low oestrogen. Bisphosphonates like ibandronate, zoledronic acid, alendronate, and risedronate limit bone resorption and increase bone density, reducing fracture risk. Although atypical femur fractures (AFFs) are uncommon, they are associated with dangerous complications of long-term bisphosphonate therapy. Early fracture identification before they occur is crucial to minimizing complications. The review examines bisphosphonate-related medical issues in postmenopausal women with atypical femur fractures. The study also addressed whether to resume bisphosphonate medication following a pharmacological holiday, which reduces fracture risk. A thorough literature search was undertaken using PubMed, Embase, and the Cochrane Library. The search criteria included atypical femur fractures, bisphosphonates, osteoporosis, and therapy duration. Following screening, studies fulfilling inclusion criteria were assessed utilizing the Cochrane Risk of Bias Tool and Newcastle-Ottawa Scale. Several studies examined the association between long-term bisphosphonate usage and atypical femur fractures. Bisphosphonates reduce osteoporotic fractures but may raise AFF risk over time. The studies also emphasize the significance of individualized bisphosphonate treatment programs and thorough monitoring, especially after a medication holiday. Bisphosphonates reduce fracture risk, although atypical femur fractures require cautious treatment duration and timing, especially following a medication holiday. Selection bias and confounding variables may have limited the evidence of this research. The research design and use of real-world data may also affect its validity and reliability. To enhance treatment recommendations and patient outcomes, longitudinal research on bisphosphonates' long-term impact on bone health and fracture risk is needed.

INTRODUCTION

Background

Postmenopausal women are particularly at risk of fractures from osteoporosis, a systemic skeletal condition that causes bone fragility (Ji & Yu, 2015). This group has increased osteoporotic fractures because of hormonal variations, specifically a drop in oestrogen levels after menopause, which demineralizes bone (Walker & Shane, 2023). It usually affects the wrist, pelvis, and vertebrae. Menopausal women often take bisphosphonates for osteoporosis. Bisphosphonates prevent fractures and increase bone density by inhibiting bone resorption (Khan *et al.*, 2022). Bisphosphonates like ibandronate, zoledronic acid, alendronate, and risedronate enable customized treatment due to their dosage and formulation possibilities. Long-term bisphosphonate medication is linked to atypical femur fractures (AFFs). Adverse effects associated with fractures may be diminished as a result of early detection and diagnosis of AFFs before their complete formation. Single energy X-ray absorptiometry, a recently developed imaging technique, has been shown to detect incomplete atypical femoral fractures (iAFF) before their complete occurrence (McKenna *et al.*, 2017). Although bisphosphonates decrease the risk of fractures, they can cause rare and adverse atypical femur fractures (Silverman *et al.*, 2018). These radiographic pattern femur fractures can develop in the diaphyseal or the sub-trochanteric region without trauma (Grygorieva *et al.*, 2023). Several research has associated bisphosphonates with atypical femur fractures while raising safety concerns specifically with its long-term intake (Black *et al.*, 2019; Donnelly *et al.*, 2012; Tile & Cheung, 2020). A comprehensive understanding is essential for the etiology, epidemiology, and risk factors of atypical femur fractures to reduce the hazards of bisphosphonates and enhance osteoporosis therapy (Hart, 2023). The British National Formulary recommends investigating each patient's treatment responsiveness, fracture risk, and tolerance of bisphosphonate therapy for osteoporosis before the initiation or discontinuation of the treatment (Crawley, 2019).

Examining the patient's history of treatment and bone condition is essential while considering bisphosphonate medication intake after the holiday. The risk of adverse effects may increase as a consequence of returning to therapy soon after a break due to the instability of bone turnover. Long-term studies are required to assess the safety and efficacy of bisphosphonate medication for atypical fractures. To address concerns about starting or discontinuing bisphosphonates after the holidays, even if they're still needed to treat osteoporosis, understand each patient's factors and treatment goals.

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Rationale

A complete investigation is needed owing to the medical difficulties associated with atypical femoral fractures in postmenopausal women who take bisphosphonates and the absence of a clear response about whether to resume treatment after a 5-year hiatus Bisphosphonates, which increase bone mineral density and prevent fractures, have raised concerns about atypical femur fractures, especially in postmenopausal women (Hart, 2024). Previous research reports that these fractures impede healing and therapy. After a 5-year gap, assess therapy resumption risk. Bisphosphonate users' atypical femur fractures and their causes must be understood by doctors to make informed decisions and manage their patients. Some physicians prescribe a "drug holiday" for a few years to lessen the risk, whereas others emphasize treatment to prevent fractures.

Due to long-term risks such as atypical femur fractures, bisphosphonate medication duration, and resume timing are contested. These concerns have caused disagreements over treatment time despite its short- to medium-term fracture risk reduction. Understanding how bisphosphonate medicine decreases fractures and identifying biomarkers might help determine its impact on bone quality and microarchitecture post-holiday. Long-term effects of bisphosphonate on bone quality, microarchitecture, and fracture reduction must be investigated to enhance clinical practice. Postmenopausal women at risk of bisphosphonate-induced atypical femur fractures are the focus of this meta-analysis.

Objectives

- To systematically examine the literature on atypical femur fracture risk in postmenopausal individuals using bisphosphonates for 5 years on holiday.
- To determine the best time to start bisphosphonate medication after the holidays to reduce the risk of atypical fractures.
- To evaluate bisphosphonate discontinuation length post-holidays to preserve bone health and reduce fracture risk.

Questions

- What is the risk for atypical fracture once we start after the holiday?
- When shall we start bisphosphonate after the holiday period?
- How long can we stop the intake of bisphosphonate after the holiday period?

MATERIALS AND METHODS

This systematic review is executed based on the methodology permitting the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements (Moher *et al*., 2009).

Search Strategy

A comprehensive search strategy is used to find relevant studies for this systematic review. The databases Embase, the Cochrane Library, and PubMed will be examined. The search strategy will include atypical femur fractures, bisphosphonates, osteoporosis, treatment duration, and fracture risk. The search strategy initially yielded 1,200 articles from the selected databases. Titles and abstracts were used to evaluate these articles for future investigation. Duplicate articles were removed, leaving 800 entries for inquiry. All 800 articles were then evaluated for inclusion and exclusion criteria.

A total of 50 articles passed full-text screening for the systematic review, these articles were assessed for methodological rigor utilizing the Cochrane Risk of Bias Tool and the Newcastle-Ottawa Scale for observational studies (Higgins *et al*., 2011; Wells *et al*., 2000). Changes in bone health throughout the holiday, atypical femur fractures, risk variables, and bisphosphonate treatment duration's influence on fracture risk reduction are important results. This thorough analysis synthesizes data on atypical femur fractures in postmenopausal bisphosphonate-treated individuals. 9 articles met inclusion requirements. Table 1 below shows the keywords and MeSH terms utilized in the review.

Table 1: Summary of the searched keywords and MeSH terms

Category	Keywords and MeSH Terms
Atypical Femur Fractures	Atypical femur fractures
	Sub-trochanteric fractures
	Diaphyseal fractures
	Femoral shaft fractures
Bisphosphonates	Bisphosphonates
	Alendronate
	Risedronate
	Ibandronate
	Zoledronic acid
Osteoporosis	Osteoporosis
	Postmenopausal osteoporosis
	Bone density
Treatment Duration	Treatment duration
	Long-term treatment
	Drug holiday

Study Selection Criteria

Data Extraction

The data extraction approach for this systematic review entails assessing and documenting important study features and outcome measures with care. These factors greatly impact the findings' robustness and applicability. Cohort studies have long-term impacts, whereas randomized controlled trials provide high-quality data. The period of follow-up also reveals the treatment effects' temporal aspects (Yong & Logan, 2021). The review

Table 2: Inclusion and Exclusion Criteria of the included studies

Criteria	Inclusion	Exclusion
Study Design	Randomized controlled trials, case-control studies, cohort studies, and systematic reviews	Studies not meeting the specified study designs (e.g., case reports, letters, editorials)
Participants	Postmenopausal patients	Studies conducted in populations other than postmenopausal patients (e.g., men, premenopausal women)
Intervention	Studies examining bisphosphonate treatment duration and timing of initiation after a holiday period	Studies focusing solely on other osteoporosis treatments or interventions
Outcome Measures	Studies reporting on atypical femur fractures	Studies without relevant outcome measures (e.g., studies focusing solely on bone mineral density changes)
Reporting Quality	-	Studies with inadequate methodology or reporting, as assessed during the quality assessment process

rigorously evaluates these qualities to place the results in the context of osteoporosis management. Detailed outcome metrics for atypical femoral fractures and bisphosphonate treatment are documented. A range of outcome indicators are used to assess the pros and cons of bisphosphonate treatment in postmenopausal individuals. During data extraction, bias, and methodological issues are carefully evaluated. Larger sample volumes and longer follow-ups may improve analytical significance. The review thoroughly evaluates the facts to satisfy the highest evidence synthesis standards and ensure the outcomes' validity and reliability. This method collects and summarises data from several research, analyses patterns and similarities, and investigates variance explanations.

Quality Assessment

Table 3 presented below highlights the quality of the selected articles for the review. This table categorizes the possible bias of each study utilizing the Cochrane Risk of Bias Tool (Higgins *et al*., 2011). Each domain has a "Low," "High," or "Uncertain" bias risk. The analysis uses methodologically rigorous research, indicating little bias. Reviewers resolved quality evaluation discrepancies and disagreements via discourse. If a consensus was not achieved, a third reviewer was hired to provide an objective assessment and help resolve the conflict.

Table 3: Quality Assessment

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk of Bias
(Bauer *et al*., 2024)	Low	High	Low	Low	Low	Uncertain
(Brown, 2021)	Low	Low	Low	High	Low	Low
(Fuggle *et al*., 2021)	Low	Low	Low	Low	High	Low
(Khan *et al*., 2022)	Low	Uncertain	Low	Low	Low	Low
(Morkos *et al*., 2022)	Low	High	Low	Low	Low	High
(Ogundipe, 2020)	Low	Low	High	Low	Low	Low
(Rudran *et al*., 2021)	High	Low	Low	Low	Low	Low
(Saag *et al*., 2021)	Low	Low	Low	High	Low	Low
(Toro *et al*., 2023)	Low	Low	Uncertain	Low	Low	High

Data Synthesis and Analysis

The selected studies included atypical femur fractures in postmenopausal bisphosphonate patients in a narrative format. Reference 1, studied Danish bisphosphonate use with uncommon femoral fractures in a case-cohort study. The research employed blinded radiography. Atypical femur fractures were infrequent in postmenopausal patients using bisphosphonates, supporting safety. The study emphasizes the need for thorough monitoring and adverse effect awareness, especially in long-term bisphosphonate users. The study discovered that extended postmenopausal osteoporosis treatments must be tailored to each patient's needs (Brown, 2021). It also underlines the significance of frequently monitoring the medicine and contemplating cessation after a break to reduce the risk of adverse effects such as atypical femur fractures. Researchers observed a gap in osteoporosis care, suggesting at-risk individuals were not addressed for

appropriate medications (Fuggle *et al.*, 2021). Many eligible patients receive insufficient bisphosphonates or no treatment, increasing their risk of osteoporotic fractures. Public awareness, educational accessibility, and evidence-based therapy utilization are needed to reduce treatment disparities. After stopping chronic oral bisphosphonate therapy, the Study investigated mineral density and bone turnover post hoc (Saag *et al.*, 2021). These findings suggest that bisphosphonate discontinuation needs switching medicines or monitoring for side effects.

RESULTS AND DISCUSSIONS

Study Selection Process

Figure 1 shows the identified databases and screened studies involved in this systematic review while meeting the inclusion and exclusion criteria. The PRISMA flow diagram was created using PRISMA2020 (Haddaway *et al.*, 2022).

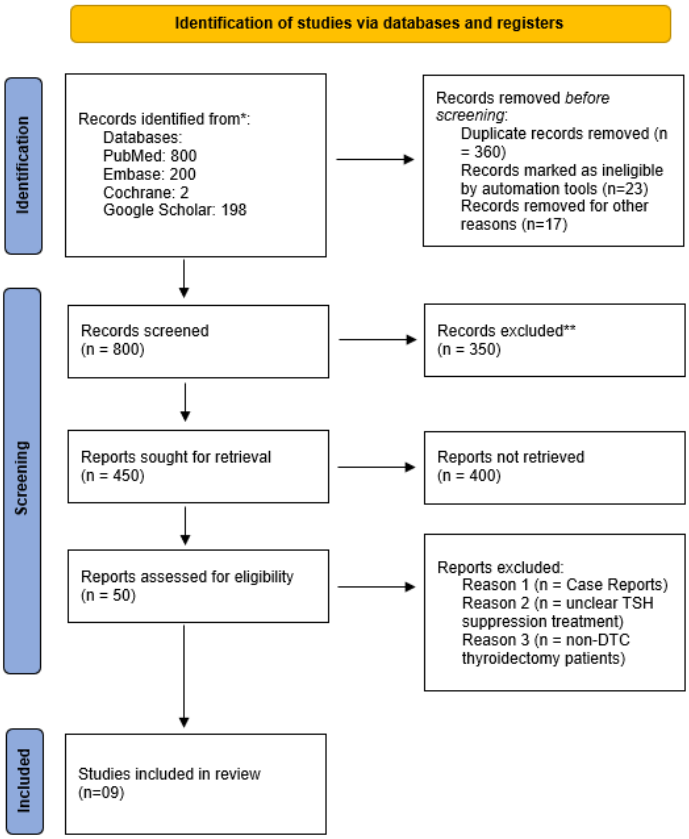

Figure 1: PRISMA Chart demonstrating the study selection process

Characteristics of Included Studies

Table 2: Inclusion and Exclusion Criteria of the included studies

Study	Study Design	Population	Intervention	Methodology
Bauer *et al.*, 2024)	Case-cohort study	Postmenopausal women receiving bisphosphonates	Bisphosphonate therapy	Blinded radiog -raphic review
(Brown, 2021)	Review article	Postmenopausal women with osteoporosis	Long-term bisphosphonate treatment	Literature review
(Fuggle *et al.*, 2021)	Review article	Population at risk of osteoporosis and fractures	Osteoporosis therapy	Literature review
(Khan *et al.*, 2022)	Guideline	Postmenopausal women at risk of osteoporosis	Management guidelines	Guideline development
(Morkos *et al.*, 2022)	Observational study	Patients with osteoporosis on a drug holiday	Osteoporosis medication selection	Real-world data analysis
(Ogundipe, 2020)	Case report	Postmenopausal woman with atypical femoral fractures	Long-term alendronate therapy	Case report
(Rudran *et al.*, 2021)	Review article	Patients with bisphosphonate-associated fractures	Management strategies	Literature review

(Saag *et al.*, 2021)	Post hoc analysis	Postmenopausal women discontinuing oral bisphosphonates	Bisphosphonate discontinuation	Post hoc analysis of clinical trial data
(Toro *et al.*, 2023)	Review article	Patients at risk of atypical femoral fractures	Fracture liaison service	Literature review

Findings Related to Atypical Femur Fractures

Several studies which are presented above in Table 4 have shown the complicated link between bisphosphonate treatment and fracture risk. These studies found variable rates of atypical femur fractures amongst postmenopausal bisphosphonate users. Atypical femur fractures may be prevented by bisphosphonates, according to blinded radiographic evaluation. However, it is reported that non-traumatic bilateral atypical femoral fractures in postmenopausal women use long-term alendronate (Ogundipe, 2020).

Researchers advised diagnosing and treating bisphosphonate-induced atypical femoral fractures immediately to minimize complications (Rudran *et al.*, 2021). Atypical femur fractures may be affected by patient characteristics, bisphosphonate duration, and risk variables, confounding fracture susceptibility assessment. When restarting bisphosphonate medication, our findings emphasize the necessity to adapt it to each patient's requirements and goals. The BNF chapter on bisphosphonate medication duration in osteoporosis highlights fracture risk, response, and drug tolerance in tailored treatment programs.

The condition of patients during exceptionally long therapy periods (e.g., over ten years) is less certain. Whilst it would be more acceptable to adopt a more precise definition of "high risk" in light of these considerations, it remains feasible to administer continuous treatment to patients who are deemed to be at an adequate risk without interruption. It is advisable to solicit expert opinion and assistance in each specific case, and whenever practicable, patients should be apprised of the current ambiguity surrounding the trade-offs between benefit and risk. The physician may recommend a one-year treatment hiatus, contingent upon the patient's circumstances (Hart, 2024). The study found that bisphosphonates increase the risk of atypical femur fractures, thus they must be monitored for adverse effects (Bauer *et al.*, 2024). According to the study, bisphosphonates, notably alendronate, may raise the risk of rare but severe atypical femoral fractures (Ogundipe, 2020). Another study examined how bisphosphonate cessation affects mineral density and bone turnover (Saag *et al.*, 2021). A recent study discovered that the risk of fractures increases after the discontinuation of the drug which is the rebound effect. Additionally, it noted the overlooked opportunities to prevent fracture fragility and deficiency of osteoporosis treatments (Fuggle *et al.*, 2021).

This therapeutic gap must be filled by addressing and investigating these aspects. Although the efficacy of fracture risk reduction of bisphosphonates is known, the potential adverse effects, duration of therapy, and patient demographics must be evaluated to lower atypical femur fractures and enhance the efficacy of the treatment. The studies included in this review completely analyse the patients' incidence rates and risk variables of atypical femur fractures. It is crucial to lower the atypical femur fractures and enhance overall patient outcomes through personalized treatment strategies, immediate adverse effect reporting, and regular progress assessments for postmenopausal women taking bisphosphonate (Hart, 2024).

Effects of Bisphosphonate Treatment Duration and Timing of Initiation

The studies included in this review examine the mechanism and treatment duration effects such as the bone mineral density modifications after the discontinuation of the treatment and reduction of fracture risk to comprehensively understand the safety and efficacy of bisphosphonate therapy in the management of osteoporosis. According to a study, bisphosphonates lower the risk of fractures during the prolonged intervention period of postmenopausal osteoporosis (Brown, 2021). Additionally, less atypical femur fractures were associated with postmenopausal women taking bisphosphonates (Bauer *et al.*, 2024). Another study investigated decisions on osteoporosis medication during drug discontinuation, highlighting the significance of treatment continuation to prevent fractures (Morkos *et al.*, 2022). A continued reduction in bone mineral density and a temporary increase in bone turnover after a long-term discontinuation of bisphosphonate was noted (Saag *et al.*, 2021). When bisphosphonate is discontinued, an augmented fracture risk and rebound effects are developed.

Discussion

Summary of Key Findings

Researchers selected literature on bisphosphonate-induced uncommon fractures in postmenopausal women to address the first difficulty of the systematic review (Bauer *et al.*, 2024; Ogundipe, 2020). According to a case report, extended alendronate use may cause atypical femoral fractures, stressing bisphosphonate safety regarding the review goals' risk assessment (Ogundipe, 2020). The findings underline the need to rapidly detect and treat bisphosphonate-induced femur fractures (Rudran *et al.*, 2021). The systematic study investigated whether continuing bisphosphonate therapy after a break increases the incidence of atypical fractures. This systematic review evaluates bisphosphonate duration and timing on bone mineral density and fracture risk. Bisphosphonates minimize the risk of fractures (Brown,

2021). Studies stress that quitting bisphosphonate therapy momentarily stimulates bone turnover and eventually reduces bone mineral density (Saag *et al*., 2021). The researcher analyses fracture liaison services and their capacity to reduce fracture risk, emphasizing the need for healthcare practitioners to adopt preventative measures after the holidays despite concerns about bone loss after cessation (Toro *et al*., 2023). The results emphasize the need for prescription bisphosphonate therapy for fracture prevention and the hazards and benefits of long-term usage and drug cessation.

Interpretation of Findings of Existing Literature

Researchers demonstrated bisphosphonate medication greatly reduces atypical femur fractures (Bauer *et al*., 2024; Brown, 2021). Bisphosphonates seldom cause these fractures. Scholars educate about bisphosphonate medication cessation-induced bone loss and fracture risk (Morkos *et al*., 2022; Saag *et al*., 2021). A 2020 case report describes unanticipated non-traumatic bilateral atypical femoral fractures produced by sustained alendronate therapy (Ogundipe, 2020). Bisphosphonates reduce fracture risk and are safe, therefore atypical femur fractures are rare (Bauer *et al*., 2024; Ogundipe, 2020). Patients using the drug long-term should be risk evaluated and monitored for adverse effects due to atypical femur fracture risk (Ogundipe, 2020). The study found that bisphosphonate removal temporarily reduced bone mineral density and augmented bone turnover, increasing the risk of atypical fracture (Saag *et al*., 2021). Atypical femur fractures, postmenopausal osteoporosis bone health, and bisphosphonate treatment have inconsistent outcomes (McKenna *et al*., 2017). Consequently, this study will identify the optimum duration to discontinue bisphosphonate after a holiday period without resulting in atypical fractures or harming bone health.

Limitations of the Evidence

In a retrospective case-cohort study, blinded radiography was utilized to analyze bisphosphonate-associated atypical femur fractures (Bauer *et al*., 2024). Bilateral atypical femur fractures were reported to be caused by a long-term alendronate dosage (Ogundipe, 2020). The case studies lack scientific evidence and have low population sizes. The clarity and authenticity can be compromised as a result of real-world data analysis potentially complicating biases and variables (Morkos *et al*., 2022). Furthermore, biased or confounding references can potentially hinder the reliability and validity of systematic reviews as selection bias can falsify or disregard significant research dependent on the review criteria. Age, comorbidities, and concurrent medications may indicate bisphosphonate-induced atypical femur fractures, altering relationships.

Clinical Implications and Future Research Directions

A comprehensive examination of atypical fractures after stopping bisphosphonate medication during a holiday break reveals clinicians should prioritize bisphosphonate therapy for postmenopausal women at risk of osteoporotic fractures. It may reduce fractures with long-term therapy (Khan *et al*., 2022). The potential incidence of femur fractures in patients on bisphosphonate necessitates particular attention. Fracture monitoring and evaluation are associated with the therapeutic success and safety of the patient. Reinitiating bisphosphonate intake after a holiday period necessitates the evaluation of patient risk and following treatment standards. The prevention of fractures must be a regular therapy to lower fractures and improve overall patient outcomes. The pros and cons of bisphosphonate therapy should be discussed with the patients while following their preferences and values. An osteoporosis management strategy highlighting patient requirements, providing personalized therapy, and broad care may benefit patients with fragility fractures. Further research is required to investigate the discontinuation of bisphosphonate after a holiday period.

CONCLUSION

Although bisphosphonates reduce the risk of fractures, atypical femur fractures may develop. Therefore, long-term patient monitoring should be prioritized. Healthcare practitioners must keep in consideration the patient's comorbidities, age, and history of fractures when evaluating the benefits and risks of bisphosphonate therapy for the prevention of fractures. Bisphosphonate therapy must be immediately re-initiated after the discontinuation of the medication. The review reported that early medication re-initiation augments the risk of atypical fractures as a result of the long-lasting bone remodeling effects of the medication. Thus, personalized treatment plans must consist of the status of bone health and risk profiles to evaluate the bisphosphonate re-initiation period and drug interruptions. The use and discontinuation of bisphosphonate requires further long-term research to a more comprehensive understanding of its long-term outcomes such as the determination of the optimum holiday period and the formulations of bisphosphonate affecting risks of fractures. Due to the limitations of the present data, further research should utilize more rigorous methodological strategies to minimize performance and selection biases. Well-designed randomized controlled trials with larger sample sizes, scientifically evident clinical studies, and comprehensive confounding variable information are required to improve the bisphosphonate dosage management policies for postmenopausal women. Bisphosphonates are crucial for the treatment of postmenopausal osteoporosis. However, it should be carefully monitored to evade atypical femur fractures. Further research and personalized treatment strategies are critical to enhance the overall health outcomes for the patients.

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