THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Systematic Review

Medication holidays in osteoporosis: evidence-based recommendations from the Italian guidelines on 'Diagnosis, risk stratification, and continuity of care of fragility fractures' based on a systematic literature review

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Abstract

Background: Noncommunicable, chronic diseases need pharmacological interventions for long periods or even throughout life. The temporary or permanent cessation of medication for a specific period, known as a 'medication holiday,' should be planned by healthcare professionals.

Objectives: We evaluated the association between continuity (adherence or persistence) of treatment and several outcomes in patients with fragility fractures in the context of the development of the Italian Guidelines.

Design: Systematic review.

Data Sources and Methods: We systematically searched PubMed, Embase, and the Cochrane Library up to November 2020 for randomized clinical trials (RCTs) and observational studies that analyzed medication holidays in patients with fragility fracture. Three authors independently extracted data and appraised the risk of bias of the included studies. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation methodology. Effect sizes were pooled in a meta-analysis using random effects models. Primary outcomes were refracture and quality of life; secondary outcomes were mortality and treatment-related adverse events.

Results: Six RCTs and nine observational studies met our inclusion criteria, ranging from very low to moderate quality. The adherence to antiosteoporotic drugs was associated with a lower risk of nonvertebral fracture [relative risk (RR) 0.42, 95% confidence interval (CI) 0.20–0.87; three studies] than nonadherence, whereas no difference was detected in the health-related quality of life. A reduction in refracture risk was observed when continuous treatment was compared to discontinuous therapy (RR 0.49, 95% CI 0.25–0.98; three studies). A lower mortality rate was detected for the adherence and persistence measures, while no significant differences were noted in gastrointestinal side effects in individuals undergoing continuous *versus* discontinuous treatment.

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Conclusion: Our findings suggest that clinicians should promote adherence and persistence to antiosteoporotic treatment in patients with fragility fractures unless serious adverse effects occur.

Keywords: adherence, bisphosphonates, compliance, discontinuation, fragility fractures, medication vacation, osteoporosis, persistence

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Introduction

Noncommunicable, chronic diseases, such as diabetes mellitus, cardiovascular diseases, Parkinson's disease, and osteoporosis, need pharmacological interventions for long periods or even throughout life.[1–4]

The cessation of medication for a specified period should be planned by healthcare professionals, although patients may avoid taking regularly prescribed medications due to a variety of factors. This phenomenon is known as a 'medication holiday' or drug holiday – a temporary or permanent interruption of therapy to alleviate side effects and tolerance or for personal reasons.[5]

Literature illustrates examples of medication holidays in chronic diseases, such as inflammatory bowel diseases,[6] attention deficit hyperactivity disorder,[7] multiple sclerosis,[8] and cancer.[9] The reintroduction of medication (or drug rechallenge) could be effective after a medication holiday following disease relapse or progression during therapy.[10–12]

Moreover, the potential role of therapy interruption in avoiding serious adverse events (AEs) has been investigated in patients affected by osteoporosis. Antiosteoporotic therapy includes antiresorptive and anabolic drugs that affect bone mineral density (BMD) in different ways, supplemented with calcium and/or vitamin D. In particular, antiresorptive drugs might increase the risk for two rare AEs, osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFFs).[4] The hypothesis on the effectiveness of antiresorptive drug holidays is based on the improvement of a surrogate endpoint, such as BMD, even after the medication holiday. Indeed, the most important randomized controlled trials (RCTs) in patients taking alendronate (ALN) or zoledronate (ZLN) – bisphosphonates (BPs) belonging to the antiresorptive class – have demonstrated the maintenance of benefits for longer periods (up to 5 years) despite discontinuation (ALN or ZLN after 5 or 3 years of treatment, respectively).[13,14] BP interruption in low-risk patients might be considered on the basis of hip BMD and a history of vertebral fragility fractures and should be reinitiated after a period no longer than 5 years.[15,16] On the other side, evidence about the incidence of fragility fractures during antiresorptive drugs holiday is limited resulting in challenging clinical decisions for drug discontinuation in patients with different risk of osteoporotic fractures.[15] Therefore, the aim of this systematic review and meta-analysis was to provide recommendations based on the best available evidence on the benefits and risks of medication holidays in patients at a high risk of subsequent fragility fractures.

Method

We conducted a systematic review to support the Panel of the Italian Fragility Fracture Guideline (published in the platform of the Italian National Institute of Health[17]) in formulating recommendations. In accordance with the GRADE-ADOLOPMENT methodology[18] and the standards formulated by the Sistema Nazionale Linee Guida (SNLG),[19,20] the multidisciplinary panel defined the following clinical question: 'Could antiosteoporotic treatment interruption be an acceptable practice in patients who have experienced fragility fractures?'

Inclusion and exclusion criteria

RCTs and observational studies were included if they met the following criteria: (1) population: patients who experienced a fragility fracture, (2) intervention: continuous use of antiosteoporotic drug defined as (i) adherence, (ii) persistence, or (iii) cyclical treatment with a dose-free interval in drug administration. Specifically, (i) adherence was defined by the number of doses dispensed with respect to the observation time and calculated as the medication possession ratio (MPR).[21,22]

Patients with MPR greater than 80% were classified as adherent.[23–29] Moreover, adherence was defined by the number of antiosteoporotic pens (e.g., each teriparatide pen could be intended for 1 month of use) prescribed within the 24-month study period. Thus, patients were classified as being adherent to antiosteoporotic treatment for more than 12 months.[30] Otherwise, adherence was be defined as taking more than 80% of pills prescribed.[31,32] (ii) Persistence was defined as the continued use of any antiosteoporotic drug during follow-up without any episode of a medication holiday.[22] Discontinuation was defined as gap of at least 30,[25] 60,[33] or 90 days[30] between antiosteoporotic prescriptions. Patients were classified as persistent if they used antiosteoporotic drugs for more than 12 months[30,33,34] or even showed >50% adherence.[34] Moreover, extension trials were included in this comparison and classified patients into continuous or discontinuous treatment groups.[13,16,35] Patients were first randomized to receive placebo or antiosteoporotic drugs and subsequently rerandomized to antiosteoporotic treatment or placebo to extend the trial period to 2,[35] 3,[16] or 5[13] years. Eventually, (iii) studies may have randomly allocated patients to continuous or cyclical treatment with 2.5 mg daily of risedronate (continuous) or 2.5 mg daily risedronate for 2 weeks, respectively, followed by 10 weeks on placebo (cyclical),[36] and 2.5 mg daily of oral ibandronate (continuous) or 20 mg of oral ibandronate every other day for 12 doses every 3 months (cyclical).[37]

Then, studies were selected if they reported (3) treatment discontinuity as comparator; (4) outcomes: (i) refracture and health-related quality of life as primary outcome measures and (ii) mortality, treatment-related AEs (e.g., abdominal pain, diarrhea, and nausea) and other AEs (e.g., upper gastrointestinal disorders and gastrointestinal-esophagus disorders) as secondary outcomes.

Studies were excluded if they (i) were not published in the English language, (ii) did not report original findings (i.e., letters, case reports), (iii) did not identify patients affected by a fragility fracture, or (iv) did not consider treatment discontinuity as a comparator.

Data source and search strategy

We performed PubMed, Embase, and Cochrane Library searches up to November 2020 and identified publications reporting on the continuity of antiosteoporotic drug use among patients with fractures. The systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[38] and is shown in Supplemental Table S1. The search strategy (see Supplemental Material) included specific keywords and/or corresponding MeSH terms related to fragility fracture AND antiosteoporotic drugs AND (adherence, persistence, medication vacation, discontinuation, compliance, and intermittent). We checked the reference lists of the studies and the systematic reviews identified during the search process.

Study selection and data extraction

Three independent authors (AB, GP, and RR) screened titles and abstracts according to the search strategy and then assessed the full text of the potentially relevant studies. Discrepancies between readers were resolved by conference.

From each included observational or RCT, the following information was extracted: (i) first author, year and country of publication, (ii) study setting, (iii) type of population, (iv) intervention and comparator, and (v) follow-up period (see Supplemental Material).

Study quality

The quality of each included publication was assessed using the Cochrane Risk of Bias (RoB) tool for RCTs[39] and the Newcastle-Ottawa scales (NOSs)[40] for observational studies. The following domains of the Cochrane RoB tool were appraised: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (such as funding bias). Each domain was classified as 'high,' 'low,' or 'unclear' RoB if the publication did not provide sufficient information for classification. The following NOS domains were evaluated: selection, comparability, and outcome. The threshold for identifying high-quality studies was more than five points.

Quality of evidence

The quality of evidence for each primary outcome was judged through five dimensions (RoB, consistency of effect, imprecision, indirectness, and publication bias) using the GRADE approach.[41]

The evidence was downgraded from 'high quality' by one level if serious or by two levels if very serious limitations were found for each of the five dimensions.

Statistical analysis

The measure of interest was the summary relative risk (RR) that evaluated the effect of medication holidays on BMD and the risk of fragility fracture; the pooled mean difference was used for continuous outcomes, such as the health-related quality of life. Where possible, we adopted the adjusted RR and pooled adjusted estimates from the original studies. Estimates were summarized if at least three studies reported the estimate of interest.

In the forest plot, we specified (i) outcome measures at different follow-up durations, (ii) first author and year of publication, (iii) site of fracture at baseline (such as pelvis, femur, hip, vertebral, upper arm, or any fracture), (iv) type of antiosteoporotic drug (such as teriparatide, BPS, etidronate, ZLN, ALN, or various), and (v) study design (observational or RCTs indicated by an asterisk).

Heterogeneity between study-specific estimates was tested using Chi-square (χ^2) statistics[42] and measured with the I^2 index (heterogeneity measure across studies).[43] Meta-analyses were performed to combine the outcome data using the DerSimonian and Laird random effects model.[44]

All tests were considered statistically significant for p-values less than 0.05. The analyses and the correspondent graphical visualization of forest plots were performed using RevMan V.5.4 (Nordic Cochrane Center; Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020).

Results

Study selection

From the 10,170 papers initially found, we excluded 1165 duplicates. After title and abstract screening, we included 218 eligible papers. Finally, after reading the full-text, only 15 articles[13,16,24–30,33–37,45] (six RCTs, nine observational studies) were included in the quantitative and qualitative syntheses (Figure 1 and Table 1).

Study characteristics

The included studies were conducted in Taiwan ($n=6$), USA ($n=5$), Europe ($n=3$), and Canada ($n=2$) (see Supplemental Material). According to RoB, all RCTs had uncertain risk about selection bias, except for the RCT by Miller *et al.*,[35] where random sequence generation was properly addressed. However, this study was characterized by high risk related to attrition bias (Supplemental Table S2). Overall, RCTs were not affected by any serious RoB (Supplemental Table S3).

Only one observational study[29] had an NOS score lower than 6 and was assigned to the low-quality category. The certainty of evidence ranged from very low to moderate RoB. We downgraded the evidence for very serious inconsistency and serious imprecision of the estimates (Supplemental Table S3).

Primary outcome

Adherence to antiresorptive treatment versus *nonadherence.* Compared to nonadherent (MPR$<$80%) subjects (Figure 2), there was a decreased risk of nonvertebral fracture RR 0.42 [95% confidence interval (CI) 0.20–0.87; three studies] in the adherent group (MPR$\geqslant$80%), with heterogeneity among studies ($I^2=90\%$). Moreover, as shown in Figure 3, there was no significant difference in the health-related quality of life at 1 and 2 years among the adherent (>80% of pills consumed) and nonadherent groups. Specifically, one study[45] measured the health-related quality of life using the generic Short Form Health Survey (SF-12),[46] the Osteoporosis Quality of Life (OptQoL) tool,[47] and the upper extremity-specific functional outcomes tool (Disabilities of the Arm, Shoulder, and Hand[48]).

Persistence to antiosteoporotic treatment versus *nonpersistence.* Figure 4 shows a decreased, nonsignificant, risk of fracture among persistent ($\geqslant$12 months) patients compared to nonpersistent ($<$12 months) patients, RR 0.88 (95% CI 0.58–1.34; three studies) with high heterogeneity between groups ($I^2=87\%$).

Continuous versus *discontinuous antiresorptive treatment.* Figure 5 shows a significant reduction of refracture risk, RR 0.49 (95% CI 0.25–0.98; three studies), among continuously treated subjects compared to patients who discontinued antiosteoporotic treatments, without heterogeneity between studies ($I^2=36\%$).

Table 1. Characteristics of included studies.

Study	Design	Fracture at baseline	Outcome measure	Treatment	Treatment duration	Timing of outcome
New fractures						
Lin 2011	Observational	Vertebral, Hip	MPR	Alendronate	2 years and 6 months	4 years
Soong 2013	Observational	Vertebral, Hip	MPR	Alendronate	3 years	3 years
Keshishian 2017	Observational	Hip, Pelvis	MPR	Various antiosteoporotic drugs	2 years	1 year
Sheehy 2009	Observational	Vertebral	MPR	Bisphosphonates	1 year	4 years
Chan 2016	Observational	Any site	Number of pre-set pens with respect to the observation period[a]	Teriparatide	2 years	2 years
Soong 2013	Observational	Vertebral, Hip	Persistence[b]	Alendronate	3 years	3 years
Black *et al.* 2006	RCT	Any site	Alendronate	Continuous: 10 years; Discontinuous: 5 years treatment + 5 years placebo		5 years
Miller 1997	RCT	Vertebral	Etidronate	Continuous: 4 years; Discontinuous: 2 years treatment + 2 years placebo		2 years
Cosman 2014	RCT	Vertebral	Zoledronate	Continuous: 6 years; Discontinuous: 3 years treatment + 3 years placebo		3 years
Chesnut 2004	RCT	Vertebral	Intermittent *versus* daily	Ibandronate	3 years	3 years
Clemmesen 1997	RCT	Any site	Ciclic *versus* continuous	Risedronate	2 years	3 years
New non vertebral fractures						
Chan 2016	Observational	Any site	Number of pre-set pens with respect to the observation period[a]	Teriparatide	2 years	2 years
Adams 2018	Observational	Vertebral, Hip	Taking treatment continuously or with suspension[c]	Bisphosphonates	10 years	4 years
Hsu 2020	Observational	Hip	Taking treatment continuously or with suspension[d]	Various antiosteoporotic drugs	1 year	3 years
Mortality						
Yu 2019	Observational	Hip	MPR	Various antiosteoporotic drugs	5 years	3 years
Chen 2017	Observational	Vertebral	Compliance or persistence[e]	Various antiosteoporotic drugs	10 years	10 years
Hsu 2020	Observational	Hip	Taking treatment continuously or with suspension[d]	Various antiosteoporotic drugs	1 year	3 years

(Continued)

Table 1. (Continued)

Study	Design	Fracture at baseline	Outcome measure	Treatment	Treatment duration	Timing of outcome
Quality of life						
McAlister 2019	RCT	Upper limbs (distal radius and/or ulna, proximal humerus)	>80% pills consumed	Alendronate or risedronate	1 year	1 year and 2 years
AEs						
Miller 1997	RCT	Vertebral	Etidronate	Continuous: 4 years treatment; Discontinuous: 2 years treatment + 2 years placebo		2 years
Chesnut 2004	RCT	Vertebral	Intermittent *versus* daily	Ibandronate	3 years	
Clemmesen 1997	RCT	Any site	Ciclic *versus* continuous	Risedronate	2 years	3 years

[a]One pen has 1 month coverage, therefore subjects with more than 12 pens in the treatment period are defined as adherent.
[b]Gap 30 days.
[c]Subjects with <50% adherence (MPR) or no drug use for <12 months are considered suspended.
[d]Subjects who do not have any new prescription of the drug in a gap of 60 days are considered discontinuing.
[e]Low adherence was also defined as noncompliance (MPR) or nonpersistence (30 consecutive days not covered by the drug).
AE, Adverse event; MPR, medication possession ratio; RCT, randomized clinical trial.

The risk of refracture (vertebral, nonvertebral, or any-site fractures) investigated in less than three studies is detailed in Supplemental Table S4.

Secondary outcomes

Three studies reported a reduced risk of mortality both for the adherence and persistence measures (Supplemental Table S4).

No significant differences were observed in treatment-related gastrointestinal adverse effects (abdominal pain, diarrhea, nausea, esophageal ulcer, esophageal structure, and esophagitis) among individuals undergoing continuous *versus* discontinuous treatment (Supplemental Table S4).

Discussion

This systematic review evaluated one clinical question of the Italian Guidelines[17]: 'Could anti-osteoporotic treatment interruption be an acceptable practice in patients who have experienced fragility fractures?' A multidisciplinary panel formulated recommendations thorough a structured and transparent process, the GRADE-ADOLOPMENT.

A previous meta-analysis[49] of eight studies on the effect of BPs medication holiday in terms of BMD and fragility fracture risk reported that women affected by osteoporosis who discontinued BPs had no significant higher risk of hip fractures neither of any clinical fractures [Hazard Ratio (HR), 1.09, 95% CI 0.87–1.37, and HR 1.13, 95% CI 0.75–1.70, respectively] compared to those who continued BPs, suggesting that discontinuation may be considered for patients without low hip BMD after 3–5 years of BPs treatment. However, according to our findings, the risk/benefit ratio in the treatment of osteoporotic patients with fragility fractures seems to be favorable to pharmacological continuity, avoiding medication holidays. The results of this meta-analysis allowed us to determine conditional recommendations on medication holidays with the aim to prevent treatment-related AEs in patients affected by bone fragility (moderate quality of evidence for all recommendations):

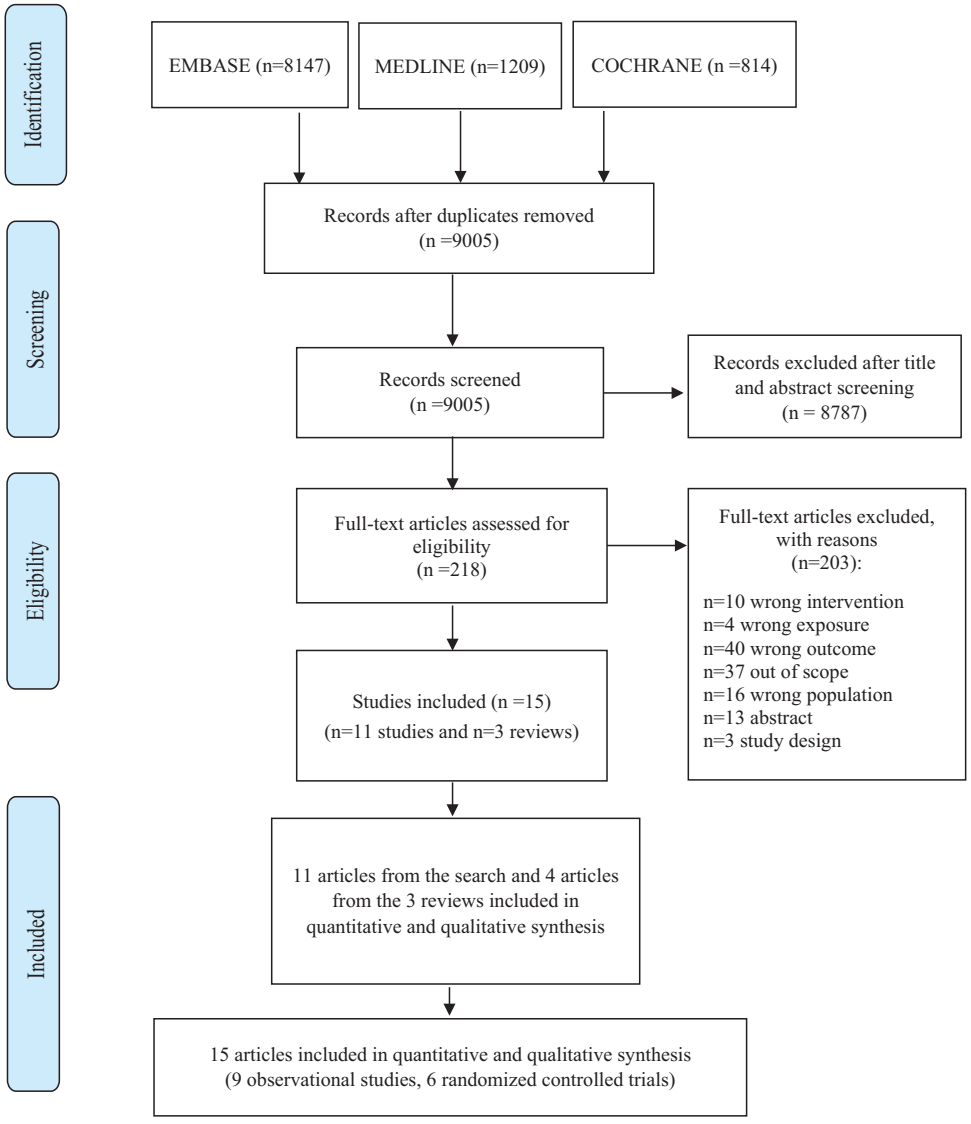

Figure 1. Flowchart of study selection.

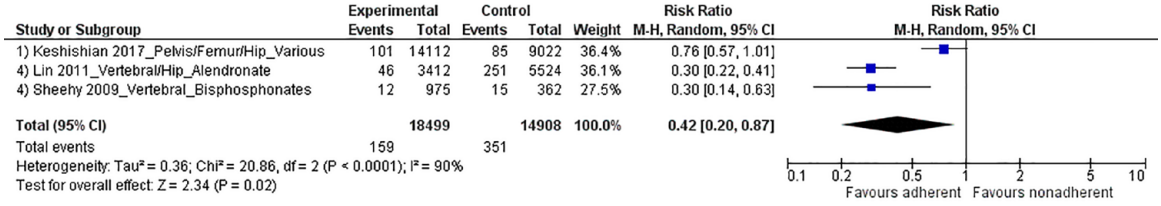

Figure 2. Risk of nonvertebral fracture between adherent (MPR ⩾ 80%) and nonadherent (MPR < 80%) subjects.
Source: Adjustments. Lin 2011: site of osteoporotic fracture, gender, age. Soong 2013: comorbidity, concomitant drugs, gender, age. Sheehy 2009: demographic and clinical characteristics.
MPR, medication possession ratio.

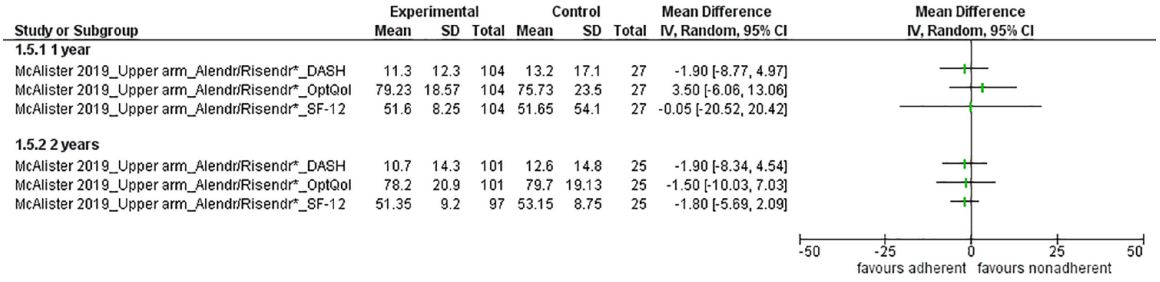

Figure 3. Health-related quality of life scores between adherent (>80% of pills consumed) and nonadherent (⩽80% of pills consumed) subjects.
Source: McAlister 2019.
OptQoL, Osteoporosis-Targeted Quality of Life questionnaire; SF-12, Short Form Health Survey, Disabilities of the Arm, Shoulder.

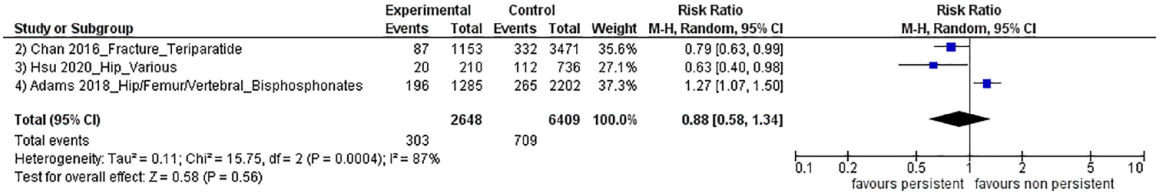

Figure 4. Risk of nonvertebral fractures between persistent (⩾12 months) and nonpersistent subjects (<12 months).
Source: Adjustments. Chan 2016: demographic variables at baseline (age, gender and previous fractures) and in the 12 months prior to the index prescription to teriparatide for concomitant antiosteoporotic drugs and other drugs that can affect bone health, and comorbidities. Adams 2018: recruitment year, recruitment site, history of previous fractures, 10-year fracture probability (FRAX score), baseline fall risk (modified FRAT score), baseline comorbidity (Quan-Charlson score), previous or concomitant exposure to proton pump inhibitors, histamine H2 receptor antagonists, statins, estrogens and thiazolidinedione. Hsu 2020: age, gender, geographic region, hospital level and Charlson score.

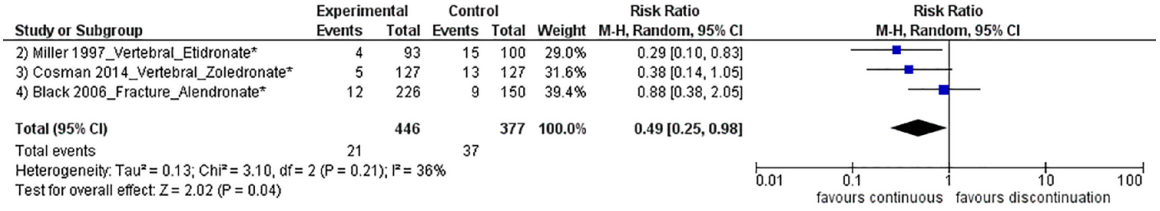

Figure 5. Risk of fracture between subjects in continuous *versus* discontinuous antiosteoporotic treatment.
Source: Cosman 2014: risk of refracture; Miller 1997, Black 2006: risk of vertebral fracture.

1. Healthcare professionals are advised to monitor and encourage high adherence and persistence to antiosteoporotic treatment in patients at high risk for fragility fracture.
2. In patients with fragility fracture at a high risk of new fractures, except for serious AEs, it is suggested not to discontinue antiosteoporotic treatment, whether permanently or temporarily.
3. It is suggested that dose reduction or temporary discontinuation of long-term BP treatment should be evaluated by the specialist only when long-term conditions have improved following drug treatment and until reassessment of the risk/benefit ratio.

Important differences between recommendations for medication holidays, formulated by

the European Scientific Societies, should be evidenced.

According to the Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF),[50] the risk of new clinical fractures is 20–40% higher in subjects who stopped treatment, and consequently, vertebral fracture risk could be approximately doubled. Recently, the National Osteoporosis Guideline Group (NOGG)[51] published guidelines for the prevention and treatment of osteoporosis, accredited by the National Institute for Clinical Excellence, which recommended the maintenance of antiresorptive treatment (BP or denosumab), which should be the first-line option in patients at risk for fragility fracture. Our recommendations are consistent with ESCEO/IOF and NOGG Guidelines, which recommend to health system decision-makers: (1) monitor and encourage drug adherence and persistence; (2) avoid discontinuation of any antiosteoporotic treatment, except for serious AEs, in patients at high risk for fracture; and (3) long-term BP treatment may be temporarily discontinued in patients with great improvements in the BMD.

However, the task force of the American Society for Bone and Mineral Research (ASBMR) reported a long-term retention of BPs in bone, suggesting that medication holidays may not directly affect skeletal health.[52] The ASBMR on Atypical Subtrochanteric and Diaphyseal Femoral Fractures recommended a median BP treatment period of 7 years and a medication holiday for patients who have not experienced any recent fractures and have femoral neck T-scores above −2.5. However, BP holidays at 4–5 years may not be effective in the prevention of atypical subtrochanteric fractures in the lower-risk group.[53] Similar recommendations have been expressed by the Endocrine Society,[54] which suggested a 'bisphosphonate holiday' for women at low-to-moderate risk of fractures after 3–5 years. Moreover, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) reported further details about medication holidays.[55] In particular, a temporary BP interruption should be considered if the fracture risk is no longer higher after 5 years of oral therapy (such as a T-score above −2.5 or in the absence of fractures); conversely, treatment should continue up to an additional 5 years if the fracture risk remains high. These guidelines suggest that the ending of BP holidays should be based on specific circumstances, such as an increased risk of fractures, a decrease in BMD beyond the least significant change detected by dual-energy X-ray absorptiometry, or an increase in bone turnover markers. However, drug interruption is not recommended for other antiresorptive drugs. According to the AACE/ACE guidelines, patients at very high risk for fracture include those with a (i) recent fracture (within the past 12 months) or multiple fractures, (ii) incident fracture while on osteoporosis therapy or drugs causing skeletal harm (e.g., long-term glucocorticoids), (iii) very low T-score (less than −3.0), (iv) high risk of falls or history of injurious falls, and (v) very high fracture probability by Fracture Risk Assessment Tool (FRAX) (e.g., major osteoporosis fracture >30%, hip fracture >4.5%).

Limitations and strengths

Some limitations of our review must be acknowledged. First, we considered the use of antiosteoporotic medications in terms of adherence, persistence, or continuity of treatment, which might limit the generalizability and interpretability of our results. Some studies may not have the same control group, and we have overcome this limitation by subgrouping the patients who showed nonadherence, nonpersistence, or discontinuation to antiosteoporotic therapy. Second, we have some concerns as to whether the findings of the selected studies could be combined into one conclusion, since all aforementioned topics result in heterogeneous study populations, antiosteoporotic treatment, and fracture site at baseline. Moreover, the certainty of the evidence for the assessed outcomes was judged as 'very low' or 'moderate' due to very serious inconsistency and serious imprecision of the estimates.

Despite these limitations, this study presented points of strength. The exhaustive search strategy allowed us to identify an overview of studies considering the effects of antiosteoporotic continuation or discontinuation among patients with fragility fractures. Then, the internal validity of the included studies was assessed using the NOS for observational studies and the RoB tool for RCTs.

Conclusion

Long-term pharmacological treatment appears to be required for preventing and managing fragility

fractures. Potential strategies to reduce the risk of adverse drug events include medication holidays although our systematic review identified moderate-quality evidence.

The available evidence was used by experts for formulating judgments and recommendations on medication holidays from antiresorptive drugs, unless patients had a history of ONJ and/or risk of AFF during the treatment period.

Declaration

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
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This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Transparency declaration
The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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