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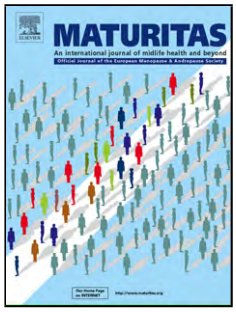

Title: Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement

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Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement

Abbreviated title: Bisphosphonate and denosumab drug holidays

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Highlights

- Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) are very rare adverse events in bisphosphonate users: 1-90 and 113 cases per 100,000 person-years, respectively; they are also rare events in denosumab users (5 cases ONJ and 1case AFF per 1,542 patients, respectively, after eight years of treatment).
- Extending bisphosphonate treatment beyond 3-5 years does not confer additional benefit in low-risk populations.
- Patients should be re-evaluated 1-3 years after bisphosphonate discontinuation. The decision to resume treatment depends on the presence of new fractures, risk factors and possibly bone mineral density.
- The evidence regarding denosumab discontinuation is limited but caution is advised, as there may be a "rebound effect" with regard to fractures.

Abstract

Background: Bisphosphonates and denosumab are used extensively in the treatment of postmenopausal osteoporosis. Despite their proven efficacy in the reduction of vertebral and non-vertebral fractures, their optimal duration of use has not been determined. The occurrence of adverse effects, such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF), has raised the issue of bisphosphonate or denosumab discontinuation ("drug holiday") after a certain treatment period.

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Aim: To assess the effect of bisphosphonate and denosumab discontinuation on fracture risk, as well as its possible benefits in reducing the risk of adverse effects.

Methods: Systematic review and consensus of expert opinion.

Results and conclusions: Discontinuation of bisphosphonates should be considered in all patients who have beentreated for more than five years with alendronate, risedronate or zoledronic acid. In view of the limited evidence, no robust recommendations can be made for ibandronate and denosumab. If the patient has not experienced fractures before or during therapy and the fracture risk is low, a "drug holiday" canbe recommended. Although there is no solid evidence, 1–2 years for risedronate, 3–5 years for alendronate and 3–6 years for zoledronic acid are suggested. After this time, the patient should be reassessed. If a new fracture is experienced, or fracture risk has increased or BMD remains low (femoral neck T-score $\leq$ -2.5), anti-osteoporotic treatment should be resumed. In the case of denosumab discontinuation, close monitoring is suggested, due to the possibility of rebound fractures.

Keywords: Bisphosphonates, alendronate, risedronate, zoledronic acid, denosumab, drug holiday.

1. Introduction

Bisphosphonates are structural analogues of inorganic pyrophosphate, wherethe oxygen atom has been substituted by a carbon atom. Differences in the R2 side-chain bound to the carbon atom and the nitrogen group determinetheir variations in duration of action, bone affinity and anti-fracture efficacy [1, 2]. Bisphosphonates inhibit enzymes involvedin osteoclasticactivity, and thus suppress bone resorption [1, 2]. The

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main bisphosphonates are alendronate, risedronate, ibandronate and zoledronic acid, which constitute the first-line therapeutic agents in both postmenopausal and male osteoporosis, as they have well-documented anti-fracture efficacy [1, 2]. Although the different bisphosphonates have not been directly compared, they all reduce the risk of vertebral fractures (38-65% compared with placebo), with the greatest effect seen with zoledronic acid. Excluding ibandronate, bisphosphonates are also effective in reducing the risk of non-vertebral and hip fractures, by 22-31% and 50-55%, respectively, compared with placebo [3].

Denosumab, a human monoclonal antibody, an inhibitor of the receptor-activator of nuclear factor kappaB ligand (RANKL), is also a very effective anti-resorptive compound. Its use has been associated with a significant reduction in the risk of vertebral, non-vertebral and hip fractures (by 68%, 20% and 40%, respectively) [4].

Despite their role in reducing fracture risk, bisphosphonateshavebeen associated with adverse outcomes. The most common include gastrointestinal adverse effects (esophageal ulcer and esophagitis, which have been associated with oral compounds), acute phase reaction (mostly seen after the first infusion of i.v. bisphosphonates) and atrial fibrillation (rarely reported with i.v. bisphosphonates) [2]. Moreover, increased concern has emerged due to major adverse effects, such asosteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF), the occurrence of which seems to be associated with long-term bisphosphonate use. ONJ is defined as exposed bone in the oral cavity that does not heal within eight weeks of diagnosis, with a history of prior treatment with an anti-resorptive agent (bisphosphonates or denosumab), without a history of craniofacial radiation [5]. ONJ is mostly seen in patients with a history of

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cancer undergoing treatment with high doses of i.v. bisphosphonates (incidence 1-15%), whereas it is very rarely seen in populations treated for osteoporosis (incidence 0.001-0.04%) [5]. The risk of ONJ increases with the duration of exposure to bisphosphonates; the risk for non-cancer patients increases substantially after five years of use [6]. AFF are defined as atraumatic or low-trauma fractures located in the subtrochanteric or diaphyseal femoral region. They are usually non-comminuted and have a transverse or short oblique configuration [7]. In general, bisphosphonate use is associated with a two-fold increase in the risk of AFF. This risk increases further when bisphosphonate use exceeds five years [8, 9]. Nevertheless, it must be emphasized that the absolute risk of AFF in patients treated with bisphosphonates is very low (from 3.2 to 50 cases per 100,000 person-years, reaching 113 per 100,000 person-years aftermore than eight years of use) [10]. ONJ and, even more rarely, AFF have also been associated with the use of denosumab [5, 11].

Taking into account the long skeletal retention time of bisphosphonates and the concern about denosumab, a “drug holiday” has been proposed as a means of reducing the risk of both ONJ and AFF. Although other factors may contribute to the occurrence of ONJ and AFF (such as poor oral health, invasive dental surgery, glucocorticoid use, diabetes and anemia for ONJ, and lower limb and hip geometry for AFF) the duration of bisphosphonate and, very probably, denosumab use with consequent long-term suppression of bone turnover seem to play a significant role [7]. A population-based case-control study showed that the risk of AFF significantlydecreases after bisphosphonate withdrawal, irrespective of the total duration of prescription [12]. The effect of bisphosphonate or denosumab discontinuation on the risk of ONJ is currently unknown.

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This position statement presents a systematic analysis of the data onthe effect of bisphosphonate and denosumab discontinuation on fracture risk, as well as its possible benefits inreducing the risk of adverse effects such as AFF and ONJ. It also provides recommendations on "drug holidays", specifically (i) the types of patient most appropriate for a drug holiday, (ii) the optimal length of a drug holiday and (iii) the timing of possible re-initiation of treatment.

2. Methods

2.1. Trial selection

The present review included randomized controlled trials (RCTs) which investigated the effect of bisphosphonate or denosumab discontinuation (for each drug separately) on bone mineral density (BMD), bone turnover markers (BTM) and clinical or morphometric vertebral and/or non-vertebral fractures (where available) in postmenopausal women or men aged over 50 years diagnosed with osteoporosis. Studies were excluded if: (i) they were non-randomized, (ii) the bisphosphonate discontinuation period was less than one year, (iii) they had no control group, (iv) they were not conducted in humans, (v) another anti-osteoporosis medication was started after discontinuationof the bisphosphonate, (vi) they were conducted in oncology patients or in those with other metabolic bone disease, such as Paget's disease of bone, or in patients in receipt of glucocorticoid treatment.

2.2. Search strategy

The MEDLINE, Scopus, EMBASE and Cochrane databases were searched for RCTs evaluating the effect of bisphosphonate or denosumab discontinuation on BMD, bone

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turnover and fractures. The search was carried out up to January 31, 2017. A basic search strategy was developed for MEDLINE and modified accordingly for the other search engines. The search items were: ("alendronate" OR "risedronate" OR "zoledronic acid" OR "zoledronate" OR "denosumab") AND ["discontinuation" OR "duration" OR "holiday" OR "stop" OR "withdrawal"]. The final set of abstracts was uploaded at the web version of the EndNote software (www.myendnoteweb.com), after removing duplicates. Selection of abstracts, extraction of information from full-text articles andevaluation of risk of bias with the Newcastle-Ottawa Scale (NOS) were done independently by three researchers (PA, SAP and GM). Discrepancies were resolved bydiscussion and if needed with the help of an additional researcher (DGG).

2.3. Data extraction

Three independent researchers reviewed all eligible studies. The following data were extracted and recorded: (i) first author, (ii) year of publication, (iii) country in which the study was conducted, (iv) study duration, (v) duration of "drug holiday", (vi) dose of bisphosphonate or denosumab and (vii) for each group (intervention and comparator) thenumber of participants, their age, the effect of bisphosphonate or denosumab discontinuation ("drug holiday") and continuation on lumbar and femoral BMD, bone turnover, and vertebral and non-vertebral fractures.

2.4. Reporting guidelines

This systematic review followed the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines [13].

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3. Data analysis

3.1. Data presentation

3.1.1. Alendronate

The initial search provided 834 results, after excluding duplicates, 13 of which were reviewed by title and abstract (Figure 1). Of those, eight articles were excluded due to: non-randomized design of the reported study, no full-text availability, concomitant use of another anti-resorptive drug, patients being on glucocorticoids, the study investigating the same population as another study included in the review and the study investigating an oncology population. Finally, five full-text articles were included in the qualitative analysis [14-18]. A post-hoc analysis [19] of the same population from one of these studies [14] is also discussed.

The hallmark study on an "alendronate holiday" was the Fracture Intervention Trial Long-term Extension (FLEX) study, in which 1099 postmenopausal women treated with alendronate (5 mg/d for two years and then 10 mg/d for another three years) were randomized to continuing treatment with alendronate, 5 mg/d (n=329) or 10 mg/d (n=333) or placebo (n=437) for another five years. The FLEX study showed that discontinuation of alendronate resulted in a significant decline in lumbar (-3.74%), total hip (-2.36%) and neck (-1.94%) BMD compared with treatmentextension. Serum levels of C-terminal telopeptide of type 1 collagen (CTX), a marker of bone resorption, as well as of N-propeptide of type 1 collagen (P1NP) and bone-specific alkaline phosphatase, both markers of bone formation, increased by 55.6%, 59.5% and 28.1%, respectively, in the placebo group compared with the alendronate groups (no significant difference between alendronate groups was observed regarding these parameters) [14]. Alendronate continuation for up to ten years led to a 55% decrease in the risk of clinical vertebral fractures [5.3% with placebo versus 2.4% with

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alendronate; relative risk (RR) 0.45, 95% confidence interval (CI) 0.24-0.85], but there was no significant difference in the incidence of morphometric vertebral fractures (11.3% with placebo versus 9.8% with alendronate; RR 0.86, 95% CI 0.60-1.22). No difference was observed in clinical or morphometric non-vertebral fractures. Of note, those who discontinued therapy did not return to their pretreatment BMD and BTM values [14].

A post-hoc analysis of the FLEX data showed that there was an interaction between femoral neck T-score at baseline and alendronate efficacy. In particular, those with T-scores of ≤ -2.5 at the femoral neck demonstrated a significant reduction in non-vertebral fractures with alendronate continuation compared with placebo (RR 0.50, 95% CI 0.26-0.96). No benefit was observed in patients with higher T-scores. No interaction was shown across femoral neck T-scores regarding alendronate efficacy on the risk of vertebral fractures. Neither was an interaction detected with respect to lumbar spine T-scores and alendronate efficacy**.** Older age was independently associated with a greater risk of fracture (relative hazard ratio 1.54 [95% CI, 1.26-1.85] per 5-year increase) [19].

In another study [15], alendronate discontinuation for five years (after 20 mg/d for two and 5 mg/d for three years, followed by five years of placebo, n=83) was compared with ten years of continuous treatment at a dose of either 10 mg/d (n=86) or 5 mg/d (n=78). Compared with baseline, ten-year treatment with alendronate, for the last five years at doses of 10mg/d or 5mg/d, led to 13.7% and 9.3% gains in lumbar BMD, respectively. The discontinuation group maintained a 9.3% increase in lumbar BMD compared with baseline. The respective increases in femoral neck BMD were

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5.4%, 2.8% and 1.5%. BTM levels remained lower than their premenopausal values in the alendronate group (10 mg/d), but increased in the discontinuation group, although remaining below the baseline values. There were no differences in the incidence of morphometric vertebral fractures between the three groups, a finding that is in line with the results of the FLEX study [15].

In a study of early postmenopausal women with normal bone mass, two years of treatment with alendronate 20 mg/d and discontinuation for three years thereafter was equally protective against postmenopausal bone loss as continuous treatment with alendronate 5mg/d for five years, in spine, femoral and total body BMD. BTM tended to reverse, but their concentrations remained 40-60% lower than their pre-treatment values [16]. No fracture data were available.

A Danish study of postmenopausal women (n=108) [17] (lumbar spine BMD from -2 to +2 SD of the premenopausal normal value) randomly allocated participants to alendronate (2.5-20 mg/d) for two, four or six years, followed by no treatment for seven, five or three years, respectively. The residual effects (that is, the total gain in BMD after the end of "drug holiday") on spine BMD after nine years were 3.8%, 5.9% and 8.6% compared with placebo. However, the rate of bone loss was comparable**.** CTX and osteocalcin concentrations tended to return to pretreatment values, but were still reduced sevenyears post-withdrawal.

In another prospective study in early postmenopausal women [18], continuous alendronate treatment (5 mg/d) for six years (n=90) was compared with four (n=86) and two years (n=94) of treatment followed by placebo for two or four years,

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respectively. These three groups were also compared with a group who received only placebo for six years (n=132). Both alendronate discontinuation groups had greater lumbar and total hip BMD values at six years than the placebo group (+2.9% for the two-year and +5.1% for the four-year treatment groupin lumbar BMD), although lower BMD than the group receiving continuous alendronate treatment for six years. Bone resorption remained suppressed, despite discontinuation for two and four years (-50.6% and -44%, respectively) compared with pre-treatment values. The respective change in the group receiving continuous alendronate therapy was -68%.

No cases of ONJ or AFF were reported in any of the aforementioned alendronate extension trials.

Regarding male osteoporosis, no study was found that fulfilled the inclusion criteria of this systematic review.

3.1.2. Zoledronic acid

The initial search provided 1,165 results, after excluding duplicates, three of which were reviewed by title and abstract (Figure 1). Of those, one article was excluded due to the non-randomized design of the reported study. The remaining two full-text articles were included in the qualitative analysis [20, 21].

In the extension of the HORIZON-Pivotal Fracture Trial (PFT), treatment with zoledronic acid (5 mg annually) for a total of up to six years (after completion of three annual infusions) in 616 postmenopausal women was compared with no further treatment for three years (after completion of three annual infusions) (n=617). Extension treatment reduced the risk of new morphometric vertebral fractures by 49%

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[3.0% in the group undergoing six years of continuous treatment compared with 6.2% in the discontinuation group (OR 0.51, 95% CI 0.26-0.95)]. No significant difference between the two groups was observed with respect to clinical fractures or morphometric non-vertebral fractures. The total gain in femoral neck BMD compared with pre-treatment values was greater in the extension than in the discontinuation group (4.5% and 3.1%, respectively, $p < 0.01$). The corresponding gains in lumbar spine BMD were 12.1% and 10.1%, respectively, without significant differences between groups. BTM slightly increased but remained below pretreatment values in the discontinuation group. Of note, no cases of AFF were reported in either treatment group, andonly one case of ONJ was recorded in the extension group [20]. A post-hoc analysis of the PFT trial, following the same rationale as the FLEX study, showed that patients with a femoral neck or hip T-score >-2.5, no incident fracture and no more than one risk factor may be considered for zoledronic acid withdrawal after three yearly infusions and for up to three years, since the risk of subsequent fracture is low [22].

The other study compared nine years of zoledronic acid treatment with six years of treatment and found no benefit for the former in terms of fracture risk, BMD and BTM. In contrast, a small increase in serious and non-serious cardiac arrhythmias was observed in the former group. It must be emphasized that no cases of ONJ or AFF were confirmed in either treatment group [21]. This study suggested that no further benefit is expected beyond six years of treatment with zoledronate.

Regarding male osteoporosis, no study was found that fulfilled the inclusion criteria of this systematic review.

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3.1.3. Risedronate

The initial search provided 387 results, after excluding duplicates, two of which were reviewed by title and abstract (Figure 1). Of those, one article was excluded because it reported a study with a non-randomized design. One full-text article was included in the qualitative analysis [23].

In the Vertebral Efficacy with Risedronate Therapy Multi-National (VERT-MN) trial, 398 patients who discontinued treatment for one year after completing three years of risedronate 5 mg/d were compared with 361 patients who received placebo. The risedronate group showed a 46% decreased risk ofmorphometric vertebral fractures compared with the placebo group (RR 0.54, 95% CI 0.34-0.86). There was no increase in non-vertebral fracture risk in the risedronate group. Femoral neck and lumbar BMD values in the risedronate group remained higher than in the placebo group (2.32% and 2.6%, respectively). BTM increased to pre-treatment values, with no difference from the placebo group [23].

In an extension of the VERT-MN trial, treatment with risedronate 5mg/d for seven years (risedronate group, n=31) was compared with placebo for five years and then treatment with risedronate5 mg/d for two years (placebo group, n=30). Both groups discontinued risedronate for one year. After one year off treatment, lumbar spine and femoral neck BMD was maintained or slightly increased in both groups, whereas total hip and great trochanter BMD decreased. Bone resorption increased to a similar extent in both groups, reaching the levels of the placebo group at five years (before risedronate). The study indicated that the cumulative effect of risedronate is small,

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perhaps due to its low affinity to bone. No vertebral fractures were reported. There were no reports of ONJ or AFF [24].

Regarding male osteoporosis, no study was found that fulfilled the inclusion criteria of this systematic review.

3.1.4. Ibandronate

The initial search provided 192 results, after excluding duplicates (Figure 1). No study fulfilled the inclusion criteria of this systematic review.

3.1.5. Denosumab

The initial search provided 450 results; after excluding duplicates, one was reviewed by title and abstract (Figure 1). However, this article was excluded, due its retrospective design.

4. Clinical question 1: Do patients need "drug holidays"?

The idea of a "bisphosphonate holiday" was introduced some time ago and gained considerable popularity overthe years. The rationale of the "holiday" lies in two different concepts: first, after a given period of time, no additional benefit is found following bisphosphonate therapy; and second, prolonged bisphosphonate use may be associated with an increased incidence of adverse events.

Regarding efficacy, additional benefit was seen only in clinical vertebral fractures when extending alendronate to an additional five years after completing five years of continuous treatment (in comparison with five years of "drug holiday"), without any

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benefit on morphometric and non-vertebral fractures [14]. Similarly, extending zoledronate to a further three years after three annual infusions (in comparison with three years of "drug holiday") reduced the risk of morphometric vertebral fracture, but not of clinical vertebral fracture or either type of non-vertebral fracture [20]. However, extending the use of alendronate and zoledronate seems to be beneficial only in patients still athigh fracture risk, particularly in those with a hip T-score < -2.5 and in elderly patients [19, 22]. Extension of zoledronate treatment to nine years provides no further benefit [21].

The major concerns associated with bisphosphonate and denosumab use are ONJ and AFF. ONJ was initially described in advanced cancer patients receiving high doses of intravenous bisphosphonates [25]. Soon it was considered a major concern in any patient receiving bisphosphonates by any route. However, evidence from RCTs of a possible association of ONJ with bisphosphonate use is scarce. Indeed, no increased risk was demonstrated in the aforementioned RCTs regarding alendronate, zoledronate and risedronate. It has been calculated that the incidence of ONJ in patients receiving oral bisphosphonates ranges from 1:10,000 to 1:250,000 [26].

An association has also been suggested between long-term bisphosphonate use and AFF [12]. Bisphosphonates significantly suppress bone remodeling, which is an essential process of the skeleton to repair microdamage. A very recent study investigated the differences in microdamage in trabecular bone among 1) patients with osteoporosis treated with bisphosphonates, 2) untreated patients with osteoporotic fractures (fracture controls) and 3) healthy individuals without fractures (non-fracture controls). By using synchrotron X-ray micro-CT and image

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segmentation technology, femoral head bone samples were tested for the density and volume of perforations (i.e. regions of complete breakage in the bone trabeculae, attributed to osteoclastic activity) and microcracks (i.e. microscopic fractures, 30-100 μm in length). Despite the small sample size (n=16), bisphosphonate-treated patients demonstrated the highest density and volume of microcracks, despite the fact that the density and volume of perforations was comparable to those in healthy individuals. Although the duration of bisphosphonate use was not controlled for, this study suggests that the accumulation of microcracks attributed to bisphosphonate use reduces bone strength and thus may predispose to fractures [27].

Importantly, it has been proposed that ongoing bisphosphonate use is the main risk factor for AFF. It seems to be higher with alendronate than with risedronate [RR 1.9 (95% CI 1.1 - 3.3)] and about three times higher in women than in men[RR 3.1 (95% CI 1.1 - 8.4)] [28]. The risk rapidly decreases, though, after drug discontinuation (70% per year after the last use of bisphosphonate), regardless of the long-term presence of the drug in the bone [12]. A study reviewing data from the US FDA (Food and Drug Administration) Adverse Event Reporting System (FAERS) from 1996 to 2011 reported a proportional reporting ratio (PRR) of 4.51 (95% CI 3.44 to 5.92) for bisphosphonate use and non-healing femoral fractures [29]. A Swedish study has shown that the relative risk of AFF increases with the duration of bisphosphonate use, reaching 126.0 (95% CI 55.1 - 288.1) after four years of treatment [28]. However, another study showed that long-term bisphosphonate use (i.e. for more than four years) is associated with a lower risk of non-traumatic subtrochanteric femoral fractures [30]. Because of the rarity of AFF, it has been calculated that for every 10,000 patients at high risk, 108 hip fractures (from 300 expected) and 750 fractures

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at other sites are prevented with bisphosphonate treatment, whereas only three subtrochanteric fractures are additionally expected [31].

The safety and efficacy of denosumab treatment extension to eight years have beentested in postmenopausal women. Only five cases of ONJ and one of AFF were reported in the group completing eight years of continuous treatment (n=1,542). BMD continued to increase at all sites and fracture risk remained low [11].

Musculoskeletal pain has also been described as a possible adverse effect of bisphosphonate therapy. However, it can develop at any point intreatment, and so prolonged bisphosphonate use is notparticularly associated with an increased risk [32].

Atrial fibrillation (AF) is another possible side-effect of bisphosphonate use, mainly suggested by the HORIZON PFT [33]. Other studies, including large observational trials, have producedconflicting results [34-36]. In any case, association does not confirm causality, and even if such an association does exist it seems to be independent of the dose and duration of therapy.

Esophageal or gastric cancer is another major concern about oral bisphosphonate use. However, according to a recent systematic review, no evidence of increased risk of esophageal or gastric cancer was found in men and women receiving bisphosphonate treatment, though evidence from the original studies is conflicting [37]. In an open-label, prospective, uncontrolled study, risedronate use was associated with significantly decreased ferritin concentration, which in turn was associated with a

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higher cardiovascular risk [38]. However, sufficient evidence to establish a causal link between risedronate and high cardiovascular risk is lacking. Anyhow, it is important to note that additional safety issues werenot raised in the clinical trialsofextensionbisphosphonate therapy, thus reinforcing the safety of bisphosphonate treatment [39, 40].

5. Clinical question 2: Who is a candidate for treatment discontinuation?

The second important question to be answered concernsthe patient population for whom a "drug holiday" is appropriate after long-term treatment with bisphosphonates. The answer to this question should be individualized, considering the long-term efficacy of bisphosphonates, their safety and the fracture risk of the individual patient. Discontinuation of bisphosphonate therapy should be considered for all patients who have been treated for more than five years with alendronate and risedronate or for more than three years with zoledronate. No recommendations can be made for ibandronate [41]. If the patient has not experienced any fractures before or during therapy and the fracture risk is low, as indicated by afemoral neck T-score $\geq$ -2.5, age < 70 years and absence of disease or medication associated with osteoporosis and/or increased fracture risk, a "drug holiday" should be considered [41, 42]. As the FRAX scores of patients in receipt of treatment have not been extensively assessed [43], this tool should not be used in this context.

The appropriate period of discontinuation is unclear. This should be individualized and the physician should take into consideration the BMD measurement at the time of discontinuation, as well as the patient's characteristics, such as age, smoking habits and factors that could increase the risk of falls. As a general rule, two to three years is

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a reasonable discontinuation period. Yearly measurement of BTM might be proposed and resuming treatment could be considered if there is an increase in bone resorption markers (above normal non-menopausal levels) although one-year changes in BTMs were not associated with risk of fracture after discontinuation of alendronate therapy [41]. If any fracture occurs during this period or another factor emerges that could affect BMD status (e.g. disease or medication), the patient should be reassessed sooner [42, 43, 45]. For patients treated with risedronate, a shorter "drug holiday" should be considered, as discontinuation for more than one year may lead to significant loss of protection [23, 24].

Regarding denosumab discontinuation, some concerns have been raised recently. Some cases of clinical vertebral fractures after its discontinuation have been reported, suggesting a possible rebound effect [46]. A recent observational study (n=82) showed that BMD decreases by 6.7% in the lumbar spine and by 6.6% in thehip, one year after denosumab discontinuation (after having completed eight years of treatment with respective gains of 16.8% and 6.2%, from baseline). Eight patients (9.8%) sustained a fracture (7.3% vertebral, 1.2% in the femoral neck and 1.2% in the radius) during the one-year observation period [47]. However, a post-hoc analysis of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study (the hallmark RCT showing fracture efficacy of denosumab in postmenopausal women) [4] did not find a difference in fracture risk between the placebo (n=470) and denosumab (n=327) groups during the off-treatment period. It must be noted that the follow-up period was relatively short (median 0.8 years) and 42% of patients in the placebo group and 28% in the denosumab group had initiated other anti-osteoporotic medication after the last dose of the investigational product

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[48]. The exact pathogenetic mechanisms involved in this rebound phenomenon are unknown. The clinical risk profile and the management of these patients need to be determined. Hypercalcemia has also been reported after denosumab discontinuation [49].

6. Clinical question 3: Who is a candidate for treatment re-initiation?

Reassessment after bisphosphonate or denosumab discontinuation should include clinical evaluation to check for the presence of new fractures and risk factors for fractures [42, 45]. BMD measurement by DEXA can be considered at this point. Analysis of the FLEX study data has shown that this is not important for patients who have obtained a significant BMD gain. For example, for a patient with a T-score around -2, DEXA could even be postponed for almost five years, as it is unlikely to change management [50]. Again, the decision should be individualized, taking into consideration each patient's specific characteristics. Measurement of BTM, especially resorption markers, such as serum CTX, has been also proposed [2]. If any new fracture is present or BMD has decreased (femur neck T-score $\leq$ -2.5), anti-osteoporotic treatment could be resumed [42-45]. An increase in bone resorption markers within the reference range of young adults could prompt treatment resumption [2].

If re-initiation of treatment has been decided, the choices include bisphosphonates, denosumab [51-53] (the latter inducing greater BMD gains and BTM suppression than the former) [51, 52], teriparatide [53], selective estrogen receptor modulators (SERMs) [53], strontium ranelate [54], or menopausal hormone therapy (MHT) [55]. The risk of venous thrombosis should be taken into account when SERMS or oral

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MHT are considered. Furthermore cardiovascular risk has to be assessed with strontium ranelate use [56]. To date, no trial has investigated the anti-fracture efficacy of re-initiation treatment with bisphosphonates following a "drug holiday". Furthermore, no bisphosphonate trial has lasted beyond ten years, and switching to other therapies after three to five years of bisphosphonate treatment has not been examined. Therefore, re-initiation of therapy should be individualized, taking into consideration the patient's profile, the duration of bisphosphonate treatment, and the efficacy and safety characteristics of other anti-osteoporotic agents [1-2, 51-55]. For any patient with osteoporosis, it is important to design a long-term therapy plan, as this disease is a lifelong condition. In accordance with the Committee of Scientific Advisors of the International Osteoporosis Foundation, a sensible order to follow would be replacement of the bisphosphonate by a more potent drug of the same class, then by an injected anti-resorptive agent and then by an anabolic drug [57]. Treatment with teriparatide should be followed by an anti-resorptive agent, so that the therapeutic effect is sustained [53, 57].

7. Conclusions

After systematically reviewing the existing data regarding the effect of bisphosphonate discontinuation on fracture risk, as well as its possible benefits on reducing the risk of adverse effects, we make the following suggestions regarding bisphosphonate drug holidays:

7.1. *Optimal patient population*

Individualized decision making should take into consideration the long-term efficacy of bisphosphonates, their safety and the fracture risk of the specific patient. In the

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absence of fractures before or during therapy and for patients with a low fracture risk, as indicated by a femur neck T-score ≥ -2.5, age < 70 years and absence of diseases or treatments associated with osteoporosis and/or increased fracture risk, a "drug holiday" should be considered.

7.2. Optimal length of drug holiday

Similarly, individualized decision making should be encouraged with regard to the optimal length of the drug holiday period. Patients' characteristics, including age and history of falls, should be taken into consideration. Patient preferences should be respected and shared decision making should alwaysbe sought. In general, two to three yearsis a reasonable drug holiday, though a shorter period (one year) should be considered in patients taking risedronate. BMD reassessment is strongly suggested, andmeasurement of BTM may also be helpful. Any patient who experiences a new fracture should be immediately reassessedand therapy re-initiation should be considered.

7.3. *Re-initiation of treatment*

Bisphosphonates, as well as other anti-osteoporotic treatments, including denosumab, teriparatide, SERMs, MHT and strontium ranelate, could be considered after a "drug holiday". An individualized long-term treatment plan should be constructed for any patient eligible for anti-osteoporotic treatment and it should be reviewed at regular intervals or after a major osteoporotic event (fracture, sudden decrease in BMD).

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Contributors

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8. Summary recommendations

- Decisions should be individualized, taking into consideration the long-term efficacy of bisphosphonates and denosumab, their safety, and the fracture risk of the specific patient.
- Discontinuation of bisphosphonatesshould be considered in all patients who have beentreated for more than five years with alendronate or more than three years with risedronate or zoledronic acid.
- In view of the limited evidence, no robust recommendations can be made for ibandronate and denosumab.
- Patients should be re-evaluated 1-3 years after bisphosphonate discontinuation. The decision to resume treatment depends on the presence of new fractures, risk factors and possibly bone mineral density.
- Caution is advised regarding denosumab discontinuation, as there may be a "rebound effect" with regard to fractures.

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- Bisphosphonates as well as other anti-osteoporotic treatments, including denosumab, teriparatide, SERMs, MHT and strontium ranelate could be considered after a “drug holiday”.

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Figure legend

Figure 1 Flowchart showing the selection strategy of the studies included in the systematic review [13].