“Taking a break” from bisphosphonates: Is it appropriate?

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Learning Objectives
By the end of this presentation, the participant should be able to:
1. Compare and contrast the clinical markers used to measure fracture risk
2. Identify unique pharmacokinetic characteristics of bisphosphonates
3. Identify adverse effects of prolonged bisphosphonate use
4. Evaluate the evidence available regarding discontinuation of bisphosphonates in order to make reasonable recommendations in clinical practice
BACKGROUND INFORMATION

I. Epidemiology
   a. 10 million Americans have osteoporosis
   b. 33.6 million have low bone density of the hip
   c. 1 out of 2 Caucasian women and 1 out of 5 Caucasian men will experience an osteoporosis-related fracture
   d. Majority of fractures occur in low bone mass rather than osteoporosis
   e. More than 4 million women take bisphosphonates

II. Pathophysiology of Osteoporosis
   Figure 1: Bone Remodeling
   a. Bone remodeling is a process that maintains a healthy skeleton by replacing older bone with new bone
   b. The balance of bone remodeling can be altered to increase the rate of bone removal by menopause and advanced aging
   c. Rapid bone remodeling increases bone fragility, lowers bone mass, and increases fracture risk by deteriorating bone tissue and disrupting bone architecture

   Figure 2: Normal vs. Osteoporotic Bone Architecture

   From: Dempster, DW et al., with permission of the American Society for Bone and Mineral Research.

III. Complications of Osteoporosis: Fractures
   a. Types of fractures:
      i. Non-vertebral: fracture of the hip, wrist, forearm, leg, ankle, foot, and other sites
      ii. Clinical: patient presents with signs and symptoms of fracture (sudden back pain)
      iii. Morphometric: fracture identified by change in shape of a bone
b. Most common: vertebrae (spine), proximal femur (hip), and distal forearm (wrist)
c. Fractures may be followed by full recovery or chronic pain, disability, and death
d. Hip fractures increase mortality 10-20% within 1 year and cause a 2.5 fold increase in future fracture risk

MEASURING THE RISK OF FRACTURES

I. Bone Mineral Density (BMD)\(^1\)
   a. Dual-energy x-ray absorptiometry (DEXA) measurement of the hip and spine is used to diagnose osteoporosis, predict future fracture risk, and monitor patients on therapy
   b. BMD can be expressed in its raw form of grams of mineral per square centimeter scanned (g/cm\(^2\))
   c. Fracture risk increases exponentially as the BMD decreases
   d. Issues with BMD Measurements
      i. BMD measurement varies depending on the brand of DEXA used and site of scan
      ii. A change <3-6% in the hip and <2-4% at the lumbar spine may be due to precision error of testing
   e. DEXA results can be standardized to reflect a relationship between two norms, expressed in standard deviations above or below the mean

   \[\text{Figure 3: T-score and Z-score}\]

   i. Z-score: compares BMD to someone of the same age and sex
   ii. T-score: compares BMD to the “young normal” of the same sex

II. WHO definition of osteoporosis based on BMD measurements of the spine, hip, or forearm
   a. Definitions:
      i. Normal: T-score ≥ -1
      ii. Low Bone Mass or “Osteopenia:” -2.5 ≤ T-score ≤ -1
      iii. Osteoporosis: T-score ≤ -2.5
      iv. Severe or “Established” Osteoporosis: History of ≥1 fracture AND T-score ≤ -2.5
   b. Can only be applied to post-menopausal women and men ≥50 years
   c. Other populations are recommended to use Z-scores (≤-2 defined as low BMD for age and >-2 defined as expected BMD for age)\(^3\)

III. BMD for Monitoring Response to Therapy
   a. Peripheral skeletal sites are NOT appropriate for monitoring response to therapy because they don’t respond in the same magnitude as the hip and spine to medications
   b. Can check 12-24 months after initiating or changing therapy, but should compare BMD, not T-score or Z-score\(^1,4\)
IV. Bone Turnover Markers (BTM)¹
   a. BTMs are substances released in the circulation during bone formation or resorption
   b. Types of BTM:
      i. Bone resorption markers: Serum C-telopeptide (CTX), Urinary N-telopeptide (NTX)
      ii. Bone formation markers: Serum bone-specific alkaline phosphatase (BSAP), Osteocalcin (OC)
   c. Can be measured to assess the risk of fracture in untreated patients and predict bone loss
   d. Reduction in bone turnover decreases fracture risk, independently from BMD effects by reducing the
      depth and size of new resorption sites⁵
   e. High degree of biological and analytical variability
      1. Changes must be large to be clinically meaningful
      2. Biological variability is reduced by standardizing sample drawings to a certain time of the day and
         season of the year
V. BTM for Monitoring Response to Therapy
   a. Suppression of bone resorption markers is detected after 3-6 months of antiresorptive therapy
   b. Usually checked 3-6 months after treatment to predict fracture risk reduction¹
   c. Increase in bone formation markers is detected after 1-3 months of anabolic therapies¹
VI. Problems with using clinical markers to measure fracture risk⁶
   a. BMD and BTM effects are not the only factors decreasing fracture risk – changes in BMD explain less
      than 20% and changes in BTM explain 50% of the observed fracture risk reduction associated with
      antiresorptive treatment
   b. The relationship between BTM/BMD and fracture risk is non-linear
VII. FRAX® tool¹
   a. 10-year fracture risk model created by WHO that predicts:
      i. 10-year probability of hip fracture (cannot use spine BMD for algorithm)
      ii. 10-year probability of major osteoporotic fracture
   b. Not validated in patients on current/previous therapy
   c. Identifies a set of risk factors independent of BMD that can increase risk of fractures:
      • Current age
      • Secondary osteoporosis
      • Low BMI
      • Femoral neck BMD
      • Gender
      • Current tobacco use
      • Rheumatoid arthritis
      • FH of hip fracture
      • Prior osteoporotic fracture
      • Alcohol intake (≥3 drinks per day)
      • Oral glucocorticoids (≥5mg/day (prednisone) for ≥3 months

GENERAL MANAGEMENT OF OSTEOPOROSIS
I. Supplementation¹
   a. Calcium 1200mg per day
   b. Vitamin D 800-1000 international units per day
      i. Desired 25-HOD level = 30ng/ml
      ii. Helps with calcium absorption, bone health, muscle performance, and balance
      iii. Can reduce hip fracture by 23%⁷
   c. Calcium and Vitamin D can decrease bone marker levels by 10-30%⁴
II. Pharmacological treatment
   a. Pharmacological treatment is started in patients who:
      i. Sustained a hip or vertebral fracture
      ii. T-score ≤ -2.5 at the femoral neck or spine
      iii. Post-menopausal women or men > 50 years old with low bone mass at the femoral neck or
          spine AND
         1. 10-year hip fracture probability ≥3% OR
         2. 10-year major osteoporosis related fracture probability ≥ 20% based on the US-adapted
            FRAX tool
b. Current FDA approved treatments\(^1\): bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid), calcitonin, estrogen/hormone therapy, teriparatide, raloxifene, denosumab

**BISPHOSPHONATES**

I. Mechanism of action\(^2\): tightly adheres to bone surfaces and inhibits the enzyme farnesyl pyrophosphate synthase which is required for formation of cytoskeleton in osteoclasts, thereby inhibiting bone resorption\(^2\,\,^4\)

![Figure 4: Bisphosphonate Mechanism of Action](http://www.nejm.org/na102/home/ACS/publisher/mms/journals/content/nejm/2002/nejm_2002.346.issue-9/nejm200202283460902/production/images/small/nejm200202283460902_f1.gif)

II. Pharmacokinetics\(^5\):
   a. Binds strongly to hydroxyapatite and remains inactive until the bone containing bisphosphonates are reabsorbed
   b. The bisphosphonate then recirculates locally and systemically and binds again to bone surfaces
   c. Half-life after incorporation into mineralized bone = 10 years\(^4\)
   d. Binding affinity: zoledronate > alendronate > ibandronate > risedronate\(^6\)
      i. Higher affinity – binds more avidly but spreads through bone more slowly
      ii. Lower affinity – distributed more widely but has shorter residence time in bone if treatment is stopped

III. Long-term adverse effects of bisphosphonates\(^8\)
   a. Current incidence of serious side effects is < 1 in 1000; risks beyond 10 years are unknown\(^2\)
   b. Esophageal cancer
      i. Seen in patients using bisphosphonates for >3 years (mean 5 years), but current evidence hasn’t proven a causal relationship\(^4\)
   c. Atrial fibrillation:
      i. Seen in patients using zoledronic acid, but current evidence hasn’t proven a causal relationship
   d. Osteonecrosis of the jaw
      i. Usually seen in cancer patients on high doses of IV bisphosphonates
         1. Doses (IV/PO) given for treatment or prevention of osteoporosis has a low risk of 0.1% and remains small for at least up to 5 years
         2. Usually follows invasive dental procedures
         3. Can be asymptomatic for weeks-months before discovery
         4. Very difficult to treat, requiring multiple surgeries and courses of antibiotics\(^10\)
         5. Causal relationship not established but is likely
e. Atypical femur fractures

Figure 5: Osteoporotic (left) vs. Atypical Fracture (right)

http://www.internalmedicine-news.com/2010/05/content_images/imn/archive_image/vol43iss6/70307_fx2.jpg

i. Long-term oversuppression (1.3-17 years, median 7 years suppression) may cause accumulation of microdamage in bone, causing increased skeletal fragility (controversial)

ii. Associated with prodromal pain in the region of the fracture, frequently bilateral

iii. Radiograph scans show transverse fractures on the lateral side of the femur – not typically seen in osteoporosis, but seen in hypophosphatasia

iv. Current evidence has not proven a causal relationship

IV. The Controversy

a. Why wouldn’t you consider a bisphosphonate drug holiday?
   i. Bisphosphonates have proven to reduce the risk of osteoporotic fracture
   ii. The efficacy of the residual bisphosphonate effect on decreasing the risk of osteoporotic fracture is questionable

b. Why would you consider a bisphosphonate drug holiday?
   i. Bisphosphonates can accumulate in the body because of the drug’s long elimination half-lives
   ii. Overaccumulation of the drug may increase risk of adverse effects due to oversuppression of bone turnover
   iii. Theoretically, a drug holiday may be a viable option to decrease risks of bisphosphonate accumulation with the possibility of continued protection from fractures
## Effects of continuing or stopping alendronate after 5 years of treatment

### The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

### OBJECTIVE
To compare the effects of discontinuing alendronate treatment after 5 years vs. continuing for 10 years

### METHODS

#### Subjects:

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Post-menopausal women</td>
<td>• FLEX baseline total hip BMD &lt;0.515 g/cm² (T-score &lt; -3.5)</td>
</tr>
<tr>
<td>• Age 55-81 years old</td>
<td>• Total hip BMD at FLEX baseline ≤ FIT baseline</td>
</tr>
<tr>
<td>• Low femoral neck BMD &lt;0.68g/cm² (T-score &lt; -1.6) at FIT baseline</td>
<td>• Currently receiving and planning to continue medications that may affect bone metabolism</td>
</tr>
<tr>
<td>• Assigned to receive alendronate during FIT and completed at least 3 years of blinded treatment during the trial and participated in the subsequent open-label period</td>
<td>• Impaired renal function (SCr &gt;2mg/dL)</td>
</tr>
</tbody>
</table>

**Study design:** Randomized, double-blind, multicenter

**Treatment:**
- At FLEX baseline, subjects were randomly allocated via permuted block design, stratified by study center and stratum, to one of the following for 5 years:
  - Alendronate 10mg/day (30%)
  - Alendronate 5mg/day (30%)
  - Placebo (40%)
- All patients were given Calcium 500mg and Vitamin D 250 units to be taken daily

**Follow-up:**
- Telephone contact every 3 months to encourage adherence, identify adverse events, and update concurrent medication use
- Adherence assessed by self-report and pill count
- Discontinuation from the study was required if any total hip BMD measurement was > 5% below the FIT baseline value

**Primary endpoint:**
- Total hip BMD (measured via DEXA annually)

**Secondary endpoints:**
- Lumbar spine, total body, and forearm BMD (measured at 36 and 60 month visits)
- BTM in patients who had a complete set of samples from FIT and FLEX studies (measured at 36 and 60 month visits; analysis for all specimens occurred at one time):
  - CTX, N-propeptide of type 1 collagen (marker of bone formation), and BSAP
- Morphometric vertebral, nonvertebral, forearm, clinical spine, and hip fracture incidence (exploratory objective)
  - Identified by self-report and confirmed by radiology or surgical reports

### STATISTICAL ANALYSIS

**Analyses:** BMD – modified intention to treat, BTM – per protocol (highly adherent patients)

**Statistical tests:** Kaplan-Meier estimator, log-rank test, proportional hazards model, logistic regression model, Mantel-Haenszel $x^2$ statistic, $x^2$, Fisher exact tests

**Power analysis:**
- 90% power to detect a difference of 0.9% in total hip BMD between the pooled alendronate vs. placebo groups
- 80% power to detect a risk reduction for fracture of 13.5-33%

### RESULTS

**Baseline demographics:**
- 1099 women, previously on alendronate, were enrolled in FLEX (met power)
- No significant differences between treatment groups
- Average age = 73 years
- Average total hip BMD = 0.73 g/cm² (T score, -1.9)
- Average femoral neck BMD = 0.61 g/cm² (T score, -2.2)
- Average lumbar spine BMD = 0.9 g/cm² (T score, -1.3)

**Primary Endpoint:** Total hip BMD (Fig 2)

- Total hip BMD decline in alendronate group was significantly lower than placebo group (-1.02 vs. -3.38%, respectively; mean difference = 2.36%, CI 1.81-2.90%)

**Secondary endpoints**

**BMD in other sites**

- Lumbar spine was the only BMD measurement that showed an increase in BMD for the duration of FLEX for both placebo and alendronate users, but was significantly greater for the alendronate group (1.52% for placebo vs. 5.26% for alendronate; mean difference of 3.74%, CI = 3.03-4.45%)
- In all other sites, BMD decline was significantly slower in patients on alendronate vs. placebo

**BTM**

- Alendronate users had relatively stable BTM measurements vs. placebo
- BTM levels increased gradually in the placebo group, but remained below FIT baseline levels

**Fractures**

- Fracture incidence was similar in FIT and FLEX studies
- No significant differences observed between treatment groups for all clinical or nonvertebral fractures [19% with placebo vs. 18.9% with alendronate (RR=1, 95% CI 0.76-1.32)]
- Upon stratification between types of fractures:
  - Statistically significant lower risk of clinical vertebral fractures among those randomized to alendronate vs. placebo [2.4% vs. 5.3%, respectively (RR = 0.45, 95% CI 0.24-0.85)]
    - Number of patients needed to resume treatment over 5 years to prevent 1 clinical vertebral fracture = 34
  - Small decrease in morphometric vertebral fractures was NOT significant [11.3% with placebo vs. 9.8% with alendronate (RR = 0.86, 95% CI, 0.60-1.22)]
Adverse effects
- No significant differences between the groups
- No cases of osteonecrosis of the jaw reported

AUTHOR’S CONCLUSION
“These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.”

CRITIQUE
Strengths
- Randomized, double-blinded, multi-center
- Monitored and encouraged adherence
- Several sensitivity analyses done for BMD results
- Standardized DEXA measurement technique
- Fracture risk reduction was powered

Weaknesses
- Stored serum specimens for BTM to be analyzed all at once
- “Many” patients entered the FIT trial without osteoporosis
- No comparison to 10 yrs of placebo

IMPLICATIONS
The BMD decline seen in this study was considered clinically insignificant (<5% change from baseline) and BTM levels remained below baseline levels suggesting residual effects of bisphosphonate therapy. However, a significant increase in risk of clinical vertebral fracture was seen and total hip BMD declined to FIT baseline by year 10 in the discontinuation group. Because of this, the proper length of drug holiday considered after 5 years of alendronate therapy may be less than 5 years in patients who are not at high risk of fractures. The results of this study also suggest that osteonecrosis of the jaw is rare with 10 years of alendronate therapy.

POST-HOC ANALYSIS
Continuation of alendronate reduced non-vertebral fracture risk in women with baseline FLEX femoral neck T-scores < -2.5 without prevalent vertebral fracture (RR = 0.5, 95% CI 0.26-0.96)

Ten years’ experience with alendronate for osteoporosis in postmenopausal women

OBJECTIVE
To investigate the effects of prolonged alendronate therapy as well as its discontinuation through the final 3-year extension, including 5 years of observation after the discontinuation of alendronate and the cumulative 10-year experience with alendronate

METHODS
Subjects:

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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</thead>
<tbody>
<tr>
<td>Age 45-82 years</td>
<td>History of metabolic disease or medication use known to alter skeletal or mineral metabolism</td>
</tr>
<tr>
<td>Post-menopausal for at least 5 years</td>
<td>History of osteoporotic fracture of the proximal femur</td>
</tr>
<tr>
<td>Diagnosis of osteoporosis based on lumbar spine BMD &lt; 0.80 g/cm²</td>
<td>History of any illness known to confound results or cause harm to study subjects</td>
</tr>
<tr>
<td>Assigned to alendronate in the phase 3 studies</td>
<td>Impaired renal function (SCr &gt; 1.5 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Illicit drug use, Tobacco use &gt; 1ppd, &gt; 6 cups coffee intake per day, &gt; 2 alcoholic beverages/day</td>
</tr>
</tbody>
</table>
**Study design:** Extension of two identical multicenter, international, double-blind, randomized, placebo-controlled alendronate phase 3 studies (designed to permit pooling of results)

**Treatment:**

<table>
<thead>
<tr>
<th>YEAR</th>
<th>DISCONTINUATION (DC) GROUP</th>
<th>ALENDRONATE 5MG GROUP</th>
<th>ALENDRONATE 10MG GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>20mg x 2 years, then 5mg for 1 year</td>
<td>Alendronate 5mg</td>
<td>Alendronate 10mg</td>
</tr>
<tr>
<td>4-5</td>
<td>Alendronate 5mg</td>
<td>Alendronate 5mg</td>
<td>Alendronate 10mg</td>
</tr>
<tr>
<td>6-7</td>
<td>Placebo</td>
<td>Alendronate 5mg</td>
<td>Alendronate 10mg</td>
</tr>
<tr>
<td>8-10</td>
<td>Placebo</td>
<td>Alendronate 5mg</td>
<td>Alendronate 10mg</td>
</tr>
</tbody>
</table>

- The original 20mg group had a similar cumulative alendronate exposure to 5 years of treatment in the 10mg group and 10 years of treatment in the 5mg groups
- All patients received Calcium 500mg daily
- Vitamin D supplements were permitted but NOT required

**Primary endpoint:** percent change in BMD at the lumbar spine (measured yearly by DEXA)

**Secondary endpoints:**
- Change in BMD at the femoral neck, trochanter, total hip, total body, and forearm
- BTM (measured annually with specimens analyzed as they were received during years 8-10; archived specimens were analyzed for other years at one time):
  - NTX and BSAP
- Fracture incidence
  - Morphometrically detected vertebral fractures, clinical fractures, and stature were collected as safety end points
  - Symptomatic non-vertebral fractures were considered adverse clinical events - fractures related to trauma were NOT excluded

**STATISTICAL ANALYSIS**

Analyses: BMD – modified intention to treat, BTM – per protocol (compliant patients)

Statistical tests:
- Analysis of variance: examined treatment effects within groups based on BTM
- 95% CI compared proportions of women with clinical and laboratory adverse events
- No formal comparisons with fracture incidence due to limited sample size

**RESULTS**

Baseline characteristics
- 247 patients participated in all 3 extensions of the study
- No significant differences between the groups in the extension at baseline of the original study
- Average age (original study)= 63
- Average BMD at the lumbar spine (original study) = 0.7 g/cm²

Primary endpoint: BMD at the lumbar spine
- No significant change after year 5 in the DC group (0.3%, CI -0.8 to 1.5%)
Secondary endpoints

BMD in other sites
- Significant decreases in total hip (-1.8%, CI -3.5 to -0.1%), femoral neck (-2.2%, CI -3.9 to -0.5%), and forearm (-2.3%, -3.8 to -0.8%) after discontinuation
- Remained significantly above baseline for trochanter, total hip, and total body at year 10

**B**

**D**

**NTX and BSAP increased within a year, but remained below baseline and placebo values**

Fractures
- Non-vertebral fractures
  - Rate of radiologically confirmed non-vertebral fractures in the DC group during years 6-10 was “similar” to the pooled alendronate groups during years 1-3
- Vertebral fractures
  - Proportion of women with new morphometric vertebral fractures: 6.6% in DC group, 13.9% in 5mg group, 5% in 10mg group
  - Stature: height loss was slightly but not significantly greater in the 5mg and discontinuation group than the 10mg group during years 6-10
  - No insufficiency fractures, fracture mal-union, or osteonecrosis of the jaw reported

<table>
<thead>
<tr>
<th>AUTHOR’S CONCLUSION</th>
<th>“The therapeutic effects of alendronate were sustained, and the drug was well tolerated over a 10-year period. The discontinuation of alendronate resulted in the gradual loss of its effects.”</th>
</tr>
</thead>
</table>
| CRITIQUE            | **Strengths**
|                     | • Randomized, multicenter, international
|                     | • Analyzed BTM specimens as they were drawn in years 8-10
|                     | **Weaknesses**
|                     | • Not powered, relatively small study size
|                     | • No formal analysis for fracture incidence |
# The effects of discontinuing long-term alendronate therapy in a clinical practice setting

## OBJECTIVE
To assess the effects of a 12-month discontinuation of alendronate on BTM and BMD in postmenopausal osteoporotic patients on long-term (at least 5 years) alendronate therapy in a bone metabolism unit.

## METHODS

### Subjects:
Post-menopausal women receiving care from a bone metabolism unit from April 2006 to June 2007 were divided into 3 groups:

<table>
<thead>
<tr>
<th>GROUP</th>
<th>PRE-STUDY TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continuous alendronate 10mg daily for at least 5 years</td>
</tr>
<tr>
<td>2</td>
<td>Continuous alendronate 10mg daily therapy for 1-4 years</td>
</tr>
<tr>
<td>3</td>
<td>Recently diagnosed and untreated osteoporotic patients (control group)</td>
</tr>
</tbody>
</table>

- Average age in all groups = 71 years old

### Study design:
Single center, follow-up study in Brazil

### Treatment:

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Discontinued alendronate treatment at baseline</td>
</tr>
<tr>
<td>2</td>
<td>Continued alendronate treatment</td>
</tr>
<tr>
<td>3</td>
<td>Untreated</td>
</tr>
</tbody>
</table>

- All patients received calcium 1000mg/day
- All patients received cholecalciferol 1000 IU/day

### Primary endpoint:
BMD of lumbar spine and proximal femur in Group 1 and Group 2 at baseline and at the end of follow-up

### Secondary endpoints:
- BTM: fasting blood samples (analyzed immediately or stored until analysis) were collected at baseline and every three months for 1 year for Group 1 and Group 2
  - CTX and Procollagen type 1 N-terminal propeptide (P1NP, marker of bone formation)
  - ONLY baseline CTX and P1NP were collected from Group 3 patients to provide reference values for untreated osteoporotic patients of similar age
- 25-HOD at baseline and after 12 months in Group 1
  - Used to check variations in vitamin D that may interfere with the results
- Parathyroid hormone (PTH) and ionized calcium measured at baseline and 12 months in Group 1 and 2

## STATISTICAL ANALYSIS

- Analysis: intention to treat (group 1 and 2)
- Statistical tests: Paired t tests, chi-square test, ANOVA, Spearman rank correlation
- BMD loss of ≥2.8% in the lumbar spine and ≥4.2% in the femur were considered clinically significant

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**IMPLICATIONS**

The 10mg/day group seems to have lower risk of fractures compared to 5mg/day group. Due to an unusual dosing regimen for the DC group, the results may not be generalized to standard dosing. However, the DC group may be at higher risk of non-vertebral fractures based on its reported incidence. Alendronate treatment over 10 years appears safe due to lack of reported adverse effects due to oversuppression of bone. Surrogate markers remained above baseline for the DC group, but femoral neck BMD had a steep decline which might have dropped below or near baseline if the group was on a standard dose. The data from this study cannot support that the residual effects of bisphosphonate therapy is sufficient to prevent fractures, suggesting patients on 10mg/day should continue therapy for at least 10 years.
RESULTS

Baseline characteristics:
- 88 patients agreed to participate in the study
- Baseline BMD level in Group 1 was statistically greater than Group 2
  - Group 1– spine: 0.868 ± 0.142 and femoral neck: 0.724 ± 0.099
  - Group 2 – spine: 0.79 ± 0.192 and femoral neck: 0.67 ± 0.112
- No other statistically significant differences seen between Group 1 and Group 2 at baseline

Primary endpoint: Lumbar spine and proximal femur BMD
- No statistically significant difference between mean BMD baseline levels compared to BMD levels after 1 year in either group
- 45.7% of Group 1 patients clinically lost BMD in the lumbar spine, femoral neck, or both vs. 5.2% in Group 2

Table 2: BMD at baseline and after 1 year of discontinuation of alendronate in G1, and during follow-up in G2

<table>
<thead>
<tr>
<th>Group</th>
<th>BMD (g/cm²)</th>
<th>Baseline</th>
<th>1 Year</th>
<th>P</th>
<th>Lost BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>spine</td>
<td>femoral neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1 (n = 35)</td>
<td></td>
<td>0.868 ± 0.142*</td>
<td>0.856 ± 0.134*</td>
<td>0.85</td>
<td>14 (40%)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>femoral neck</td>
<td>0.724 ± 0.099*</td>
<td>0.730 ± 0.101*</td>
<td>0.86</td>
</tr>
<tr>
<td>G2 (n = 19)</td>
<td></td>
<td>0.790 ± 0.192</td>
<td>0.798 ± 0.211</td>
<td>0.89</td>
<td>1 (5.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>femoral neck</td>
<td>0.670 ± 0.112</td>
<td>0.656 ± 0.102</td>
<td>0.66</td>
</tr>
</tbody>
</table>

* P < 0.01 vs. G2. ** P < 0.001 vs. G2.
Lost BMD: patients with clinically significant BMD loss (at least 2.5% in spine or 4.2% in hip, or both).

Secondary endpoints:

BTM
- Group 1 had a statistically significant increase of CTX and P1NP compared to baseline at 3 months
  - After 3 months, no additional statistically significant increases in CTX were seen
- Comparison to Group 3
  - Group 1 CTX levels remained significantly below Group 3 levels after 1 year of follow-up
  - Group 1 P1NP levels were equivalent to Group 3 after 9 months of follow-up
  - Group 2 patients maintained baseline BTM levels

Fractures
- No fractures independent of trauma were reported in Group 1 or Group 2

Relationship of BMD to other factors
- No significant correlations were found between BMD losses and BTM, PTH, 25-HOD, and ionized calcium levels
- No statistically significant differences were seen between patients with or without clinically significant BMD loss and baseline or follow-up BMD/BTM levels

AUTHOR’S CONCLUSION

“Observed BMD loss and BTM rise after alendronate withdrawal imply that bone turnover was not oversuppressed, and alendronate discontinuation may not be safe.”

CRITIQUE

Strengths
- Evaluated correlations of 25-HOD, ionized calcium, and PTH levels with BMD losses
- Included patients in a “real life” environment
- Evaluated significance of BMD differences at baseline with or without BMD loss

Weaknesses
- Baseline BMD levels for Group 1 was significantly greater than Group 2
- Not powered (small number of patients)
- Subjects volunteered to participate
- Measured only baseline BTM levels for Group 3
- No baseline or follow-up BMD measurements for Group 3
- Relatively short follow-up (1 year)
- Did not measure fracture risk
- Single center

IMPLICATIONS

The percentage of patients who clinically lost BMD may have been over reported because the strict definition of clinically significant BMD loss. No adverse effects were reported with 6 years of continuous therapy. No fractures were reported after 5 years of alendronate 10mg/day therapy. Therefore, 1 year drug holiday may be considered for patients who are not at high risk for fractures.
Asias

Fracture risk remains reduced one year after discontinuation of risedronate

OBJECTIVE

To assess the resolution of effects of risedronate therapy in postmenopausal women with osteoporosis who completed a 3-year, double-blind treatment period in which they received risedronate 5 mg daily or placebo and were then followed for an additional year without risedronate therapy

METHODS

Subjects:

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Women at least 5 years post-menopausal enrolled in the original study</td>
<td>• Conditions that might interfere with evaluation of spinal bone loss</td>
</tr>
<tr>
<td>• Age &lt; 85 years</td>
<td>• Received drugs known to affect bone metabolism, including calcitriol or cholecalciferol within 1 month prior to study entry</td>
</tr>
<tr>
<td>• Either ≥2 vertebral fractures or 1 vertebral fracture and low lumbar spine BMD (T-score ≤ -2)</td>
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</tbody>
</table>

Study design: Follow-up extension of a randomized, double-blind, placebo-controlled study

Treatment:

<table>
<thead>
<tr>
<th>YEAR</th>
<th>RISEDRONATE 2.5MG</th>
<th>RISEDRONATE 5MG</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>STOPPED early – protocol amendment</td>
<td>Risedronate 5mg daily</td>
<td>Placebo daily</td>
</tr>
<tr>
<td>4</td>
<td>---</td>
<td>STOPPED</td>
<td>STOPPED</td>
</tr>
</tbody>
</table>

• All women were supplied with Calcium 1000mg daily throughout the study and extension
• Vitamin D was supplied if baseline serum 25-HOD levels were low

Primary endpoint: mean percent change in lumbar spine BMD, from the original study’s baseline to month 36 and month 48 for each treatment group separately

Secondary endpoint:

• Femoral neck BMD: mean percent change from baseline
• BTM: mean percent change from baseline (all stored samples from original study and extension were analyzed at one time)
  o BSAP and NTX
• Fractures
  o Incidence of new vertebral fracture during the extension, determined by lateral spine radiographs
• Adverse events
  o Reported at study center visits every 3 months during year 1-3 and at 6 and 12 months during year 4
  o Non-vertebral fractures were considered an adverse event regardless of location or cause

STATISTICAL ANALYSIS

• Analysis: intention to treat
• Statistical tests: paired T-tests, analysis of variance model, Wilcoxon Signed Rank tests, Wilcoxon Rank Sum tests, analysis of variance model
• New vertebral fracture was compared between groups using Cochran-Mantel-Haenszel (CMH) test, and stratified by the number of vertebral fractures at month 36
  o 3 stratified groups: 0 vertebral fractures, 1 vertebral fracture, and ≥ 2 vertebral fractures

RESULTS

Baseline characteristics

• 599 patients completed the follow-up period
• No significant differences in baseline characteristics at the start of original study
• At the start of the extension, the risedronate group had higher BMD and lower BTM than placebo group (expected), but all other baseline characteristics were similar between the groups
• Average age at the beginning of the extension study = 71 years

Primary endpoint: Lumbar spine BMD

• BMD in the former risedronate group remained significantly higher than the placebo group at the end of the extension (2.6% difference, p<0.001, 95% CI = 1.56-3.65%)
• BMD in the former risedronate group decreased but remained significantly higher than the group’s
baseline in the original study (-0.83%, p < 0.001, 95% CI = -1.3 to -0.35%))

- BMD in the former placebo group had no significant change in BMD during the extension year compared to baseline

**Secondary endpoints**

**BMD in other sites**

- Femoral neck and trochanter BMD both decreased significantly (-1.23 and -1.57%, respectively; p<0.001) after discontinuation of risedronate but remained significantly higher than placebo and baseline at the end of year 4
  - Femoral neck BMD at the end of year 4 was only ~0.5% higher than baseline BMD levels

**Fractures**

- Seen in 11.6% of former placebo patients and in 6.5% of former risedronate patients
- Relative risk of vertebral fractures in the former risedronate group was reduced by 46% compared with placebo group (RR = 0.54, 95% CI=0.34-0.86, p=0.009)
Adverse events
- No significant difference between the two groups
- Non-vertebral fractures
  - 5% incidence in the previous placebo group
  - 4.8% incidence in the previous risedronate group

AUTHOR’S CONCLUSION
"Despite the apparent resolution of effect on BMD and BTM, the risk reduction of new vertebral fractures remained in the year after stopping treatment with the former risedronate group."

CRITIQUE
Strengths
- Maintained double-blind during the extension
- All patients had a history of a vertebral fracture
- Compared results to a placebo-controlled group
Weaknesses
- Did not have an active treatment comparison group
- Voluntary for subjects to continue participation into the extension study
- Non-vertebral fractures were considered adverse events and did not undergo statistical analysis
- No surrogate marker measurement between year 3 and 4

IMPLICATIONS
Before considering discontinuation of risedronate, more studies are required to evaluate the safety of a drug holiday due to its weaker affinity to bone compared to alendronate. Residual effects of risedronate were seen after discontinuation of therapy, shown by decreased new vertebral fracture risk and increased lumbar spine BMD compared to placebo (both groups were on calcium and vitamin D). However, BMD levels decreased significantly at the femoral neck and trochanter. BAP levels increased to pre-treatment levels, equivalent to the placebo group, but fracture risk was maintained, questioning the correlation between BTM levels and fracture risk. Unfortunately, this study only compared a drug holiday to patients who had never been treated, so it is difficult to evaluate the benefits of continuing vs. discontinuing risedronate therapy.
<table>
<thead>
<tr>
<th>STUDY, DESIGN, TREATMENT GROUPS</th>
<th>SUBJECTS</th>
<th>BMD RESULTS</th>
<th>BTM RESULTS</th>
<th>FRACTURE RISK &amp; ADR RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtis et al 2007&lt;sup&gt;7&lt;/sup&gt;</td>
<td>• INCLUDED women ages 60-78 yrs with pharmacy and medical benefits</td>
<td>• N/A</td>
<td>• N/A</td>
<td>• Fracture incidence rates in MPR &gt; 80% x 2 years remained ≥ MPR &lt;50% x 3 years*</td>
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<td></td>
<td>• EXCLUDED those with a claim for hip fracture, malignancy, HIV, Paget’s disease</td>
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<td>• No statistically significant difference in MPR &gt;80% x 3 years vs. MPR&gt;80% x 2 yrs in hip fracture incidence rate (6.34/1000 person-years vs. 6.12 per 1000, respectively)</td>
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<td></td>
<td>• N = 9063</td>
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<td>• Association between time since discontinuation and risk of hip fracture seen (risk attenuated with ↑ duration of treatment and greater compliance)</td>
</tr>
<tr>
<td>Mellstrom et al 2007&lt;sup&gt;7&lt;/sup&gt;</td>
<td>• INCLUDED women ≥ 5 years post-menopausal and ≥2 vertebral fractures at baseline</td>
<td>• Lumbar spine BMD (primary outcome): 11.5% ↑* from year 1 in RSD group – the increase from year 5-7 was not statistically significant (1.8%) 6.1% ↑ from year 1 in placebo/RSD – increase from year 5-7 was statistically significant (4.3%) Total hip BMD increased significantly in both groups at year 7 compared to year 1 and year 6 Proximal femur BMD – no significant changes during year 6 &amp; 7 in RSD group</td>
<td>• NTX</td>
<td>• New fractures: 6.2% in placebo/RSD group and 6% in RSD group</td>
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<td>• EXCLUDED age &gt; 85 yrs Average age (at original study) = 69</td>
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<td>• Incidence of new vertebral fractures in 6-7 yr was similar to year 0-3 in RSD group and decreased in placebo/RSD group compared to year 0-3 and 4-5</td>
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<td></td>
<td>• N=164</td>
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<td>• Incidence in vertebral fractures not statistically significant for RSD group in year 4-5 compared to 6-7</td>
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<td>• Incidence in non-vertebral fractures not statistically significant between RSD group and placebo/RSD group (6 vs. 7.4%)</td>
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<tr>
<td>Meijer et al 2008&lt;sup&gt;8,7&lt;/sup&gt;</td>
<td>• INCLUDED post-menopausal women diagnosed with osteoporosis and ≥1 osteoporotic fracture at baseline Difference seen between groups in HRT (54% vs. 44.7%)* and calcitonin use (44.7 vs. 27.9%)* Majority age &gt;75 years at baseline</td>
<td>• N/A</td>
<td>• N/A</td>
<td>• Length of compliant bisphosphonate therapy and % fracture risk reduction compared to &lt;1 year compliant bisphosphonate use: 1-2 years – 12%, 3-4 years – 46%* 5-6 years DID NOT have a decreased risk of fractures compared to &lt;1 year compliant bisphosphonate use (OR 1.12, 95 CI 0.66-1.88)</td>
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<td>• N = 387 cases, 3950 controls</td>
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<td>Greenspan et al 2002&lt;sup&gt;9,7&lt;/sup&gt;</td>
<td>• INCLUDED women with a history of hysterectomy and lumbar spine BMD T score &lt; -2</td>
<td>• No significant change in BMD at year 3 compared to year 2 for all sites in ALD/placebo group and ALD+HRT/placebo group</td>
<td>• NTX: ↑* in HRT/placebo group, HRT+ALD/placebo group, and ALD/placebo group during the extension (↑ by 72.3%, CI 48.2 – 100.3%) – not significant between groups ↓* in the ALD/placebo group compared to placebo x 3 yrs group (-38.6%, CI -47.8 to -27.7%)</td>
<td>• N/A</td>
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<td>• EXCLUDED patients with low serum 25-HOD level</td>
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<td>• N = 244</td>
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<td>• Average age: 63</td>
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<td></td>
<td>• N/A</td>
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<td><strong>Wasnich et al 2004</strong>&lt;sup&gt;15&lt;/sup&gt;</td>
<td>• Design: 6 year randomized, blinded, multinational, placebo-controlled</td>
<td>• INCLUDED ≥ 6 months post-menopausal women age 45-59 years</td>
<td>• After 6 years, hip BMD in the ALD x 4 years group remained &gt; baseline at the end of year 6 but the ALD x 2 years group was &lt; baseline at the end of year 6</td>
<td>• NTX remained below baseline at year 6 in ALD x 2 and 4 years group</td>
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<td></td>
<td>• EXCLUDED prior nontraumatic vertebral or hip fracture</td>
<td>• Differences in spine BMD vs. placebo: 2.9%* for ALD x 2 years and 5.1%* for ALD x 4 year</td>
<td>• Only statistically significant difference vs. placebo in NTX seen in ALD x 4 years group (-12.7%)*</td>
<td>• N/A</td>
</tr>
<tr>
<td></td>
<td>• Treatment groups: o ALD</td>
<td>• &lt;10% had lumbar spine BMD &lt; 0.8g/cm²</td>
<td>• NTX levels in ALD &lt; HRT and placebo groups</td>
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<td></td>
<td>1/3 discontinued after year 2 and 1/3 after year 4</td>
<td>• N = 1609</td>
<td>• NTX in placebo x 4 years slightly decreased</td>
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<td></td>
<td>o Placebo</td>
<td>• Average age: 53</td>
<td>• Fracture incidence: 8% in placebo, 8% in ALD x 4 years, 9% in ALD x 2 years, 5% in HRT (non-significant)</td>
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<td></td>
<td>o Encouraged “adequate” dietary Ca intake</td>
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<td><strong>Ravn et al 1999</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>• Design: RCT, 4 year results of Wasnich et al study</td>
<td>• INCLUDED ≥6 months post-menopausal women ages 45-59 years with BMD of spine &gt;0.8g/cm² in 90% of participants</td>
<td>• Rate of bone loss in ALD x 2 years group in year 3-4 were similar to those who had placebo in yrs 1-2</td>
<td>• 131 fractures, not considered to be drug related and no dose-response trend seen</td>
</tr>
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<td></td>
<td>• Treatment: o ALD 5mg vs. placebo vs. open label HRT</td>
<td>• HRT group had more recent menopause</td>
<td>• At year 4, ↑ in BMD at all skeletal sites in ALD x 2 years was &lt; ALD x 4 years BUT was &gt; placebo x 4 years</td>
<td>• Fracture incidence: 8% in placebo, 8% in ALD x 4 years, 9% in ALD x 2 years, 5% in HRT (non-significant)</td>
</tr>
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<td>o All ALD groups treated x 2 years then either continued or replaced with placebo x 2 years</td>
<td>• Average age = 55</td>
<td>• NTX at the end of year 4 in ALD x 2 years &lt; placebo*</td>
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<td></td>
<td>• Replaced Ca via diet or supplements in those with deficiency</td>
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<td>• NTX in placebo x 4 years slightly decreased</td>
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<tr>
<td><strong>Michalska et al 2005</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>• Design: randomized, double-blind, single-center 2-year extension</td>
<td>• INCLUDED age 50-80 years treated with ALD 10mg/day for at least 3 years and a diagnosis of osteoporosis (lumbar spine or proximal femur T score &lt; -2.5)</td>
<td>• Lumbar spine BMD ↓ only in the discontinuation group at the end of the study (12 months)* and remained decreased at year 2</td>
<td>• Number of patients with non-vertebral fractures over the 2 years: 2 in discontinuation, 1 in ALD, 1 in raloxifene</td>
</tr>
<tr>
<td></td>
<td>• Treatment: raloxifene vs. discontinuation vs. alendronate</td>
<td>• EXCLUDED patients with other bone disorders, thromboembolic disorders, severe chronic disease, on drugs that affect bone turnover</td>
<td>• ALD and raloxifene groups had unchanged lumbar spine BMD compared to baseline</td>
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<tr>
<td></td>
<td>• Ca 500mg/day and VitD 800 IU/day</td>
<td>• N = 99</td>
<td>• ALD and raloxifene groups had superior lumbar spine BMD compared to discontinuation through year 2*</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Average age = 65</td>
<td>• Changes in total femur and femoral neck BMD were not significantly different between the 3 groups</td>
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<td></td>
<td></td>
<td>• Average years on ALD: 3.5</td>
<td>• PINP, CTX, and OC were unchanged in ALD group</td>
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<tr>
<td></td>
<td></td>
<td>• Did NOT exclude patients with previous non-vertebral fracture</td>
<td>• PINP and CTX increased in discontinuation and raloxifene groups*</td>
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<td></td>
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<td></td>
<td>• Discontinuation group had mean CTX ↑ above pre-menopausal mean*</td>
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<td>• Discontinuation group &gt; alendronate group in CTX and OC*</td>
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<td></td>
<td></td>
<td></td>
<td>• Compared to pretreatment values, all BTM in all treatment groups remained significantly suppressed</td>
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</table>

*Statistically significant
CONCLUSIONS

I. General Recommendations
   a. All patients started on bisphosphonate therapy should meet National Osteoporosis Foundation guideline recommendations for initiation of therapy
   b. All patients should be on the recommended doses of calcium and vitamin D supplement to help decrease risk of osteoporotic fracture

II. The current data concerning the appropriateness of a drug holiday is inadequate due to the small number of studies evaluating fracture risk, and the lack of standardization of these studies (i.e. patient population, bisphosphonate dose and duration of treatment, duration of discontinuation)

III. **Recommendations**: The benefit of continuing bisphosphonate therapy for up to 10 years outweighs the risk of adverse effects due to oversuppression of the bone
   a. The studies described indicate that bisphosphonate therapy for up to 10 years seems relatively safe, and the incidence of severe adverse events (osteonecrosis of the jaw, atypical fractures) was rare
   b. There is evidence that bisphosphonates may have a post-discontinuation effect, but the strength of this residual effect in protecting the risk of fractures is still unknown

IV. Data supporting a bisphosphonate drug holiday is weak; however if a drug holiday must be considered, clinical judgment should determine the appropriateness of this based on the patient’s risk of fracture and expected residual bisphosphonate efficacy post-discontinuation based on compliance, duration of previous therapy, and dose/bisphosphonate used
   a. **Risk of fracture**: Those at high risk (based on fracture history, FRAX Tool®, or BMD) should either remain on bisphosphonates or use non-bisphosphonate therapy during the drug holiday
   b. **Compliance**: Those with MPR<50% may have much less residual bisphosphonate effects compared to more compliant patients
   c. **Duration of therapy prior to drug holiday**: 3-5 years of compliant, standard dose, bisphosphonate therapy
   d. **Dose/bisphosphonate**: Alendronate and risedronate are the only two drugs with published data and should be the only bisphosphonates considered for a drug holiday since different bisphosphonates may have different pharmacokinetic properties
      i. Drugs/doses studied: alendronate 10mg/day, risedronate 5mg/day
      ii. Risedronate may have less of a residual post-discontinuation effect compared to alendronate
      iii. Unpublished data has shown zolendronic acid may be stopped after 3 years, but data is still scarce
   e. **Duration of discontinuation**: Between 1-4 years based on current data regarding fracture risk after discontinuation of a bisphosphonate
   f. **Monitoring**: Patients should be monitored for rapid declines in BMD or BTM
      i. BMD decrease > 3-4% in the spine or 4-5% in the hip
      ii. NTX level increase > 40 nmol
      iii. If a rapid decline is seen, the bisphosphonate or other therapy (if only BMD is affected) can be restarted

V. Future research
   a. Additional well-designed studies evaluating the risk of fracture (not only surrogate markers) after discontinuation are required with similar patient populations, therapy, and duration of discontinuation compared to those who remain on bisphosphonate therapy in order to make more concrete recommendations
   b. Safety of bisphosphonate therapy for more than 10 years of treatment
   c. Changes in surrogate markers and risk factors that correlate with an increased risk of fractures during a drug holiday
   d. Studies evaluating the effect of restarting bisphosphonates after a drug holiday
ABBREVIATIONS

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>DEFINITION</th>
<th>ABBREVIATION</th>
<th>DEFINITION</th>
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<tbody>
<tr>
<td>25-HOD</td>
<td>25-Hydroxyvitamin D</td>
<td>IU</td>
<td>International Units</td>
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<tr>
<td>ALD</td>
<td>Alendronate</td>
<td>HRT</td>
<td>Hormone Replacement Therapy</td>
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<td>BMD</td>
<td>Bone Mineral Density</td>
<td>MPR</td>
<td>Medication Possession Ratio</td>
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<td>BSAP</td>
<td>Serum Bone-Specific Alkaline Phosphotase</td>
<td>NTX</td>
<td>Urinary N-Telopeptide</td>
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<tr>
<td>BTM</td>
<td>Bone Turnover Marker</td>
<td>OC</td>
<td>Osteocalcin</td>
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<tr>
<td>Ca</td>
<td>Calcium</td>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
<td>P1NP</td>
<td>Procollagen Type 1 N-Terminal Propeptide</td>
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<tr>
<td>CTX</td>
<td>Serum C-Telopeptide</td>
<td>PTH</td>
<td>Parathyroid Hormone</td>
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<tr>
<td>DC</td>
<td>Discontinuation</td>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<td>DEXA</td>
<td>Dual-Energy X-Ray Absorptiometry</td>
<td>RR</td>
<td>Relative Risk</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
<td>RSD</td>
<td>Risedronate</td>
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<td>FIT</td>
<td>Fracture Intervention Trial</td>
<td>SCr</td>
<td>Serum Creatinine</td>
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<td>FLEX</td>
<td>Fracture Intervention Trial Long-Term Extension</td>
<td>VitD</td>
<td>Vitamin D</td>
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<tr>
<td>FRAX</td>
<td>Fracture Risk Assessment Tool</td>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

REFERENCES

2. Ott, Susan. What is the optimal duration of bisphosphonate therapy? JAMA 2006; 296: 2927-2938