OSTEOPOROSIS: Does Your Patient Need A Drug Holiday?

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Learning Objectives:
● Describe the risks of long term use of bisphosphonates.
● Identify which patients are appropriate candidates for a shorter duration of treatment or a drug holiday.

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**Drug Holidays for Osteoporosis**

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**Osteoporosis**

Characterized by:

- Low bone mass
- Deterioration of bone tissue
- Disruption of bone architecture
- Compromised bone strength
- And increased risk of fracture

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**Osteoporosis**

Defined by the WHO as:

- BMD at hip or spine ≤2.5 standard deviations below the young normal reference population
- It is a risk factor for fracture just as hypertension is for stroke

Osteoporosis – Mortality Risk

Fractures - the clinical consequence of osteoporosis

Hip Fx – 10-20 % excess mortality
Increased mortality risk continues for 10 yrs after hip Fx


-- Mortality risk after vertebral Fx

Increased mortality risk persists 5-10 yrs in women and 3 yrs in men after clinical vertebral Fx

Increased mortality risk continues for 5 yrs after other types of Fxs

Subsequent Fx increases risk for another 5 yrs


Do Bisphosphonates Decrease Fracture Risk?

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### Evidence of Fracture Reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertebral</th>
<th>Nonvertebral</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Ibandronate</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Teriparatide</td>
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<td>Raloxifene</td>
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<tr>
<td>Calcitonin</td>
<td>Yes</td>
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<td>No</td>
</tr>
</tbody>
</table>

### Treatment of Osteoporosis

Bisphosphonates are the preferred treatment

Proven antifracture efficacy in Osteoporotic patients

### Bisphosphonates

Discovered in 1800s. Used as antiscaling agents in industry due to binding with divalent cations such as Ca, Mg

Binds to hydroxyapatite crystals on bone (especially sites of active bone remodeling)

1960s began use for Tx of metabolic bone diseases (Not yet osteoporosis)

Alendronate approved for osteoporosis in 1995; risedronate in 2000; ibandronate in 2005; zoledronic acid in 2007

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**Action of Bisphosphonates**

Decrease bone resorption by:

- Causing loss of osteoclastic resorptive function
- Causing accelerated osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase

**Action of Bisphosphonates**

Binding affinity to bone (in order of binding affinity)

- Zoledronic acid
- Alendronate
- Ibandronate
- Risedronate

Lower affinity medications stay in bone for shorter time when medication is stopped

**Action of Bisphosphonates**

Cause decrease in bone turnover markers

- Maximum effect in 3-6 months
- Effect is dependent on dose and type of bisphosphonate
- Effect maintained in steady state for 10 years or more with continued treatment
Benefits of Bisphosphonates

Bisphosphonates decrease mortality

Bisphosphonate use for 3 years associated with 28% decrease in mortality in patients with recent fragility fractures

Older men and women using BPs over 5 years had 27% reduction of risk of death compared to those not on BPs


Lyles study in New England Journal, November 2007

Randomized double blind placebo controlled study

1065 pts w yearly zoledronic acid infusions (5 mg)
1062 pts on placebo

Both started their “infusions” 90 days after hip Fx
Mean age 74.5 – all on Ca and Vitamin D
Follow up 1.9 years – end point –new fractures

Any new fracture:
8.6 % in zoledronic acid group
13.9 % in placebo group—35 % risk reduction p=0.001

New clinical vertebral Fx:
1.7 % (zoledronic acid)
3.8 % (placebo) ————p=0.02

101/1054 died in zoledronic acid group (9.6 %)
141/1057 died in placebo group (13.3 %)
28 % reduction in deaths  p= 0.01
Fracture efficacy and safety mainly from controlled phase III trials lasting about 3 years with < 50,000 patients

These include:
FIT trial for alendronate
VERT NA trial for risedronate
HORIZON trial for Zoledronic acid

In patients with osteoporosis:
40-70% decreased risk of new vertebral fracture
77-96% decreased risk of multiple vertebral fractures
40-50% decreased risk of hip fracture


Phase III Studies of Bisphosphonates

All Bisphosphonates decreased vertebral Fx risk
Hip Fxs significantly ↓ for alendronate and zoledronic acid
Non vertebral Fxs significantly ↓ with risedronate and zoledronic acid.
Bisphosphonates

Alendronate 3 year study
FIT I (Fracture Intervention trial)
Relative Fracture Risk Reduction
Vert Fx 47.1%; Non vert Fx 18.9%; Hip Fx 50.8%

NNT to prevent one Fracture
Vert Fx 14; Non vert Fx 36; Hip Fx 90


FIT study (Fracture Intervention Trial)
Vertebral fracture study arm—2027 pts
T-score < −2.1 and at least one vertebral Fx
Risk of vertebral Fx reduced 50 %
Risk of hip or wrist Fxs reduced 30 %
Clinical fracture arm—2232 pts T-score < -1.6 but no vertebral Fxs—
Vertebral Fx risk decreased by 44 % (not hip Fxs)

In those with osteoporosis (T-score < -2.5)
Risk of hip Fxs reduced by 56 %; all Fxs by 36 %

Action of Bisphosphonates

Risedronate – 3 year study (818 pts)
VERT-NA (Vertebral Efficacy with Risedronate Therapy-North America)

Relative Fracture Risk Reduction
Vert Fx 30.7%; Non Vert Fx 38.1%; Hip Fx 19.7%

NNT to Prevent one Fracture
Vert Fx 20; Non Vert Fx 31; Hip Fx 276

**Action of Bisphosphonates**

Zoledronic acid - 3 year study (7736 pts)
HORIZON PFT (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial)

Relative Fracture Risk Reduction
Vert Fx 70%; Non Vert Fx 25.2%; Hip Fx 44.0%

NNT to Prevent One Fracture
Vert Fx 13; Non Vert Fx 37; Hip Fx 91


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**Action of Bisphosphonates**

Ibandronate (BONE) 3 year study

Relative Fracture Risk Reduction
Vert Fx 62%; Non Vert Fx -11% Hip Fx NA

NNT to Prevent One Fracture
Vert Fx 20 Non Vert Fx NA; Hip Fx NA


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**Bisphosphonates work**

But do they continue to work with prolonged use?

Do they continue to work after they have been stopped?
Some of these trials were extended:

- Alendronate for 10 years (Black et al. 2006)
- Risedronate for 7 years (Mellstrom et al. 2004)
- Zoledronic acid for 6 years (Black et al. 2012)

No placebo controlled data after 5 years

No extension studies with ibandronate

Extension of the FIT trial called FLEX (Fracture Intervention Trial Long Term Extension)

Pts on 5 years of alendronate randomized into another 5 years on alendronate or another 5 years on placebo

At conclusion of study:

- 55% reduction in clinical vertebral fractures in long term treatment group: 5.3% vs 2.4% RR 0.45 p = 0.013

- No difference for morphometric (radiologic) vertebral or nonvertebral fxs

Black DM, Schwartz AV, et al, effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long Term Extension (FLEX) JAMA, 2006; 296:2927-2938
At conclusion of study:
Spine BMD increased 3.8% more in treated group

D/C of alendronate assoc with ↑ BTMs (bone turnover markers) but after 5 years STILL below original baseline

Black et al, JAMA 2006;296: 2927-2938

Post hoc analysis of FLEX data noted:
In pts still on alendronate:

Non vertebral fracture risk decreased 50% in pts with original T-scores of -2.5 or lower at femoral neck

Patients who were more severely affected benefitted the most

Schwartz AV, Bauer DC et al, Efficacy of continued alendronate for fractures in women without prevalent vertebral fracture: the FLEX trial, J Bone Miner Res 22 (suppl 1): S16-S17 (Abstract)

Risk of Vertebral Fx and NNT to prevent one clinical vertebral Fx for 5 years in the FLEX study

<table>
<thead>
<tr>
<th>Femoral neck T-score at start of Extension trial</th>
<th>NNT</th>
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<tbody>
<tr>
<td>No previous vertebral Fxs</td>
<td></td>
</tr>
<tr>
<td>≤ -2.5 ........................................</td>
<td>24</td>
</tr>
<tr>
<td>&gt; -2.5 and ≤ -2.0 ................................</td>
<td>63</td>
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<tr>
<td>&gt; -2.0 .........................................</td>
<td>102</td>
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<tr>
<td>WITH previous vertebral fxs</td>
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<tr>
<td>≤ -2.5 ........................................</td>
<td>17</td>
</tr>
<tr>
<td>&gt; -2.5 and ≤ -2.0 ................................</td>
<td>17</td>
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<tr>
<td>&gt; -2.0 .........................................</td>
<td>51</td>
</tr>
</tbody>
</table>

Alendronate continues to work with prolonged use

Patients had fewer clinical vertebral fractures if therapy was continued

Extended Trials of Bisphosphonates

Extension of the VERT Trial was called VERT NA (Vertebral Efficacy with Risedronate Therapy –NA)

1 year follow up of blinded pts taking either daily risedronate (5 mg) or placebo for 3 years and then stopped

In the year after treatment, BMD decreased in previous risedronate users but remained above their previous baseline AND above previous placebo users

VERT-NA

In previous risedronate users:

BTMs (bone turnover markers) increased after 1 year and were now similar to the placebo patients

Risk of new vertebral fractures still reduced 46% compared to placebo patients

Watts NB 2008 Fracture risk remains reduced one year after discontinuation of risedronate Osteoporos Int 19:365-372
Extended Trials of Bisphosphonates

3 year extension of the HORIZON-Pivotal Fracture Trial (PFT):
Patients given additional 3 years of yearly zoledronic acid or placebo

Pts continuing Tx had 52% lower relative risk of morphometric vertebral fxs (compared to placebo group) 14 vs 30; Fx rates: 3.0% vs 6.2% p=0.035

Risk of other fxs (including clinical vertebral fxs) not different
Black DM, Reid IR et al, the effect of 3 vs 6 years of zoledronic treatment of osteoporosis J Bone Miner Res. 2012;27(2):243-254

HORIZON – Pivotal Fracture Trial

In those on BP for 6 years: BMD stable for 6 years
In those on BP for only 3 years – femoral neck
BMD decreased 1.04% but remained above baseline from 6 years earlier

BTMs remained reduced (and stable) in those on BP for 6 years
Increased significantly in those off BP (after 3 yrs)
But still less than baseline from 6 years earlier.
Black DM, Reid IR et al, the effect of 3 vs 6 years of zoledronic treatment of osteoporosis J Bone Miner Res. 2012;27(2):243-254
Fewer morphometric fractures when pts remained on prolonged therapy with zoledronic acid

Effect lasted after discontinuation


Effects Off Bisphosphonates vs On

Extended Drug Trials

Indicate prolonged benefit with alendronate, risedronate, and zoledronic acid

Effect persists even after Bisphosphonates have been stopped
Effect of 1 year (one dose) of Zoledronic acid lasts for at least 3 years. In patients with osteoporosis, treatment with alendronate for 5 years lasts longer than treatment for only 2-3 years.

Stopping risedronate after 3 years results in more rapid loss of BMD and BTMs than 2 years of alendronate or 3 years of zoledronic acid.


Prolonged Action of Bisphosphonates

Binding sites are abundant.

This leads to large reservoir that continues to be released for months to years after treatment is stopped.

Amount of Alendronate released from bone after 10 year treatment is similar to taking 25% of the usual dose (for the next several years).


Is Efficacy Lost after Certain Period of Time?

No Data to prove loss of efficacy at present time.

Alendronate – still effective over at least 10 years. Risedronate – still effective over at least 7 years. Zoledronic acid – still effective over at least 6 years.
### Prolonged use of Bisphosphonates

Unexpected rare side effects noted after prolonged use such as:

- Osteonecrosis of the Jaw
- Atypical Femoral Fractures
- Atrial Fibrillation ??
- Esophageal Cancer ??

### Action of Bisphosphonates

Potential dangerous side effects with prolonged use—

- But demonstrated prolonged effects even after discontinuation
- Thus the concept of a Drug Holiday evolved

Drug Holiday implies that drug may be restarted in the future

### Minor Side effects of Bisphosphonates

- Gastrointestinal Intolerance
  - (not in original clinical trials—but later in clinical use)
  - GI upset
  - Esophageal irritation or erosion
  - Rare upper GI bleeding
    - Noted mostly when taken incorrectly

Need to follow instructions on how to take appropriately
Contraindications to oral bisphosphonates

- Esophageal stricture
- Achalasia
- Esophageal motility problems
- Severe (or poorly controlled reflux)

- GFR < 35 (with alendronate or zoledronic acid)
- <30 (risedronate or ibandronate)

Acute renal failure reported after zoledronic acid given IV

- Nephrotoxic when high doses are given too rapidly
**Side effects of Bisphosphonates**

**Acute phase reactions with mild/moderate influenza like symptoms**

Reported with monthly oral or with IV infusions

Presents as Flu like symptoms

Decreases with repeated treatments or with pretreatment with analgesics


**Hypocalcemia**

Prevents release of calcium from the bone – results in minor transient decrease in calcium

Do not give until pretreatment hypocalcemia is corrected

Risk factors for symptomatic hypocalcemia:

Vitamin D deficiency, hypoparathyroidism, impaired renal function


**Inflammatory eye Disorders**

Rare reports of inflammatory eye problems (scleritis)

Visual loss or ocular pain days after bisphosphonates should prompt ophthalmological referral

Osteonecrosis of the Jaw
Exposed bone (maxillofacial region) without healing in 8 weeks with bisphosphonate exposure and no Hx of previous radiation to the area

95% of cases after invasive dental procedures in oncology patients on high doses of IV bisphosphonates

Incidence in users of ORAL bisphosphonates
Estimated between:
1 in 1000 and 1 in 263,000 patient years

incidence between 1 and 10% with IV BP use (Pamidronate or Zoledronic acid) for cancer therapy


Unclear if bisphosphonates should be held prior to invasive dental surgery
American Dental Association states:

“The decision to discontinue therapy should be a medical decision based primarily upon the risk for skeletally related events (fractures) secondary to low bone density, not the potential risk of osteonecrosis of the jaw.”

For users of ORAL BPs: Robert Marx DDS (2007) suggested fasting serum CTX to stratify risk of developing ONJ after invasive dental procedures.

CTX (C-terminal telopeptide crosslink) is breakdown product of type 1 collagen released during bone resorption – declines weeks to months after BP Tx is begun.


Bisphosphonate use lowers CTX values

Low CTX values indicate suppression of bone remodeling

Discontinuation of Bisphosphonates causes elevation of bone turnover markers (CTX) (Approx 25 pg/ml for each month of a drug holiday)

Marx study (2007)

30 women (mean age 64.8) current (17) or prior(13) oral BP users w suspected ONJ

17 on BPs had mean sCTX of 72.9 pg/ml (30-102)
After 6 months off BPs mean sCTX rose to 228.
He concluded risk of ONJ based on sCTX

CTX < 100 pg/ml – high risk
CTX between 100 and 150 pg/ml – moderate risk
CTX > 150 pg/ml minimal risk (subsequent study used 200)
Proposed to use CTX to assess risk of osteonecrosis

Proposed safe zone for preventing osteonecrosis after invasive dental surgery around 200 pg/ml

Holding bisphosphonates until CTX rises > 200 might prevent ONJ ???

Marx et al, 2007

Using CTX to modify risk of ONJ

Example:

Pt on bisphosphonates with CTX of 100

Needs to reach 200 – so hold med for 4 months

(25 pg/ml X 4 months = 200 pg/ml before dental surgery

Using CTX to modify risk of ONJ

Problems with sCTX include:

Variability with:

fasting vs non fasting, calcium intake, exercise, smoking, alcohol use, diurnal variation, medications

Lack of standardized post menopausal reference range

Lab variation
Using CTX to modify risk of ONJ

In FLEX study after 10 yrs mean sCTX remained < 150 pg/ml yet no cases of ONJ

In patients with sCTX levels >150...

Not all patients heal ONJ (despite d/c of BPs)
Cases of ONJ can occur even without BP use
Cases of ONJ have healed even w/out d/c of BP (in cancer pts)

Hoff AO, Toth BB, Frequency and risk factors assoc with osteonecrosis of the jaw in cancer pts treated with IV bisphosphonates. J Bone Miner Res 23: 826-836

Using CTX to modify risk of ONJ

Use of CTX not studied in large trials

Insufficient data to support use of CTX to decrease ONJ risk
Not endorsed by American Dental Association

Use in managing Drug Holidays??

Buim S, Miller P, assessing the Clinical Utility of Serum CTX in Postmenopausal Osteoporosis and Its Use in Predicting Risk of Osteonecrosis of the Jaw, J Bone Miner Res 2009; 24 (4):561-574

Severe side effects with Prolonged Use

Atypical Fractures of the Femur

Fracture located in subtrochanteric region or femoral shaft with transverse or short oblique orientation without comminution, occurring spontaneously or after minimal trauma.

First reported in 2005
More likely in patients on long term bisphosphonates – but also in BP naïve pts

Possible additional risk factors include:
Asian race, use of steroids, or PPIs

40% of pts with an AFF sustain similar Fx on opposite side
Thigh pain in 70-80% for weeks/months before Fx

Incidence Rises with longer duration of BP use

Review of >15,000 femoral fxs in US:
142 apparent Atypical Femoral Fractures (AFF)
128 had taken bisphosphonates for avg 5.5 years
Atypical Fractures of the Femur

Risk increased with duration of Tx

2 per 100,000 pt/yr if treated for 2 years

78 per 100,000 pt/yr if treated for 8 yrs


Swedish national population study

>12,000 femoral Fxs (11,000 hip Fxs)
59 confirmed AFFs – 78% with Hx of BP use

For users of BPs:
1.8 AFFs per 10,000 pt/yr for up to 2 yrs of Tx
8.4 per 10,000 pt/yr with > 2 yrs of BP use

Risk decreased 70% within 1st year BPs stopped


Swedish national population study

Relative risk with BPs ↑ 47.3%
This means only 3 more cases per 10,000 pt yrs

Also noted:
Risk ↓ 70% within 1st year BPs stopped

**Atypical Fractures of the Femur**

Risk of AFFs with BP use small compared to benefit of BPs in pts with Osteoporosis and high risk of fractures

Analysis of 90 million hospital discharge records (1996-2007) suggested:

**100 hip Fxs were prevented for each subtrochanteric Fx (typical and atypical)**


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**Risks vs Benefits of prolonged BP treatment**

NNT for 8 years – between 3-23 to prevent a vertebral Fx
NNT Between 7-26 for a non vertebral fracture

Risk of ONJ: 1 case for every 1000-100,000 pts Tx
1 AFF in 1282 pts treated for 8 yrs* (California data)
1 AFF for every 149 pts Tx for 8 yrs ** (Swedish data)

**Schilcher J, Michaelsson K et al, Bisphosphonate use and atypical fractures of the femoral shaft N Engl J Med 2011;364:1728-1737

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**Risk vs Benefit**

American Society for Bone and Mineral Research concluded:

BPs used for women at high risk of Fx:
Prevent 700–1000 nonvertebral Fxs per 100,000 person yrs
Prevent 1000-2300 clinical vertebral Fxs per 100,000 person yrs----
vs----
Incidence of AFF from BPs 78-100 per 100,000

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Atrial Fibrillation
In one of the two HORIZON Fracture Trials
Incidence of A Fib associated with hospitalization higher on zolendronic acid (1.3%) compared to placebo group (0.5%)
Overall incidence of A Fib or other arrhythmias, CVD or CVA not increased
FDA: Causal link could not be demonstrated

Esophageal Cancer
Several cases of esophageal cancer reported in pts with Hx of BP exposure.
One large case controlled analysis reported increase in esophageal cancer with long term BP use
Other reports found NO increases
(Decreased risk of breast and colorectal cancer noted in observational studies)
FDA concluded: not enough information to make definitive conclusions about a possible association between oral BPs and esophageal cancer

Long Term Bisphosphonate Use
Data indicate that in postmenopausal women with osteoporosis:
After 3-5 years of bisphosphonate (BP) therapy:
Fracture protection persists for some time after BP is stopped but slowly decreases over 3-5 years
Risk of AFF increases with duration of BP therapy and decreases after withdrawal of BP
Drug Holidays
Reasonable to consider drug holiday after prolonged use of bisphosphonates
Little data available to guide Drug Holidays
Recommendations are “Expert Opinion”

FDA Limitations of Use Statement
Optimal duration of BP therapy is not known and need for continued therapy should be reevaluated at regular intervals
...decisions to continue treatment must be based on individual assessment of risks and benefits and on pt preference

FDA Statement about Drug Holidays
“Pts at low risk for Fxs (eg. younger pts w/out Fx Hx and BMD near normal) may prove to be good candidates for discontinuation of BP therapy after 3-5 years,
whereas pts at increased risk for Fxs (eg. older pts w Hx of Fx and a BMD remaining in the osteoporotic range) may benefit further from continued therapy.”

Evaluate patients after 3-5 years of BP therapy

If BMD is stable (or increased) and no new fractures—consider Drug Holiday of one or more years (with annual follow up)

Resume therapy if BMD has decreased or fracture has occurred (or if Bone Turnover Markers have increased)

If fracture is AFF then Do Not restart BP

Drug Holidays and Duration

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment Duration</th>
<th>Duration of Drug Holiday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>treatment not needed</td>
<td>—</td>
</tr>
<tr>
<td>Mildly increased</td>
<td>treat 3-5 years</td>
<td>restart if BMD ↓ or Fx occurs</td>
</tr>
<tr>
<td>Moderately Increased</td>
<td>treat 5-10 years</td>
<td>Off 2-3 years (unless BMD ↓ or Fx)</td>
</tr>
<tr>
<td>High</td>
<td>treat 10 years</td>
<td>Off 1-2 years (or less if BMD ↓ or Fx) consider other med (marlacotide) during holiday</td>
</tr>
</tbody>
</table>

Expert Recommendations

Low Risk
- Baseline fracture risk
- No new fractures in last 10 yrs
- No additional risk factors

Mild Risk
- Baseline fracture risk
- BMD in normal range
- No additional risk factors

Moderate Risk
- Baseline fracture risk
- BMD in low-normal range
- One or more risk factors

High Risk
- Baseline fracture risk
- BMD in low-normal range
- Multiple risk factors
- Previous fracture

Osteoporosis Clinical Updates Fall 2013, NOF, Bone Source, Angelo Licata MD, PhD, Editor-in-Chief
Expert Recommendations

McClung: “A Drug Holiday is never required unless patient is experiencing complications of therapy”

“For patients at moderate risk, discontinuing Tx for 1 year after risedronate or for 2-3 years after alendronate or zoledronic acid is appropriate...”


When to reassess while on Holiday

If patient was on risedronate: reassess after 1 year
If patient was on alendronate: reassess after 1-2 years
If patient was on zoledronic acid: reassess after 2-3 years

Examples

55 year old woman
Lowest T-score -1.4, no risk factors
Bisphosphonate therapy for 3 years
**Examples**

55 year old women
Lowest T-score -1.4, no risk factors
Bisphosphonate therapy for 3 years

**LOW RISK for fracture**

Plan: stop treatment
Restart only if her T-score declines to osteoporotic range or she has a fracture

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**Examples**

70 year old woman
Lowest T-score -2.3
Risk factors: parent with hip Fx
Treated for 5 years
BMD stable during Tx

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**Examples**

70 year old women
Lowest T-score -2.3
Risk factors: parent with hip Fx
Treated for 5 years
BMD stable during Tx
BMD is >-2.5 and no previous or NEW Fxs
(Can also use FRAX Tool to assess her risk) ...............  

**Mild Risk for Fracture**

Plan: treat for 3-5 years then consider Drug Holiday
Cont Holiday until significant loss of BMD or pt fractures
**Examples**

75 year old woman
Lowest T-score -2.7
No risk factors
Therapy for 8 years
BMD improved on therapy to T-score of -2.2

**Moderate Risk of Fracture**

Treat for 5-10 years then Drug Holiday for 3-5 years
(or until significant decrease in BMD or a fracture)

80 year old woman
Lowest T-score -3.4
Risk factors: on steroids, previous vertebral Fx
Treatment for 8 years
80 year old women
Lowest T-score -3.4
Risk factors: on steroids, previous vertebral Fx
Treatment for 8 years
High Risk of Fracture

Plan: treat for 10 years
Consider Drug Holiday of 1-2 years
(or until significant decrease in BMD or new fracture)
Consider treatment with teriparatide or raloxifene during Holiday

Summary of Findings

1) Hip and Spine BMD decline following D/C of BPs but remain ABOVE pretreatment levels recorded up to 10 years earlier
2) No difference in Fx rates for non-vertebral Fxs between those on alendronate for 5 vs 10 years
   (unless starting with T-score < -2.5)

Summary of Findings

Post hoc analysis of FLEX trial:
In pts without existing fractures:
Risk of non-vertebral fractures ONLY reduced in those with original T-score < -2.5 (in those who continued on alendronate for 10 years)
(not in those with T-score > -2.0)

Summary of Findings

3) In those continuing BPs over 5 yrs:

- **Reduced risk of vertebral fractures**
  - clinical Fractures in FLEX
  - morphometric Fractures in HORIZON PFT

4) After D/C, bone loss most rapid with
risedronate --- so best drugs for Holidays are
alendronate and zoledronic acid

Suggestions from the Experts

If risk of fracture is HIGH

due to previous fragility fracture
T-score < -2.5 or
Results of FRAX Tool

Then BP treatment should not be stopped for at least 10 years

Benefits Outweigh the Risks

NNH for 1 AFF was 667
NNT for 3 years to prevent fractures:
91 for hip fractures
14-21 for vertebral fractures

After 10 yrs
age adjusted rate for AFF is 1.1/1000 pt yrs
Rate of non-vertebral Fxs: 37/1000 pt yrs
Rate of vertebral Fxs: 62.7/1000 pt yrs

Ringe JD, Doherty JG, absolute risk reduction in osteoporosis Rheumatal Int 2010;30:863-9
Summary

Bisphosphonates should not be stopped for at least 10 years in pts at high risk of fracture

Initial duration of 2-3 yrs w good adherence needed to maintain Fx benefit after BPs are D/C’d

Benefits of treatment greatly outweigh the risks

Safety beyond 10 years not yet established