1. **Introduction:** MOA, adverse effects, monitoring, and administration

2. **Where are we with incidence of HIP fractures, are we making a difference?**

3. **Do bisphosphonates differ in their efficacy and/or tolerability?**

4. **Where in the osteoporosis GUIDELINES do bisphosphonates fit?**

5. **Is there such thing as bisphosphonate treatment failure and when do you switch therapies?**

6. **Does vitamin D deficiency affect a patient's response to a bisphosphonate?**

7. **What role do bisphosphonates play in corticosteroid-induced osteoporosis?**

8. **What type of men benefit from bisphosphonate therapy?**

9. **Is osteonecrosis of the jaw something all patients and practitioners should worry about?**

10. **Preserved bone mineral density versus bone quality: what are the true incidences of low-impact fractures**

11. **What are the benefits and drawbacks of using long-term continuous therapy versus giving “drug holidays”?**

12. **Does patient compliance significantly affect the benefits seen with bisphosphonates?**

13. **What about bisphosphonates in patients with renal impairment?**

14. **How concerned should we be about the association of bisphosphonates and risk of serious atrial fibrillation?**

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**Osteoporosis Focus on Bisphosphonates (oral and IV)**

<table>
<thead>
<tr>
<th>Oral Bisphosphonates:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosamax (Alendronate)</td>
</tr>
<tr>
<td>Actonel (Risendronate)</td>
</tr>
<tr>
<td>Boniva (Ibandronate)</td>
</tr>
<tr>
<td>Didronel (Etidronate)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV Bisphosphonates:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aredia (pamidronate)</td>
</tr>
<tr>
<td>Zolendronic acid (Reclast)</td>
</tr>
</tbody>
</table>

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**Highlights: The Quick-Read Information**

1. Which one of the following bisphosphonates is available in combination with calcium?
   a. [Alendronate]; b. [Ibandronate]; c. [Risendronate]; d. [Zoledronic acid]

2. Which bisphosphonate is FDA-approved for treatment of osteoporosis in MALES?
   a. [Alendronate]; b. [Ibandronate]; c. [Risendronate]; d. [Zoledronic acid]

3. Pharmacologic therapy is recommended by the AACE in which of the following patients?
   a. A postmenopausal woman with history of an osteoporotic fracture
   b. A 60 year old MALE with a BMD DEXA T-score of -2.8
   c. A women who’s BMD is still declining regardless of nonpharmacologic therapy (Calcium/vit D)
   d. All of the above

4. True or False, by the age of 65, both men AND women are losing bone mass at the same rate?
   a. [True]; b. [False];

5. True or False, bisphosphonates are known to reduce the risk of VERTEBRAL fracture by 15%?
   a. [True]; b. [False];

6. Bisphosphonate induced osteonecrosis is more likely to occur with which route administration?
   a. [Oral]; b. [IV]; c. [Oral = IV]; d. [IM]

7. At what dose of corticosteroids should you consider using bisphosphonate therapy?
   a. [20 mg prednisone x 7 days]; b. [7.5 mg prednisone expected to be used daily for at least 6 months];
   c. [5 mg prednisone x 5 days]; d. [Medrol Dosepak x 6 days]
### Bisphosphonates – General Information

<table>
<thead>
<tr>
<th>Generic name (Brand)</th>
<th>Bone T&lt;sub&gt;1/2&lt;/sub&gt; (**)</th>
<th>PO/IV (***</th>
<th>Combinations Available</th>
<th>Generic Available?</th>
<th>Pregnancy Category</th>
<th>FDA approved for osteoporosis?</th>
<th>IHA Tiers Commercial</th>
<th>IHA Tiers Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax) (Fosamax Plus D)</td>
<td>&gt;10 years</td>
<td>PO (tabs and solution)</td>
<td>Alendronate 70mg + Vit D 2800IU OR + Vit D 5600IU</td>
<td>Yes</td>
<td>C</td>
<td>Yes</td>
<td>Tier 1 (generic)</td>
<td>Tier 1 (generic) Tier 3 (brand)</td>
</tr>
<tr>
<td>Ibandronate (Boniva) (Boniva solution)</td>
<td>60 hours</td>
<td>PO (tabs and solution)</td>
<td>No</td>
<td>No</td>
<td>C</td>
<td>Yes</td>
<td>Tier 3</td>
<td>Tier 3</td>
</tr>
<tr>
<td>Risedronate (Actonel) (Actonel with Calcium)</td>
<td>220 hours</td>
<td>PO (tabs)</td>
<td>Risedronate 35mg + Ca&lt;sup&gt;2+&lt;/sup&gt; 1250mg</td>
<td>No</td>
<td>C</td>
<td>Yes</td>
<td>Tier 2</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Etidronate (Didronel)</td>
<td>3-6 months</td>
<td>Both (tabs and caps)</td>
<td>No</td>
<td>Yes</td>
<td>C</td>
<td>No</td>
<td>Tier 1 (generic) Tier 2 (brand)</td>
<td>Tier 1 (generic) Tier 2 (brand)</td>
</tr>
<tr>
<td>Pamidronate (Aredia)</td>
<td>10 months</td>
<td>IV</td>
<td>No</td>
<td>Yes</td>
<td>D</td>
<td>No</td>
<td>Billed as Medical Benefit (not self-administered)</td>
<td>Tier 1 w/ PA (generic home infusion)</td>
</tr>
<tr>
<td>Zoledronic Acid (Reclast)</td>
<td>146 hours</td>
<td>IV</td>
<td>No</td>
<td>No</td>
<td>D</td>
<td>Yes</td>
<td>Tier 3</td>
<td>Tier 3</td>
</tr>
</tbody>
</table>

** : Comparing the half-lives (t<sub>1/2</sub>) of different bisphosphonates is difficult due to their unpredictable rates of re-distribution; these half-lives are what have been predicted by package inserts.

*** : PO Administration…Oral bisphosphonates must be taken on an empty stomach with a full 8 oz. glass of water (no coffee, juice, etc) in order to maximize drug absorption.
<table>
<thead>
<tr>
<th>Generic name (Brand)</th>
<th>Strength</th>
<th>Osteopenia</th>
<th>Osteoporosis</th>
<th>Renal Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax) (Fosamax Plus D)</td>
<td>Tab – 5, 10, 35, 40, and 70mg Solution – 70mg/ml</td>
<td>5mg po QD OR 35mg po q wk</td>
<td>10mg po QD OR 35mg po BIW OR 70mg po q wk</td>
<td>concentrations may ↑ with ↓ CrCl; however NO adjustment is needed for CrCl &gt;35ml/min NOT recommended in CrCl &lt;35ml/min</td>
<td>- Nitrogen-containing bisphosphonate → alters protein synthesis in osteoclasts - Proven effective for up to 7 years (longest study duration) - Discontinuation has NOT been shown to cause accelerated bone loss compared to placebo - High bone mineral affinity, moderate FPPS affinity</td>
</tr>
</tbody>
</table>
| Ibandronate (Boniva) (Boniva solution) | Tablets – 2.5, and 150mg Solution – 3mg/3ml | 2.5mg po QD OR 150mg po q mo OR 0.5-2mg IV bolus q 3 mo | 2.5mg po QD, OR 20mg QOD x 12 doses q 3 mo, OR 150mg po q mo, OR 3mg IV bolus q 3 mo | concentrations may ↑ with ↓ CrCl; however NO adjustment is needed for CrCl >30ml/min NOT recommended in CrCl <30ml/min | - Nitrogen-containing bisphosphonate → alters protein synthesis in osteoclasts - High bone mineral affinity, moderately strong inhibitor of FPPS - High affinity results in less redistribution to other skeletal bone sites = potentially not very effective for nonvertebral fractures (see VIBE study 2009 results below…)
| Risedronate (Actonel) (Actonel with Calcium) | Tablets – 5, 30, 75, 150mg | Same as osteoporosis dose → | 5mg po QD OR 35mg q week OR 75mg po 2 days/mo OR 150mg po q mo | concentrations may ↑ with ↓ CrCl; however NO adjustment is needed for CrCl >30ml/min NOT recommended in CrCl <30ml/min | - Nitrogen-containing bisphosphonate → alters protein synthesis in osteoclasts - Proven effective for up to 3 years (longest study duration) - Effect of termination of treatment on bone loss has not been studied - Low to moderate bone mineral affinity, very high affinity for FPPS (one of the strongest inhibitors) |
| Etidronate (Didronel) | Tablets – 200 and 400mg | Corticosteroid-induced 400mg po QD x 14 days q 3 mo | 400mg po QD x 14 doses q 3 mo Use IV tx over oral tx in SCr 2.5-4.9mg/dl (IV now OFF market) NOT recommended in SCr >5mg/dl | - Non-nitrogen-containing bisphosphonate → induces osteoclast apoptosis - Low potency, low bone mineral affinity, rapid reversal effect on BMD (first approved for osteoporosis) |
| Pamidronate (Aredia) | Powder for injection – 30, 60, 90mg | Corticosteroid-induced 30mg IV infusion (1hr) q 3 mo | 15mg IV infusion (3hr) QD x 3 days (total 45mg) q 3 mo OR 30mg IV inf q 3 mo ↑ infusion duration (>2hr) for mild-moder. impairment; withhold tx if SCr ↑ (>0.5mg/dl) during tx; not recommended in severe impairment | - Nitrogen-containing bisphosphonate → alters protein synthesis in osteoclasts - High bone mineral affinity, moderate FPPS inhibitor - Insufficient data for effects on fracture risk |
| Zoledronic Acid (Reclast) | IV solution – 5mg/100ml | 5mg infusion (15min) once every 2 years | 5mg IV infusion (15min) once yearly ↑ chance of nephrotoxicity; NO adjustment needed for CrCl>35ml/min **monitor SCr, hydrate, and DO NOT exceed infusion rate NOT recommended in CrCl <35ml/min or SCr >4.5mg/dl | - Nitrogen-containing bisphosphonate → alters protein synthesis in osteoclasts - Very high bone mineral affinity AND very strong FPPS inhibitor - Rapid effect on vertebral fractures but slower time to effect on nonvertebral |

Bone mineral affinity → the ability for the bisphosphonate molecule to adhere to bone surfaces. Mechanistically, bisphosphonates with high affinity should have quicker and more complete extraction from circulation, less recycling within bone, and less re-entry into circulation making distribution to other sites (nonvertebral) less likely. Theoretically, this means that high affinity bisphosphonates don't protect as well against nonvertebral fractures. However, other characteristics of the molecule (such as enzyme inhibition) can make up for this phenomenon; ie. ibandronate has high affinity and moderate enzyme inhibition and yet an observational study has demonstrated equal efficacy for hip fractures between monthly ibandronate, and weekly alendronate or risedronate.

FPPS → bisphosphonates inhibit this enzyme which is responsible for making vital osteoclast proteins (inhibition causes decreased osteoclast function). High FPPS inhibition correlates with better resorption inhibition and quicker onset of fracture protection; ie zoledronic acid and risedronate decrease vertebral fracture in < 12 months.
INTRODUCTION

Over the years osteoporosis has grown into a major health issue effecting over 44 million nationwide and targeting 55% of the population over age 50. The disorder, characterized by low bone mineral density and increased bone fragility, is a large contributor to disability, economic burden, and mortality. In 2005 it was estimated that osteoporosis was responsible for more than 2 million fractures, $19 billion dollars in medical costs, 293,000 hospital admissions, and over 70,000 deaths due to hip fractures alone. Despite these tremendous effects on morbidity and mortality, patients with low bone mineral density are still often overlooked and undertreated. Bisphosphonates are currently the most common and effective antiresorptive agents used in both the treatment and prevention of osteoporosis.

MECHANISM OF ACTION

As a class, bisphosphonates have a unique mechanism of action which gives them the ability to preferentially adhere to their target sites (bone mineral). After adhering to bone mineral, bisphosphonates are taken up into osteoclasts through endocytosis where they alter cellular structures, impair osteoclast function, and induce apoptosis. Thus, by inhibiting osteoclasts, bisphosphonates decrease the amount of bone resorption and increase bone mineral density. After binding to bone mineral, the drug molecule can be released back into the bloodstream by initiation of bone turnover. This unique property is why bisphosphonate half-lives are so long and yet difficult to predict.

Common Adverse Events

Oral Bisphosphonates
- Esophageal irritation
- Abdominal pain
- Nausea
- Heartburn
- Constipation
- Diarrhea
- Flatulence

IV Bisphosphonates
- Injection site reaction
- Fever
- Headache
- Arthralgia
- Myalgia
- Bone pain
- Nausea/anorexia

Serious Adverse Events

[Are most common with IV formulations]
- Osteonecrosis of the jaw [section link]
- Serious Atrial fibrillation [section link]
- Electrolyte disturbances (hypocalcemia, hypophosphatemia, hypokalemia, and hypomagnesemia)
- Renal failure

Figure 1 - Adapted from Am J Health-Sys Pharm. 2008:65. Ref 40
Figure 2 - Adapted from National Osteoporosis Foundation. Clinician's Guide: to Prevention and Treatment for Osteoporosis. 2008.
Medications that may contribute to Osteoporosis

- Oral or intramuscular glucocorticoids [section link]
- Excessive levothyroxine
- Aromatase inhibitors
- Long-term use of anticonvulsants (phenytoin)
  - Via interference with Vit D metabolism
- Immunosuppressives or cytotoxic agents
- Gonadotropin-releasing hormone agonists/analogues
- Intramuscular medroxyprogesterone contraceptive

MONITORING

The American Academy of Clinical Endocrinology (AACE) recommends an annual follow up for patients being treated with bisphosphonate therapy which includes a history and exam, assessment of adherence to medication, Ca\(^{2+}\)/vitamin D supplements, and exercise program. They also recommend yearly assessment of bone mineral density using appropriate tools for the first 2 years then every 2 years (if stabilized) thereafter.

Bisphosphonates are one of the only classes of antiresorptives that will adequately relate BMD values to fracture risk endpoints, making monitoring more accurate.

GUIDELINES

Information extracted from Guidelines specifically regarding bisphosphonate use:

The AACE and the America College of Endocrinology recommend initiating FDA approved pharmacologic therapy (bisphosphonates are first-line treatment) in addition to Ca\(^{2+}\) and vitamin D for the treatment and prevention of osteoporosis in the following:

- Women with postmenopausal osteoporosis
  - Low trauma fracture with low BMD (T-score ≤ -1.5)
  - Single BMD T-score ≤ -2.5
- Women with borderline-low BMD (T-score ≤ -1.5) with risk factors
- Women in whom preventative nonpharmacologic therapy was ineffective
  - Continuing bone loss
  - Low trauma fracture occurs

The North American Menopause Society recommends pharmacologic therapy in the following postmenopausal women:

- All postmenopausal women with history of an osteoporotic vertebral fracture
- All postmenopausal women with a BMD T-scores ≤ -2.5
- All postmenopausal women with a low T-score (-2.0 to -2.5) PLUS a risk factor for fracture:
  - Thinness (<127 lb or BMI <21 kg/m\(^2\))
  - History of fragility fracture since menopause
  - Primary family history of hip fracture (parent)

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Sites Measured</th>
<th>Units</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEXA</td>
<td>PA spine, lateral spine, proximal femur, total body, forearm, heel, phalanges</td>
<td>Areal density (g/cm(^2))</td>
<td>Diagnosis and monitoring</td>
</tr>
<tr>
<td>QCT</td>
<td>Spine</td>
<td>Volumetric density (g/cm(^3))</td>
<td>Diagnosis and monitoring</td>
</tr>
<tr>
<td>pQCT</td>
<td>Forearm, hip</td>
<td>Volumetric density (g/cm(^3))</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>QUS</td>
<td>Heel, forearm, tibia, phalanges, metatarsals</td>
<td>SOS, BUA</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>RA</td>
<td>Phalanges</td>
<td>Volumetric density (various units)</td>
<td>Risk assessment</td>
</tr>
</tbody>
</table>

Adapted from AACE Osteoporosis Guidelines

<table>
<thead>
<tr>
<th>World Health Organization Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Osteopenia</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>
AACE Treatment Goals
- Prevent fractures
- Stabilize or increased BMD
- Relieve symptoms of fractures and/or skeletal fragility
- Maximize physical function

| Recommended Daily Ca\textsuperscript{2+} Intake |  
|-----------------|-----------------|-----------------|
| **Age Group**   | **Ca\textsuperscript{2+} (mg/day)** |
| 1-3             | 500 mg           |
| 4-8             | 800 mg           |
| 9-18            | 1,300 mg         |
| 19-50           | 1,000 mg         |
| >50             | 1,200 mg         |
| >65             | 1,500 mg         |
| <19 and pregnant or lactating | 1,300 mg |
| 19-50 and pregnant or lactating | 1,000 mg |
| < 65 post-menopausal and using estrogen | 1,000 mg |
| Postmenopausal not using estrogen | 1,500 mg |

Adapted from the National Institutes of Health and the Institute of Medicine\textsuperscript{5,6}

### Recommended Daily Dietary Reference Intakes of Elemental Calcium and Vitamin D\textsuperscript{a}

<table>
<thead>
<tr>
<th>Supplement</th>
<th>National Academy of Sciences</th>
<th>National Osteoporosis Foundation</th>
<th>NIH Consensus Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elemental</strong> Calcium</td>
<td>Age 31 – 50 yr: 1000 mg</td>
<td>Age &lt;50yr: 1000 mg</td>
<td>Age 25 – 65 yr and women &gt; 50 yr receiving estrogen: 1000 mg</td>
</tr>
<tr>
<td></td>
<td>Age &gt;50yr: 1200 mg</td>
<td>Age ≥50yr: 1200 mg</td>
<td>Age &gt;65 yr and women &gt; 50 yr NOT receiving estrogen: 1500 mg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Age 31 – 50 yr: 200 IU</td>
<td>Age &lt;50yr: 400-800 IU</td>
<td>... \textsuperscript{b}</td>
</tr>
<tr>
<td></td>
<td>Age 50 – 70 yr: 400 IU</td>
<td>Age ≥50yr: 800 – 1000 IU</td>
<td>Age 51 – 70 yr: 400 IU</td>
</tr>
<tr>
<td></td>
<td>Age &gt;70 yr: 600 IU</td>
<td>Age &gt; 70 yr: 600 IU</td>
<td>Age &gt; 70 yr: 600 IU</td>
</tr>
</tbody>
</table>

\textsuperscript{a} – Recommendations are for BOTH men AND women unless otherwise stated. NIH = Nation Institutes of Health
\textsuperscript{b} – The 1994 NIH consensus panel did NOT provide recommendations for vitamin D supplementation, above is from current NIH web page 2009 [http://www.nia.nih.gov/HealthInformation/Publications/osteoporosis.htm].

### Some Quick Facts

**What are the risks?**
Fractures are the most important and modifiable risk factor in postmenopausal osteoporosis

**Hip fractures**
- Result in permanent disability for 1 out of every 3 patients
- 25% of patients suffering a hip fracture will die within 1 year
- More than half the patients who survive a hip fracture are no longer able to live independently and many end up in a nursing home\textsuperscript{1}
- Complications include severe pain, deformity, disability, muscle wasting due to inactivity, and depression
The addition of medications to control these co-existing conditions may result in further risk for falls

Ex. Opiates for pain cause dizziness and drowsiness; antidepressants can cause significant sedation…

**Reduce falls → adjust dosage of drugs with sedative effects which could slow reflexes or decrease coordination and impair patient’s ability to break impact of a fall**

Where are we with incidence of HIP fractures, are we making a difference?

A recent study published this month in JAMA examines the incidence of hip fractures over 20 years (1986-2005). Due to the increasing awareness about calcium and vitamin D supplementation, and the introduction of bisphosphonates, it is interesting to see if the changes we’re making are truly having an impact.


- Brauer et al looked at hip fracture trends and resulting mortality in 20% of the Medicare population (786,717 patients). They found that during the period from 1986 to 1995 hip fractures were increasing for both males and females, while mortality after a fracture was decreasing. Before 1998, surgical and medical management advances decreased mortality. After 1998, there were few advances in surgical or medical management to impact mortality. After 1995, hip fracture incidence shifted and began decreasing while mortality after a fracture was unchanged. The largest impact seen was in women over the age of 85; hip fracture decreased by 24% in this population.

- The authors couldn’t exactly determine why this trend occurred but they speculated that the shift in 1995 was a result of the introduction of bisphosphonates to the market.
  - So, the moral of the story here is prevent a fracture → prevent a death, despite not improving mortality after a fracture has occurred.

Do bisphosphonates differ in their efficacy and/or tolerability?

It is difficult to directly compare the efficacy among different bisphosphonates due to the lack of head to head clinical trials with determinant endpoints. Nonetheless, there still a few things we can compare and contrast in order to select the most appropriate drug for a specific patient.

**Tolerability** - The main difference in adverse effects is between oral and IV formulations.

- Oral bisphosphonates are not well tolerated in patients with esophageal or gastric disorders as they can cause significant gastrointestinal upset, esophageal erosions, and dyspepsia. **The best way to avoid this in patients without GI disorders is to take the medication with a full glass of water and remain upright (not lying down) for 30 to 60 minutes.**
  
  NOTE: There is a documented interaction between the H₂ antagonist ranitidine and oral alendronate that results in increased concentrations. Although the clinical significance of this interaction has not been determined, patients receiving H₂ antagonists and PPIs should use bisphosphonates cautiously as they could have an increased risk of developing adverse GI effects.

- IV bisphosphonates are an alternative for patients who cannot tolerate oral formulations. The patient would have to be willing to have an infusion at a hospital and they are more likely to experience flu-like symptoms, electrolyte disturbances, and bone pain. **The best way to manage these would be analgesics, antipyretics, and monitoring for hypocalcemia, hypophosphatemia, hypokalemia, and hypomagnesemia.**

**Efficacy**

The table below demonstrates various aspects that contribute to efficacy of a bisphosphonate. [As mentioned above, due to the lack of head-to-head trials it would be inaccurate to make direct conclusions from this data. However, there are some differences worth mentioning].

- Risedronate and zoledronic acid appear to have the quickest onset of fracture prevention at 1 year
- Alendronate has the highest reported increase in lumbar spine and trochanter BMD
- Zoledronic acid seems to have the most impact on vertebral fractures at 3-years and risedronate has the most effect on nonvertebral.
<table>
<thead>
<tr>
<th>Fracture Risk Reduction</th>
<th>Onset of Antifrac</th>
<th>BMD Changes</th>
<th>Fracture Reduction Data Available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vertebral</td>
</tr>
<tr>
<td>Vertebral</td>
<td>Trochanter</td>
<td>+8.2%</td>
<td>+5.3%</td>
</tr>
<tr>
<td></td>
<td>Lumbar Spine</td>
<td>+10.2%</td>
<td>+6.4%</td>
</tr>
<tr>
<td></td>
<td>Femoral Neck</td>
<td>+6.1%</td>
<td>+2.1%</td>
</tr>
<tr>
<td>1-year</td>
<td>Vertebral</td>
<td>59%</td>
<td>62%</td>
</tr>
<tr>
<td>3-years</td>
<td>Vertebral</td>
<td>47%</td>
<td>49%</td>
</tr>
<tr>
<td>1-year</td>
<td>Nonvertebral</td>
<td>47%</td>
<td>69%</td>
</tr>
<tr>
<td>3-years</td>
<td>Nonvertebral</td>
<td>19%</td>
<td>59%</td>
</tr>
<tr>
<td>Hip</td>
<td>Vertebral</td>
<td>50%</td>
<td>No sufficient data</td>
</tr>
<tr>
<td></td>
<td>Vertebral</td>
<td>No sufficient data</td>
<td>34%</td>
</tr>
</tbody>
</table>

### Agent

<table>
<thead>
<tr>
<th>Agent</th>
<th>Typical Dosage</th>
<th>Fracture Reduction Data Available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vertebral</td>
</tr>
<tr>
<td>Alendronate²</td>
<td>10 mg daily or 70 mg weekly</td>
<td>YES</td>
</tr>
<tr>
<td>Ibandronate³</td>
<td>2.5 mg daily or 150 mg monthly 3 mg IV q 3 months</td>
<td>YES</td>
</tr>
<tr>
<td>Risedronate³⁻¹³</td>
<td>5 mg daily, 35 weekly, 75 mg given on 2 consecutive days monthly</td>
<td>YES</td>
</tr>
<tr>
<td>Zoledronic Acid¹⁶</td>
<td>5 mg IV once yearly</td>
<td>YES</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>1 spray (200IU) intranasally, alternate nostrils daily</td>
<td>YES</td>
</tr>
<tr>
<td>Estrogen-replacement therapy</td>
<td>0.625 mg of conjugated estrogens daily</td>
<td>YES</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>60 mg daily</td>
<td>YES</td>
</tr>
<tr>
<td>Teraparatide²</td>
<td>20 mcg subQ daily</td>
<td>YES</td>
</tr>
</tbody>
</table>

Adapted from Am J Health-system Pharm-Vol 65. 2008.⁴⁵

§ - The eVAluation of IBandronate Efficacy (VIBE) head-to-head database fracture study was just published in 2009 (prior to the articles supplying the above comparative charts). It compared fracture rates between patients treated with monthly ibandronate and weekly oral bisphosphonates in women ≥45 yrs, newly prescribed one of the study drugs and without malignancy or Paget’s disease of bone.⁴¹

* This study provided data suggesting that ibandronate was statistically significantly better in reducing fracture incidence and relative risk of fracture compared with weekly bisphosphonates, even when >65 yr age group analyzed.

* The data indicated a non-significant trend toward less efficacy in regards to Hip fractures specifically.
This potential reduction in efficacy appears to be in agreement mechanistically as discussed in the comparative chart on p. 3.

That is, due to ibandronate’s HIGH bone mineral affinity, moderately strong inhibition of FPPS enzyme, predicting less redistribution to other skeletal bone sites and less efficacy for nonvertebral fractures.

However, the difference was NOT determined to be significant and appeared to weaken when >65 yrs analyzed.

**PharmD Comment:**
I would interpret this data as indicating that compliance, duration of therapy and age, as likely more important than type or formulation of bisphosphonate chosen.

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Unadjusted relative risk</th>
<th>Adjusted relative risk (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>0.44</td>
<td>0.36 (0.18–0.75)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hip</td>
<td>1.07</td>
<td>1.06 (0.61–1.83)</td>
<td>0.840</td>
</tr>
<tr>
<td>Nonvertebral</td>
<td>0.97</td>
<td>0.88 (0.71–1.09)</td>
<td>0.255</td>
</tr>
<tr>
<td>Any clinical</td>
<td>0.90</td>
<td>0.82 (0.66–1.00)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

[Link to Abstract from BONE Journal]

**Where in the osteoporosis GUIDELINES do bisphosphonates fit?**

See above [Link]

**Is there such thing as bisphosphonate treatment failure and when do you switch therapies?**

Yes and No…

It is difficult to define treatment failure in patients using bisphosphonates for osteoporosis for a few reasons. Unlike most medications, bisphosphonates take a long time (6 to 24 months) to exert their effect, making it difficult to determine their short term benefits. Also, monitoring parameters such as BMD can only be assessed for changes every 12 months.

Treatment failure is **NOT** defined as…

“A lack of increase in BMD or even a slight decrease in BMD after 1 to 2 years of bisphosphonate therapy”

-This particular presentation does not warrant a change in therapy

Treatment failure **IS** considered if…

“A significant decrease in BMD of ≥ 5% after 1 to 2 years of bisphosphonate therapy”

-This presentation would warrant further consideration of patient adherence, secondary causes, and alteration of therapy

**NOTE:** The 1 – 2 year timeframe is based on the fact that bisphosphonates will typically demonstrate BMD changes in the spine after 1 year and the hip after 2 years.
Does vitamin D deficiency affect a patient’s response to a bisphosphonate?

No…At onset of therapy that is Vitamin D deficiency is a very common problem among patients with low bone mineral density and treating it (similar to treating low calcium levels) is crucial to the management and prevention of osteoporosis. Some practitioners may wonder whether a patient’s vitamin D status at initiation of bisphosphonate therapy would impair or affect their overall response. If so, should a patient’s vitamin D deficiency be treated before initiating a bisphosphonate? This question is worth discussing because it could unnecessarily delay the start of therapy in a patient at risk for fracture.

**Literature Highlight:**

* A cohort analysis of 1,000 patients from the Fraction Intervention Trial of alendronate showed that both total hip and spine BMD response did NOT differ by vitamin D status at baseline.\(^{17}\)
* Over 80% of these patients had insufficient levels of vitamin D compared to 14% with sufficient levels.
* Most patients (83%) received calcium (500mg/day) and cholecalciferol (250 IU/day) during treatment with alendronate or placebo.
* This data supports the idea that having a low vitamin D level **upon initiation** of a bisphosphonate does NOT reduce responsiveness to therapy.
* **However, this assumes that patients with insufficient vitamin D levels are being treated with recommended daily amounts of cholecalciferol to replenish their stores.**

**PharmD Comment:**

Thus, bisphosphonate therapy initiation should NOT be delayed based upon baseline Vit D status.

What role do bisphosphonates play in corticosteroid-induced osteoporosis?

Corticosteroid-induced osteoporosis is a major concern for patients on long term steroid therapy or even those who used multiple courses of short term steroids. Osteoporosis prophylaxis in this population is underutilized and it appears that a more clear set of guidelines would help practitioners make better use of prophylactic measures in these patients.

**Guideline Highlight:**

Summary of The American College of Rheumatology corticosteroid-induced osteoporosis guidelines (updated 2001)\(^{18}\)

- Obtain a baseline BMD of the lumbar spine and/or hip prior to initiating long-term (>6 months) glucocorticoid therapy in men or women
- Monitor BMD every 6 months to assess bone loss in glucocorticoid treated patients
- Follow up yearly with patients receiving prophylactic therapy
- Patients receiving long-term glucocorticoid therapy should take calcium and vitamin D supplements daily
- Bisphosphonates should be used **in addition** to calcium and vitamin D in the following patients:
  - Patients first starting glucocorticoid therapy at a dose of prednisone equivalent ≥ 5mg/day with plans of continuing therapy for ≥ 3 months
  - Patients receiving long-term glucocorticoid therapy (≥ 5mg/day) with documented osteoporosis (low BMD or history of osteoporotic fracture)
  - Patients receiving long-term glucocorticoid therapy who do not tolerate or have had a fracture while taking HRT
- Alendronate, risedronate, and etidronate have been proven effective by randomized controlled trials and therefore alendronate and risedronate are recommended for both the treatment and prevention of glucocorticoid-induced osteoporosis
### BISPHOSPHONATE DOSING FOR CORTICOSTEROID-INDUCED OSTEOPOROSIS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient population</th>
<th>Dose</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Men and women taking systemic corticosteroids (oral prednisone ≥ 7.5 mg/day or equivalent)</td>
<td>5mg po once daily along with Ca(^{2+}) and vitamin D supplementation</td>
<td>Clinical trials show a significant increase in BMD and decrease in vertebral fractures in patients taking this dose for 2 years compared to placebo.(^{19})</td>
</tr>
<tr>
<td></td>
<td>Postmenopausal women taking systemic corticosteroids</td>
<td>10mg po once daily along with Ca(^{2+}) and vitamin D</td>
<td>As mentioned above, except incidences of vertebral fractures were more common among this population</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Patients taking systemic corticosteroids (oral prednisone ≥ 7.5 mg/day or equivalent)</td>
<td>5mg po once daily</td>
<td>This dose of risedronate for 1 year has been shown to be effective in phase III trials for increasing BMD of the lumbar spine, femoral neck, and femoral trochanter.(^{20})</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>In patients with established corticosteroid-induced osteoporosis</td>
<td>2mg IV q 3 months</td>
<td>In a clinical trial this dose was shown to be effective for up to 2 years.(^{21})</td>
</tr>
<tr>
<td>Zoledronic Acid</td>
<td>In patients taking systemic corticosteroids (oral prednisone ≥ 7.5 mg/day or equivalent) for ≥ 12 months</td>
<td>5mg IV once yearly along with 1200mg calcium and 800-1000IU vitamin D once daily</td>
<td>This dose was compared to an oral bisphosphonate for 1 year and was found to increase lumbar spine BMD by 4.1% (oral bisphosphonate 2.7%)</td>
</tr>
<tr>
<td>Etidronate</td>
<td>In patients at risk for corticosteroid-induced osteoporosis:</td>
<td>400mg po once daily for 14 days followed by 76 days of Ca(^{2+}) supplements; repeated 3 times in 1 year</td>
<td>This dosage regimen was shown to increase lumbar spine and trochanter BMD versus placebo (decrease in BMD) in patients taking at least 12 months of prednisone therapy.(^{22})</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>In patients taking 14mg oral prednisolone per day:</td>
<td>30mg IV q 3 months for 1 year</td>
<td>This dose was shown to be effective in a small observational study of patients taking corticosteroids for 14 years to treat steroid-dependent lung disease. A significant increase in lumbar BMD was found with treatment.(^{23})</td>
</tr>
</tbody>
</table>

**NOTE:** This chart presents ‘evidence-based’ recommendations. It is likely that formulations other than daily, would provide similar benefits. It appears that studies are lacking at present.

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**What type of men benefit from bisphosphonate therapy?**

Although postmenopausal women are exceptionally prone to developing osteoporosis it’s not exclusively a female disease. Men make up approximately 20% of the osteoporosis population and their risk factors are similar to women. Although there aren’t published guidelines on the screening, diagnosis, and treatment of male osteoporosis, professional recommendations are available.\(^{24}\)

- Men with any risk factors should be considered for osteoporosis testing (DEXA, vitamin D and calcium levels, etc)
- Men over the age of 70 should be routinely monitored due to the rapid increase in fractures in this population
- Men with asymptomatic vertebral fractures can be identified by a loss of height ≥1.5in

- Once an osteoporosis diagnosis has been made, secondary causes should be identified in order to prevent further complications
- Nonpharmacologic treatment should consist of adequate Ca\(^{2+}\) (1,000-1,500mg/day) and vitamin D (400IU-800IU/day)
- Initiation of a bisphosphonate should be strongly considered after the diagnosis of osteoporosis
  - Alendronate has been **approved** for the treatment of osteoporosis in men
    - 10mg po QD or 70mg po q week\(^{25}\)

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11 | Page
Risedronate has **been studied** in men with osteoporosis. Compared to placebo, men taking risedronate 35mg po once weekly (along with calcium and vitamin D) for 2 years were found to have a significant increase BMD by 4.5%, 1.1%, 2.2%, 1.5% at the lumbar spine, femoral neck, trochanter, and total proximal femur respectively. 

Although other bisphosphonates haven’t been specifically studied in male osteoporosis, they are still viable options.

### Male Risk Factors

<table>
<thead>
<tr>
<th>Higher-risk</th>
<th>Intermediate Risk</th>
<th>Lower-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/o of nontraumatic fractures (hip, vertebral or wrist)</td>
<td>Anticonvulsant drug use (phenytoin or phenobarbital)</td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Osteopenia seen on radiograph</td>
<td>Alcohol abuse</td>
<td>Chronic liver or kidney disease</td>
</tr>
<tr>
<td>Glucocorticoid use (≥5 mg/day for ≥6 months)</td>
<td>Tobacco abuse</td>
<td>Low BMI</td>
</tr>
<tr>
<td>Hypogonadism (post-orchietomy or steroid induced)</td>
<td>Rheumatoid arthritis</td>
<td>Gastric resection</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Multiple myeloma or lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism or hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased fall risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(nursing home, gait disorder, dementia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family h/o osteoporosis</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from AAFP

**NOTE:** The development of osteoporosis in men is primarily due to aging and genetic predisposition. However, almost HALF of the men experiencing bone loss have at least one secondary risk factor.

### Is osteonecrosis of the jaw something all patients and practitioners should worry about? [Back to Top]

No, not ALL…

Rare but very serious postmarketing reports of bisphosphonate induced osteonecrosis have raised concern in patients, practitioners, and oral surgeons. Bisphosphonate associated osteonecrosis is the first reported long-term complication of therapy and many of the reported cases have been in patients receiving high dose IV bisphosphonates during the treatment of various cancers including multiple myeloma, bone metastasis, breast, prostate, and lung cancer. The question of how these case reports apply to patients being treated for osteoporosis in an outpatient setting remains uncertain. What we do know is that there have been very few instances of osteonecrosis in patients (with minimal risk factors) receiving oral bisphosphonates.

**IV formulations**

- Nitrogen-containing IV bisphosphonates
  - Pamidronate and zoledronic acid
    - pose the highest risk in certain patients

**Oral formulations**

- Nitrogen-containing bisphosphonates
- Alendronate and risedronate
  - have also been linked to osteonecrosis in certain patients

There are many other risk factors that appear to contribute largely to the occurrence of osteonecrosis:

- Cancer (highest risk)
- Infection
- Dental extraction
- Smoking
- Oral surgery with bone exposure
  - **No** cases have been identified in patients having restorative dental work, dental prophylaxis, conventional root-canal, orthodontic procedures, denture construction, or other routine dental procedures.

→ Duration of treatment and number of treatments have been implicated as risk factors. However, they **have NOT been proven**. Case reports have placed the *onset of osteonecrosis within the first few months* of therapy so it would be hard to say that the risk increases with length of bisphosphonate therapy.

- The International Myeloma Foundation surveyed 904 patients with multiple myeloma and 299 patients with breast cancer for risk factors for bisphosphonate associated osteonecrosis.
- The patients were taking pamidronate or zoledronic acid and were followed for at least 36 months.
- After observation, 10% of the patients receiving zoledronic acid and 4% of the patients receiving pamidronate developed osteonecrosis.
- This, and many other studies have implicated an increased risk of osteonecrosis in cancer patients (especially multiple myeloma) receiving IV bisphosphonates.


- After zoledronic acid was approved for the treatment of osteoporosis, researchers began to look closer at the instances of osteonecrosis.
- A major trial observed over 7,500 patients being treated with IV zoledronic acid 5mg once yearly for a total of 3 years.
- Within the follow up time, only one case of osteonecrosis was reported in the treatment group with one in the placebo group as well, making the risk for osteonecrosis no more than placebo.
- This and several other studies have suggested MINIMAL to NO risk of osteonecrosis in patients (with minimal risk factors) being treated with IV or oral bisphosphonates for osteoporosis.

**So what do we do for patients taking oral bisphosphonates who have multiple risk factors?**

- The benefits of using a drug holiday to prevent bisphosphonate induced osteonecrosis have not been established.
  - However, studies have supported their (drug holiday) use so it might be helpful. Considering the VERY long half lives of these drugs, benefit in this regard seems unlikely.
- Patients on a bisphosphonate with multiple risk factors should AVOID unnecessary invasive oral procedures, maintain pristine oral health, and as always, optimize the management of co-morbid disease states that put them at greater risk.

**Preserved bone mineral density versus bone quality: what are the true incidences of low-impact fractures**

One of the debatable topics surrounding bisphosphonate therapy is whether the extent of inhibition on bone resorption compromises the structure and quality of the preserved bone.

- In normal bone physiology day-to-day microdamage is repaired by osteoclast bone turnover.
- However, in the presence of a bisphosphonate bone turnover is suppressed which allows for accumulation of microdamage over time.
- Patients are thought to be at increased risk for low-impact fractures after long-term bisphosphonate therapy due to the over suppression of bone resorption, alteration of bone quality, and buildup of microcracks.
- These microcracks cause bone to become fragile and there are reports of patients with low-impact fractures and delayed healing after using bisphosphonates.

It is important to take into account that most of the data supporting the risk of low-impact fractures is after long-term treatment with a bisphosphonate. The short-term benefits of increasing bone mineral density, reducing fracture risk, and improving bone strength have been well documented for all bisphosphonates.

- With these two statements, it appears that there is a need for guidelines to clarify how long patients should receive bisphosphonates.
- Some literature suggests that bisphosphonates should be stopped after 5 years in low to moderate risk patients and they can continue on Ca++ and vitamin D.
- In high risk patients it would be crucial to initiate an alternative therapy (calcitonin, teriparatide) following the discontinuation of a bisphosphonate.
What are the benefits and drawbacks of using long-term continuous therapy versus giving “drug holidays”?  

The idea of a “drug holiday” during bisphosphonate therapy is supported by their unique mechanism of action. Bisphosphonates have been found to last within skeletal bone for years and during bone resorption they are released back into the bloodstream. This mechanism allows for prolonged antiresorptive action, even after discontinuation of the drug.

Given the controversy regarding effects of bisphosphonates effect on bone quality and the reports of low-impact fractures, some practitioners and patients are looking for an alternative to continuous, long-term bisphosphonate therapy. A “drug holiday” lasting around one year hasn’t been shown to increase fracture rates and could be a viable option for certain patients.

This discontinuation period has NOT been adequately studied and is NOT recommended in HIGH-risk patients.

**Literature Highlights:**
A recent study identified over 9,000 women from a national database who were using common bisphosphonate therapies for at least 2 years. They compared the rates of hip fracture among the women that continued therapy and those who discontinued and found that discontinuation of bisphosphonate therapy was associated with more hip fractures (8.43 versus 4.67 per 1000 person years).

Researchers then identified women within the same groups who were using a bisphosphonate for 3 or more years and women with exceptionally high adherence rates. Among these women, there was NO increased risk of hip fracture upon discontinuation of the bisphosphonate.

The results of this study support the idea that the benefits of persistent bisphosphonate therapy of 3 or more years would not be diminished by instituting a “drug holiday”.

A follow up analysis to the FIT study took women who had been taking alendronate for an average of 4.5 years and randomized them to either placebo or alendronate for an additional 5 years. Results indicated that although spine BMD increased slightly in the alendronate group and decreased slightly in the placebo group, there was NO difference in the number of clinical fractures or morphometric vertebral fractures between the two groups.

Given that fracture endpoints are better indicators of risk than BMD endpoints, this follow up study supports the use of a “drug holiday”.

**Benefits**
- Decreased risk of low-impact fracture
- Maintained bone quality
- Decreased cost
- Decreased side effects

**Drawbacks**
- Risk of fracture (low)
- Decreased BMD (slight)
- Risk of noncompliance

**Does patient compliance significantly affect the benefits seen with bisphosphonates?**

Some social, economic, and observational studies says YES…

They suggest that noncompliance does lead to compromised benefit, increased risk of fracture, increased hospitalizations, as well as increased health care costs.

**Literature Highlight:** “S. Rietbrock, M. Olson and T.P. van Staa. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. QJM. 2008;102(1):35-42.”

A study done in the UK observed adherence rates in a very large group (44,531) of women using bisphosphonates for osteoporosis. After collecting data such as age, gender, bisphosphonate dose, fracture risk factors, and compliance
(medication possession ratio) the researchers designed a patient-based decision model to estimate the probability of fracture outcomes in different scenarios over a 4-year time period (3 years bisphosphonate and 1 year off).

- Results claimed that an increase of 10% adherence for a typical patient would prevent 14.4 more hip fractures per 10,000 patients.
- They also found that if patients taking weekly therapy were to be switched to yearly treatment (essentially no room for noncompliance), it would prevent 68.4 more hip fractures per 10,000 patients.
- The authors concluded that...

   “Improvements in treatment persistence and compliance may improve the impact of bisphosphonates in reducing the risk of fractures. Yearly administration may also improve the impact on fracture risk reduction, unless long-term persistence is substantially reduced.”


In 2008 the Osteoporosis Foundation published an economic study evaluating the effect of compliance on health care costs in women taking daily or weekly alendronate.

- Persistence and compliance were the two main endpoints measured over a total of 3 years in 32,000 women.
- Compliance was defined by medication possession ratio and persistence was the presence of no refill gaps of greater than 30 days.
- Results demonstrated that total health care costs were 8.9% lower for persistent patients 3.5% lower for compliant patients.
- Another interesting and relevant conclusion was that patients who were deemed persistent had a 47% reduction in hospitalizations.

**What about bisphosphonates in patients with renal impairment?**

See comparative chart above [Link]

**How concerned should we be about the association of bisphosphonates and risk of serious atrial fibrillation?**

Currently, there is a lack of evidence to conclude that serious cases of atrial fibrillation are linked to bisphosphonate therapy. However, further studies might provide more insight into the issue.

- The concerns about serious atrial fibrillation occurring with bisphosphonate therapy were first addressed after the HORIZON Trial[30] found that 1.3% of women receiving IV zoledronic acid experienced life threatening atrial fibrillation (versus 0.5% placebo).
- These findings lead to further observational studies, one of which was able to demonstrate a nonsignificant trend of increased atrial fibrillation with alendronate.[31]
- Results from three more observational studies[32-34] consistently found NO increased risk with bisphosphonate use.

The FDA looked into both adverse event reporting data AND data from original clinical trials and found NO association between bisphosphonate use and increased atrial fibrillation.[35]

FDA News Drug Daily Bulletin:

“Bisphosphonates Get FDA OK After Heart Risk Review

After reviewing data on a potentially increased risk of atrial fibrillation in patients receiving bisphosphonates to treat bone disease, the FDA advises physicians not to change their prescribing habits. “No clear association between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation was observed,” the FDA says in a statement. The agency says it is considering whether to seek additional epidemiological studies and will keep monitoring postmarket reports of arrhythmia in bisphosphonate patients.”

Regardless of the fact that researchers and the FDA were unable to identify a link between atrial fibrillation and bisphosphonate use, package inserts still list this as an adverse event. It’s important to clarify the implications of this specific adverse event with concerned patients.
Wrong answer...try again or read on.

[Back to quick-read info and quiz question]

Some Key references:

Individual product information sheets for each drug were also utilized. Links to each provided in first chart.

References:

34. FDA. Update of safety review follow-up to the October 1, 2007 early communication about the ongoing safety review of bisphosphonates. Silver Spring, MD: US Food and Drug Administration; 2008.