Wednesday, June 29, 2011

VIRTUAL EDUCATION FORUM
Osteoporosis Medications and You

Presented by: Dr. Rowena Ridout MD FRCPC
UHN/MSH Osteoporosis Program

Moderator: Tanya Long, National Education Manager

Presentation Times by Time Zones
PT: 10:00 a.m. to 11:30 a.m.
MT: 11:00 a.m. to 12:30 p.m.
CT: 12:00 p.m. to 1:30 p.m.
ET: 1:00 p.m. to 2:30 p.m.
AT: 2:00 p.m. to 3:30 p.m.
What is Osteoporosis?

2000 NIH Definition

A skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture.

Bone strength reflects the integration of two main features; bone density and bone quality.

Osteoporotic bone with trabecular thinning and perforation

Bone Remodeling

Remodeling completed

Resting stage

Initiation

Resorption

(~ 2 week process)

Osteoclast

Reversal phase

Formation

osteoblasts

Bone Remodeling Imbalance after Menopause

Osteoclasts  >  Osteoblasts

Bone resorption  >  Bone formation

Net bone loss  ➔  low bone mass  ➔  osteoporosis
Modalities Used to Prevent Fracture

Lifestyle modifications
- Vitamin D
- Calcium
- Exercise
- Falls prevention

Pharmacologic therapy
- Anti-resorptives
  - Bisphosphonates
  - Calcitonin
  - Denosumab
  - Hormone therapy
  - Raloxifene
- Anabolic agents
  - Parathyroid hormone
Medications Approved for Osteoporosis in Canada

- Bisphosphonates—oral and IV
- Calcitonin
- Denosumab (RANK ligand inhibitor)
- Hormone therapy
- Raloxifene (SERM)
- Teriparatide (PTH analogue)
Who Needs Drug Therapy?

Fracture Risk Assessment

FRAX Canada 3.1

CAROC 2010
Initial BMD testing

Assessment of fracture risk

**Low risk**
(10-year fracture risk < 10%)
- Unlikely to benefit from pharmacotherapy
- Reassess in 5 yr

**Moderate risk**
(10-year fracture risk 10%-20%)
- Lateral thoracolumbar radiography (T4-L4) or vertebral fracture assessment may aid in decision-making by identifying vertebral fractures

**High risk**
(10-year fracture risk > 20% or prior fragility fracture of hip or spine or > 1 fragility fracture)
- Always consider patient preference

Good evidence of benefit from pharmacotherapy

Factors warranting consideration of pharmacologic therapy...
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Factors warranting consideration of pharmacologic therapy:
- Additional vertebral fracture(s) (by vertebral fracture assessment or lateral spine radiograph)
- Previous wrist fracture in individuals aged > 65 and those with T-score ≤ -2.5
- Lumbar spine T-score << femoral neck T-score
- Rapid bone loss
- Men undergoing androgen-deprivation therapy for prostate cancer
- Women undergoing aromatase inhibitor therapy for breast cancer
- Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use
- Recurrent falls (≥ 2 in the past 12 mo)
- Other disorders strongly associated with osteoporosis, rapid bone loss or fractures

Repeat BMD in 1-3 yr and reassess risk

Good evidence of benefit from pharmacotherapy
Pharmacological Therapy

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women*

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Antiresorptive Therapy</th>
<th>Bone Formation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Vertebral</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hip</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Non-Vertebral*</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

+ In clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

* For postmenopausal women, ✓ indicates first line therapies and Grade A recommendation. For men requiring treatment, alendronate, risedronate, and zoledronic acid can be used as first line therapies for prevention of fractures [Grade D].

** Estrogen or hormone therapy can be used as first line therapy in women with menopausal symptoms.
Bisphosphonates

How do they work?

- Bind to the surface of bones
- Taken up by osteoclast
- Slow down the resorbing action of osteoclasts
  - Stop ongoing bone loss
  - Improve bone strength
## Oral Bisphosphonates

<table>
<thead>
<tr>
<th>Drug (Brand name)</th>
<th>Dosing Schedules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax®, Fosavance®)</td>
<td>10 mg daily</td>
</tr>
<tr>
<td></td>
<td>70 mg weekly</td>
</tr>
<tr>
<td>Risedronate (Actonel®, Actonel Plus Calcium®)</td>
<td>5 mg daily</td>
</tr>
<tr>
<td></td>
<td>35 mg weekly</td>
</tr>
<tr>
<td></td>
<td>150 mg monthly</td>
</tr>
<tr>
<td>Etidronate (Didrocal®)</td>
<td>Cyclical therapy of daily 200 mg for 14 days followed by calcium supplements for 10 weeks</td>
</tr>
</tbody>
</table>
How to Take Oral Bisphosphonates

- First thing in the morning on an empty stomach (except for etidronate)
- With water (not coffee, tea, etc.)
- Avoid Calcium supplements with breakfast
- Tablet should not be crushed or chewed
- Don’t eat or take other medication for ½ -1hr
- Don’t lie down for 30 minutes
## Side Effects of Oral Bisphosphonates

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI irritation</td>
<td>Common</td>
</tr>
<tr>
<td>Esophageal erosions</td>
<td>Rare</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Controversial</td>
</tr>
</tbody>
</table>
Who Should not Take Bisphosphonates

- Women who are pregnant or planning a pregnancy
- Chronic kidney disease
- Hypocalcemia (low blood calcium)
- Vitamin D deficiency
- Osteomalacia
- Serious esophageal disease
- Patients unable to stay upright
## IV Bisphosphonates

<table>
<thead>
<tr>
<th>Drug (Brand name)</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid (Aclasta®)</td>
<td>5 mg intravenously once yearly</td>
</tr>
</tbody>
</table>
# Side Effects of IV Bisphosphonates

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Common</td>
</tr>
<tr>
<td>Transient leukopenia</td>
<td>Mild, no symptoms</td>
</tr>
<tr>
<td>Acute phase reaction</td>
<td>Common, lasts 1-3 days</td>
</tr>
<tr>
<td>Eye inflammation</td>
<td>Rare</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Rare</td>
</tr>
</tbody>
</table>
## Side Effects of Bisphosphonates

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia</td>
<td>Mild common, severe rare</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Rare</td>
</tr>
<tr>
<td>? Atrial fibrillation</td>
<td>FDA found no association</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>Unusual</td>
</tr>
<tr>
<td>Subtrochanteric fracture</td>
<td>Rare, after long-term use</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>High dose, primarily IV, cancer</td>
</tr>
</tbody>
</table>
Subtrochanteric Fractures

- Subtrochanteric or shaft of the femur
- Minimal or no trauma
- Often preceded by thigh pain
- Bilateral in 47% of cases
- Patients younger than typical femur fractures (mean age 64)
- Bisphosphonate use longer than 5 years in 75% of cases
- Specific X-ray findings (thick cortices)
Hip Fractures

Subcapital
Femoral neck
Inter trochanteric
Subtrochanteric
Fracture of the greater trochanter
Fracture of the lesser trochanter
Other Medications

<table>
<thead>
<tr>
<th>Drug (Brand name)</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin (Miacalcin®)</td>
<td>200 IU intranasally daily</td>
</tr>
<tr>
<td>Denosumab (Prolia®)</td>
<td>60 mg subcutaneous injection every six months</td>
</tr>
<tr>
<td>Hormone therapy (many formulations)</td>
<td>Many dosing schedules</td>
</tr>
<tr>
<td>Raloxifene (Evista®)</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>20 µg subcutaneouslyally daily</td>
</tr>
</tbody>
</table>
Calcitonin

*How does it work?*
- Inhibits the action of osteoclasts

*Common side effects*
- Nasal congestion and dryness
- Occasional nose bleeds
Denosumab

**How does it work?**
- Inhibits the development and activation of osteoclasts

**Common side effects**
- Muscle and joint pain
- Skin rash
- Skin infections
Hormone Therapy (estrogen +/- progesterone)

**How does it work?**
- Blocks bone resorption by osteoclasts
- Used at menopause when estrogen levels fall

**How is it prescribed?**
- Pills, patch, gel
- In combination with progesterone in women with an intact uterus
Hormone Therapy

**Common side effects**  
- Increased risk of heart attack, stroke and breast cancer  
- Increased risk of blood clots  
- Vaginal bleeding  
- Headaches  
- Breast tenderness
Hormone Therapy

**When is it used?**
- In women with menopausal symptoms

**When should it not be used?**
- Active thromboembolic or vascular disease
- Acute liver disease
- Unexplained vaginal bleeding
- Breast cancer
Raloxifene

**How does it work?**
- Acts like estrogen at some sites (bone)
- Blocks estrogen effects at some sites (breast, uterus)

**Common side effects**
- Hot flushes
- Leg cramps
- Increased risk of blood clots
Parathyroid Hormone

How does it work?

- Activates osteoclasts
- Increases bone formation

Common side effects

- Dizziness
- Nausea
- Leg cramps
- Hypercalcemia (elevated blood calcium)
- Redness/tenderness at injection site
Effect of Parathyroid Hormone on Bone Structure

Before

After

Parathyroid Hormone

When is it used?

- Severe osteoporosis with compression fractures
- Fractures despite prolonged bisphosphonate use
- Can be used in steroid-induced osteoporosis
Parathyroid Hormone

*When should it not be used?*

- Renal failure
- Kidney stones
- Hyperparathyroidism/hypercalcemia
- Paget’s disease
- Extensive radiation
- Don’t use in:
  - children or young adults
  - women who are pregnant or nursing
Importance of Adherence in Treatment Success

- The expectation is that treated patients will experience anti-fracture benefits similar to those reported in clinical trials.
- Suboptimal adherence reduces or eliminates anti-fracture benefits\(^1\)\(^-\)\(^3\).

Non-adherence in Osteoporosis Therapy

- **Types of non-adherence:**
  - Frequently missed doses
  - Failing to take the medication correctly to optimize absorption and action
  - Discontinuation of therapy

- **Reported one-year adherence rates:** 25% – 50%1,3
  - Marginally better with less frequent dosing regimens

Taking 50% of the Medication is the Same as Not Taking Any

Refill Compliance (MPR) Over 24-Month Period

Probability of Fracture

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

0.070
0.075
0.080
0.085
0.090
0.095
0.100
0.105
0.110
0.115
0.120

A B C

No benefit

MPR = medication possession ratio.
A = a refill compliance level equivalent to taking one dose in every two;
B = equivalent to missing one weekly dose a month;
C = equivalent to missing 1 month out of 12 months.

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QUESTION AND ANSWER

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