Osteoporosis Medications: Benefits and Risks in 2013

Virtual Education Forum
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Outline

• Who needs medication for osteoporosis?
• What are the choices of medications?
• What are the benefits?
• What are the risks?
• How long should treatment be?
• What’s new and coming soon?
Osteoporosis “porous bone”

• Skeletal disorder of comprised bone strength
  • Low bone density (quantity)
  • Deterioration of bone microarchitecture (quality)

• most serious consequence is fragility fracture
  • A fracture that occurs spontaneously or from minor trauma (such as a fall from standing height or less)
Bone Strength

- Bone Density
- Bone Architecture
- Bone Mineral
- Bone Turnover

Courtesy of Dr. Sophie Jamal
Bone Density using DXA

- Osteoporosis:
  T-score ≤ -2.5
- Correlate with fracture risk
- Captures one component of risk
Common Sites for Fracture

Spine

Hip

Wrist

Courtesy of Dr. Sophie Jamal
Incidence of Osteoporotic Fractures in Canadian Women

- Hip: 21,200
- Wrist: 22,000
- Pelvic: 31,100
- Other: 37,000
- Vertebrae: 39,500

Total Osteoporotic Fractures: 138,600

- Heart Attack: 19,500
- Stroke: 22,300
- Breast Cancer: 20,000

Consequences of Fractures

- More fracture(s)
- Chronic pain
- Immobility
- Loss of independence
- Decreased quality of life
- Institutionalization
- Costs to healthcare
- Death
Many people who have sustained a fragility fracture do NOT appreciate the link to osteoporosis.
Who Needs Medication for Osteoporosis?

- Men and women at HIGH fracture risk
  - Based on risk factors
  - Estimation of 10-year fracture risk >20%

- If you had a spine or hip fracture, or multiple fragility fractures, you are HIGH risk for more fractures
Fracture Risk Assessment

Canadian CAROC Tool

WOMEN

-4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0.0

FEMORAL NECK T-Score

AGE (years)

LOW RISK

MODERATE RISK

HIGH RISK

<10%

10-20%

>20%

Hip / vertebral fracture

High risk (> 20%)

> 1 non-vertebral fragility fracture

Fragility fracture after age 40

Prolonged corticosteroid therapy*

Fracture Risk Assessment

FRAX tool (by WHO)

• Computes 10-yr absolute risk for hip fracture or major osteoporotic fracture
  ▪ Gender, Age
  ▪ Bone density at femoral neck
  ▪ Fragility fracture
  ▪ Glucocorticoid use
  ▪ Low weight (BMI)
  ▪ Smoking, Excess Alcohol
  ▪ Parental hip fracture
  ▪ Rheumatoid arthritis or other secondary causes
Who Needs Medication?

- **LOW:** NO Treatment
- **MODERATE:** Depends - other Risk factors
- **HIGH:** YES – need Rx
What are the BENEFITS of Medications?

- Reduction of fracture risk by approximately 50%
- Improve or stabilize bone density
- HIGH risk patients benefit the most
What are the RISKS of Medications?

- No medication is absolutely safe
- All drugs have side effects
- Safe means that benefits of drug therapy outweigh the risks for a person
- Rare concerning risks:
  - Osteonecrosis of the Jaw (ONJ)
  - Atypical Femur Fracture (AFF)
Osteoporosis Medication Choices

**Anti-Resorptive (Inhibits Bone Loss)**
- Bisphosphonates
  - Alendronate (Fosamax)
  - Risedronate (Actonel)
  - Zoledronic Acid (Aclasta)
- Denosumab (Prolia)
- Raloxifene (Evista)
- HRT

**Anabolic Agent (Bone Forming)**
- Teriparatide (FORTEO)
Bone Remodelling Cycle

Healthy Bone → Resorption ≈ Formation

Menopause, Aging, Disease, Drugs → Resorption > Formation
Bisphosphonates

Bisphosphonates bind to bone and inhibit osteoclasts.
Bisphosphonates

- Alendronate oral weekly (Fosamax®, Fosavance®)
- Risedronate oral weekly or monthly (Actonel®, Actonel DR®)
- Zolendronic Acid IV yearly (Aclasta®)

Benefits
- Reduces all fracture types
  - Vertebral/spine
  - Hip
  - Non-vertebral
- Longest experience
- Oral or IV options
- Long retention in bone
- Reduce mortality (iv Zol)
- Other benefits?
  - Decrease breast cancer?
  - Decrease colon cancer?

Risks
- GI issues/acid reflux (oral)
  - Inconvenience (oral)
  - Poor absorption (oral)
- Acute phase reaction (iv)
- Kidney toxicity (iv)
- ONJ
- AFF
- Muscle/bone ache?
- ?esophageal cancer
- ?Atrial fibrillation
- ?eye inflammation
Osteonecrosis of Jaw (ONJ)

• Exposed bone in jaw area for 8 weeks or longer in absence of radiation therapy
• More common in cancer patients on high dose, high frequency bisphosphonates
• Rare risk: 1/10000 to 1/100000
• Mechanism unclear
• Accumulation dose effect
• Associated with invasive dental surgeries, poor dental hygiene and dental infection
Approach to ONJ

• Remember risk is very low
• Good dental care and hygiene
• Dental surgeries before start BP agent
• Inform about planned dental extractions
• American Dental Association (Nov 2011)
  ▪ No need to modify dental surgery if on BP agent
  ▪ No need to stop BP if need dental surgery
    (may not decrease risk of ONJ but may increase osteoporosis-related risks)
Atypical Femur Fracture (AFF)

- Unusual fracture of femur below hip joint
- No trauma or minimal trauma
- Complete or incomplete
- Rare: 1 to 5 cases per 10000 patient-years
- Related to duration of BP use
- Increased risk > 5 yrs on BP
- Unclear mechanism
- Prodromal thigh pain
- Up to 60% occur both femurs
Approach to AFF

• Remember that the risk is low
• Review risk of fracture, the benefit to risk ratio of continuing longterm BP therapy at every assessment visit
• Watch for thigh pain/discomfort
How long to treat with Bisphosphonate?

• Long retention in bone
• Unknown optimal duration of therapy
• Not much long-term studies (most 3-5 yrs)
• Longest clinical study is 10 years (FLEX trial)
• Many women who stopped Fosamax after 5 years did not have increased fracture (residual benefit)
• But women at high risk (prior vertebral fracture or very low BMD at hip) appeared to have continued benefit beyond 5 yrs
Drug Holiday?

• Based on sparse data
• **LOW risk** → can safely stop drug
• **MODERATE risk** → consider drug holiday after 3-5 years of stability
• **HIGH risk** → continue or switch to another effective agent without drug holiday (OC guidelines 2010)
• Consider drug holiday or switch agent after 10 years (AACE guidelines 2010)
• Restart treatment after 1-2 years?
• During drug holiday → monitor bone density and for fractures
Health Canada (Dec 2011)

• “Although the risk is higher with bisphosphonate use, it is extremely small. The benefits of using bisphosphonate drugs in preventing fractures associated with osteoporosis outweigh the risk of an atypical femur fracture”

• Decision to stop or continue bisphosphonate must be based on individual risks, benefits and preference
Denosumab (Prolia)

RANK Ligand

Denosumab
RANK Ligand
Inhibitor
**Denosumab**

- **Prolia® 60mg SC every 6 months**

### Benefits
- Reduces all fracture types
  - Vertebral/spine
  - Hip
  - Non-vertebral
- SC injection (no GI effect)
- May be more potent vs BP
- No retention in bone
- But extended (legacy) effect
- Not excreted by kidneys

### Risks
- Less experience (newer)
- Low blood calcium
- Skin infections
- Skin rash, eczema
- ONJ
- AFF
Raloxifene and Estrogen

Raloxifene and Estrogen reduce RANK Ligand.
# Raloxifene (SERMS)

- **Evista® 60mg PO daily**

## Benefits
- Reduces only vertebral fractures
- Reduces breast cancer
- Not associated with ONJ or AFF

## Risks
- No hip fracture protection
- Increased risk of blood clots
- Increased risk of heart disease and stroke
- Leg cramps
- Hot flashes
Estrogen (HRT)

- Postmenopausal women with menopausal symptoms

### Benefits

- Reduces all fracture types
  - Vertebral/spine
  - Hip
  - Non-vertebral
- Alleviates menopausal symptoms
- Not associated with ONJ or AFF

### Risks

- Increased risk of blood clots
- Increased risk of heart disease and stroke
- Increased risk of breast cancer
- Increased risk of estrogen-dependent tumors
Teriparatide (FORTEO)
**Teriparatide**

- **FORTEO® 20 mcg SC daily**

### Benefits

- Reduces vertebral fractures and non-vertebral fractures
- Bone forming agent
- Improves BMD well
- SC injections (no GI issues)
- Not associated with ONJ or AFF
- May help fracture healing
- May reduce back pain

### Risks

- High blood calcium
- Nausea, dizziness
- Leg cramps
- Kidney stones
- Black box warning of bone cancer in rat studies
- Only approved for 2 years
Osteoporosis Medications
Balance Benefits vs Risks

**BENEFITS**
- Reduce fracture
- Improve quality of life
- Reduce mortality

**RISKS**
- Fracture…more fractures
- Reduce quality of life
- Increase mortality
- ONJ (rare)
- AFF (rare)
Perception vs Reality

- Fracture Risk without Tx: 25%
- Fracture Risk with Tx: 12.5%
- ONJ: 0.01%
- AFF: 0.5%
- Fatal MVA: 0.11%
- Murder: 0.06%
Informed and Shared Decision Making

• Individualized approach
  ▪ What is my 10-yr fracture risk?
  ▪ Does the benefits outweigh risks?
  ▪ Preference based on pros/cons

• Other things to consider
  ▪ Prior experience/response
  ▪ Convenience/adherence
  ▪ Cost/affordability

• Monitor and regular re-assessments of fracture risk, tolerance, side effects and benefit/risk ratio
Other Important Factors

• Calcium 1000-1200 mg (combined diet +/-supplement)
• Vitamin D 800-2000 units
• Weight-bearing exercises
• Fall prevention
• Avoid smoking, excess alcohol
• Reverse underlying secondary causes
What’s new and coming?

• Novel molecular targets for therapy
• Sclerostin inhibitors (Anabolic agent)
  ▪ Sclerostin blocks bone formation
  ▪ Monoclonal Ab against sclerostin
• Cathepsin K inhibitors (Anti-Resorptive)
  ▪ Cathepsin K is an enzyme made by osteoclast cells that degrades bone
• Combination therapy (Teriparatide together with Denosumab)
Summary

• Focus on the 10-yr fracture risk
• Osteoporosis medication recommended if HIGH risk for fracture
• Many choices of medications
• Very good anti-fracture effectiveness
• Overall safe with rare risks
• Individualized approach (benefit vs risk)
• Promising new therapies coming soon
Questions?
Evaluation

www.surveymonkey.com/s/virtualeducationforum
Upcoming Virtual Education Forum

Men and Osteoporosis:
So you think it can’t happen to you?

- Friday, November 8, 2013
- 1:30 to 3:00pm EST
- Speaker:
  Jonathan D. Adachi MD, FRCPC, St. Joseph’s Healthcare - McMaster University

www.osteoporosis.ca