Drug-Induced Osteoporosis

Bone Matters Webinar

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Conflicts of Interest

- I have been on Advisory Boards/Speakers Bureaus for Pfizer Canada and Merck Canada
What is Drug Induced Osteoporosis?

Medications that can cause bone loss and fractures
Objectives

1. To understand the effects of drug induced osteoporosis.
2. To consider how drugs that may affect bone health are assessed.
3. To review the management of drugs leading to bone loss and fractures.
4. To discuss common agents associated with drug-induced bone loss and/or fractures.
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Introduction

- Osteoporosis is a major public health concern.
- One in 3 women and one in 5 men over the age of 50 will suffer a broken bone from osteoporosis.
- Many classes of drugs have been shown to lower bone density and/or increase fracture risk.\(^2\)
- The overall incidence of drug induced osteoporosis is not known.

What is the Issue?

- People are not always screened and actions are not always taken to prevent drug induced osteoporosis.
- Careful screening and assessment is required to manage drug induced osteoporosis.
- Though guidelines exist for a few drugs that affect bone health, guidelines do not exist for many of them.
Objectives

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Considerations When Assessing Drugs That Impact Bone Health

- The “cause and effect” on bones has not been proven for all drugs.
- Mechanism of action of the drugs on bones is not clear.
- Need to consider other factors as well that may impact bones.
Considerations When Assessing Drugs That Impact Bone

Need to consider other factors:

- Effect of the underlying disease on bone health.
- Effect of other drugs taken at the same time to treat the underlying disease.
- Effect of the medication on falls.
Things to think about when looking at drugs that impact bones...

- How does the drug affect bone health? does it decrease bone density? can it lead to fractures?
- What is the mechanism of action on bones?
- How good are the studies?
- Is the effect on bones dependent on: dose of the drug? how long the drug is used?
How to Assess Drugs that Impact Bone Health

- How do we identify people at highest risk of bone loss/fracture?
- What can be done to prevent bone loss/fractures?
- Are there guidelines to guide us?
## Drugs Shown to Impact Bone Health

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Bone Mineral Density (BMD)</th>
<th>Fracture risk</th>
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<tbody>
<tr>
<td>Glucocorticoids</td>
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<td>Aromatase Inhibitors</td>
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<td>Androgen Deprivation Therapy</td>
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<tr>
<td>Anticonvulsants</td>
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<td>Proton Pump Inhibitors</td>
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<td>Selective Serotonin Reuptake Inhibitors</td>
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<td>Thiazolidinediones</td>
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<td>Depot medroxyprogesterone (DMPA)</td>
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<td>Anticoagulants: chronic heparin therapy</td>
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<td>warfarin</td>
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<td>Loop diuretics</td>
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<td>Excess thyroid replacement</td>
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<tr>
<td>Certain antiretrovirals</td>
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**Stronger evidence**

- Glucocorticoids
- Aromatase Inhibitors
- Androgen Deprivation Therapy
- Anticonvulsants
- Proton Pump Inhibitors
- Selective Serotonin Reuptake Inhibitors
- Thiazolidinediones
- Depot medroxyprogesterone (DMPA)
- Anticoagulants: chronic heparin therapy
  - warfarin
- Loop diuretics
- Excess thyroid replacement
- Certain antiretrovirals
Objectives

1. To understand the effects of drug induced osteoporosis.
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Screen for Drugs that Impact Bone Health

To identify people at high risk of bone loss/fractures
To treat those at high risk of bone loss/fractures

Assessing risk:
- Tools to assess fracture risk based on risk factors and bone density (ie FRAX, CAROC)
- Issue is that these are not designed to assess fracture risk for all drugs (other than glucocorticoids)
Managing Drugs That Affect Bone Health

General recommendations

Balance the benefits of treatment to risk of bone loss or fractures

Reassess need for that medication if possible

Use lowest dosage, shortest duration

Adequate calcium and vitamin D

Consider lifestyle measures
Lifestyle Measures

Be educated on risk factors and lifestyle measures

- **Exercise** – ~30 minutes physical activity most days of the week
- **Stop smoking**
- **Limit alcohol intake** (<2 drinks per day)
- **Limit caffeine** (<400 mg daily, ~4 cups of coffee)
- **Reduce fall risk** – be careful of medications that increase risk of falls

Papaioannou A et al. CMAJ 2010;182:1864-1873,
Management of Drug Induced Osteoporosis

Options include:
Consider switching to different medication if possible.
Or
Start osteoporosis medications to prevent bone loss or fractures if high risk.
Or
No additional action, lifestyle measures only.
Objectives

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Glucocorticoids are a common cause of drug induced osteoporosis
  – Glucocorticoids includes prednisone, dexamethasone

Role: anti-inflammatory, used for many conditions

Mechanism:
  – Reduces activity of bone forming cells (osteoblasts)
  – Increases activity of bone cells that break down bone (osteoclasts)

Glucocorticoids

- Effect on bones depends on dose and duration of glucocorticoid\(^1\)
  - Concerned with doses of 7.5 mg prednisone daily for 3 months or more (in previous year)
- Bone loss can start in first 6 months\(^1,2\)
- Mainly occurs with systemic routes (ie pills, injection)
- There are guidelines to help manage

Glucocorticoids

How to manage:

- Get bone density, assess fracture risk
- Reduce dose of glucocorticoid to lower dose if possible or discontinue if not needed
- Educate on risk factors/lifestyle measures
- Start osteoporosis medications if on 7.5 mg prednisone for longer than 3 months of therapy

(or if lower dose such as >2.5 mg/day and moderate to high risk of fractures)

Glucocorticoids

- Osteoporosis medications for preventing bone loss and fractures with glucocorticoids:
  - oral bisphosphonates (alendronate, risedronate)
  - Others:
    - intravenous bisphosphate (zoledronic acid)
    - denosumab
    - teriparatide
Aromatase Inhibitors for Breast Cancer

- **Role**: treatment for hormone receptor positive breast cancer
- **Mechanism for bone loss**: prevent estrogen production in the body, estrogen levels become very low

### Types

- Aromatase Inhibitors:*
  - Letrozole (Femara®)
  - Anastrazole (Arimidex®)
  - Exemestane (Aromasin®)

Aromatase Inhibitors

- Most bone loss occurs in first year after starting.
  - Reversible on discontinuation
- Guidelines available

Aromatase Inhibitors

Who to treat?

- Get bone density, look at risk factors
- Assess fracture risk
- Educate risk factors/lifestyle measures
- Start osteoporosis medications if high risk for bone loss and/or fracture

Aromatase Inhibitors

Options for Treatment:

- oral bisphosphonates (alendronate, risedronate)
- intravenous bisphosphonates (zoledronic acid)
- denosumab

Androgen Deprivation Therapy (ADT) For Prostate Cancer

- Role: treatment for prostate cancer
- Mechanism for bone loss:
  – decrease testosterone in the body

### Types

<table>
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<tr>
<th>Types</th>
<th>Medications</th>
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<tr>
<td>GnRH Agonists</td>
<td>Leuprolide (Eligard®)</td>
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<tr>
<td></td>
<td>Goserelin (Zoladex®)</td>
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<tr>
<td>Androgen receptor blockers</td>
<td>Enzalutamide (Xtandi®)</td>
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<tr>
<td>Androgen synthesis inhibitors</td>
<td>Bicalutamide (Casodex®)</td>
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<td>Abiraterone (Zytiga®)</td>
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Androgen Deprivation Therapy (ADT)

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Androgen Deprivation Therapy (ADT)

Who to treat?
- Get bone density, look at risk factors
- Assess fracture risk
- Educate risk factors/lifestyle measures
- Start osteoporosis medications if high risk for bone loss and/or fracture

Androgen Deprivation Therapy (ADT)

Options for treatment:

- oral bisphosphonates (alendronate, risedronate)
- intravenous bisphosphonates (zoledronic acid)
- denosumab

Note some guidelines state preference for denosumab over bisphosphonates—shown to decrease fractures in this population.¹

Proton Pump Inhibitors (PPI)

- **Role:** acid suppression

- **Mechanism of effect on bones:** not known\(^1\)
  - Theory: PPI suppress acid secretion, ↓ calcium absorption
  - Possibly direct action on osteoclasts

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<td>Proton pump inhibitors: omeprazole, esomeprazole, lansoprazole, deslanzoprazole, pantoprazole, rabeprazole</td>
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Proton Pump Inhibitors (PPI)

- Increases risk of fractures, but bone loss not clearly associated.\(^1\)
- Risk is with higher doses and longer duration of use.
- Fracture risk goes down when PPI discontinued\(^2\)
- PPI use may also increase risk of falls.

2. Panday et al. Therapeutic Advances in Musculoskeletal Disease. 2014;6(5):185–20,
Proton Pump Inhibitors

No guidelines available to guide

Suggestions:

- Stop PPI if not needed
- Use lowest dose, shortest duration
- Consider switching to a different drug (ie ranitidine)

Note: If taking a calcium supplement, use calcium citrate if on a PPI

1. Panday et al. Therapeutic Advances in Musculoskeletal Disease. 2014;6(5):185–20,
2. Farrell et al Canadian Family Physician May 2017, 63 (5) 354-364
Anticonvulsants

- Mechanism not well understood
  - May increase breakdown of vitamin D in body

- Fractures may also be associated with seizures

Types

Anticonvulsants at risk:
phenytoin,
phenobarbital,
carbamazepine,
valproic acid,
topiramate

Anticonvulsants

No guidelines available to guide.

Suggestions:

- Screen for risk factors for osteoporosis.
- Consider lifestyle measures for bone health.
- Some people may require higher vitamin D doses (i.e. 2000 – 4000 IU)
- Change to a different anticonvulsant without bone effects if concerns about risk.

Selective Serotonin Reuptake Inhibitors (SSRI)

- Role: antidepressant
- Mechanism on bones not very clear.
  - May be direct effect on serotonin receptors on bone.

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<td>SSRI’s: fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine</td>
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Selective Serotonin Reuptake Inhibitors (SSRI)

- Increase in fractures, bone loss not clear.
- Complicating factor: SSRI’s can increase fall risk.
- Increase in fracture risk has been seen within few weeks of starting SSRI
  - Falls may be the initial reason for increase fractures
Selective Serotonin Reuptake Inhibitors (SSRI)

No guidelines available to guide.

Suggestions:

- Use lowest doses of SSRI
- Screen for risk factors for osteoporosis
- Consider lifestyle measures for bone health
- Change to a different antidepressant if concerns about bone health
Final Points

When using drugs with negative effects on the bone:
– Consider the benefits to risks of using the drug
– Assess bone health and risks of fractures
– Consider other factors that may increase fracture risk (i.e. fall risk)
– Remember lifestyle approaches for bone health, including calcium and vitamin D, exercise, and quitting smoking.