Drug-Induced Osteoporosis

Bone Matters Webinar

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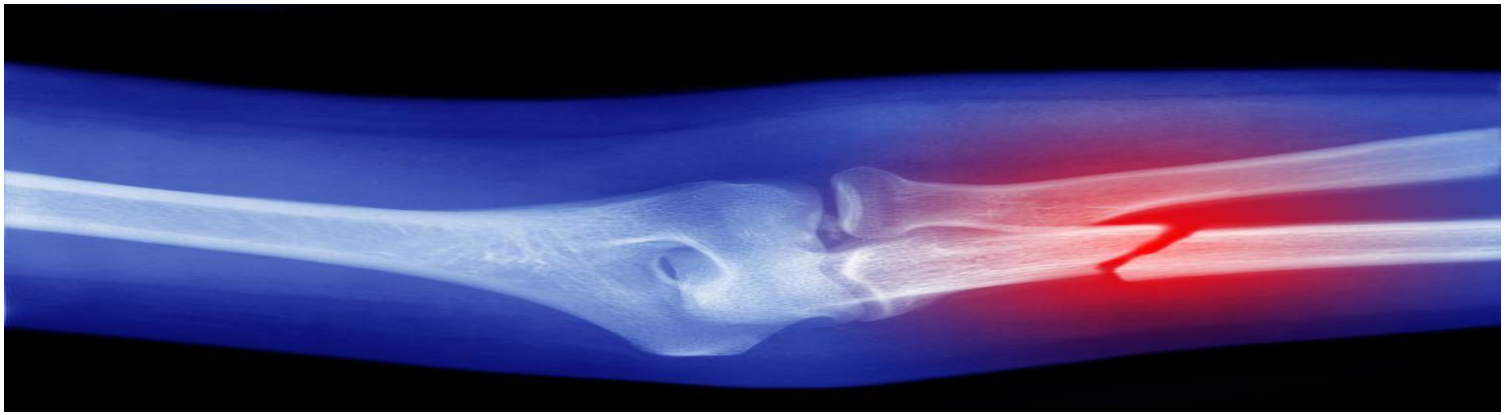
Conflicts of Interest

- 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.

1. Roterman et al. Statistics Canada, Catalogue no. 82-003-X, Health Reports, Vol. 25, no. 6, pp. 3-9, June 2014, 2. Byreddy et al. Climacteric 2015:18(Suppl 2):39-46

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.

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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.

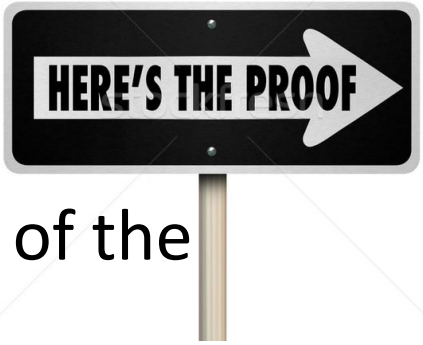
Considerations When Assessing Drugs That Impact Bone

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

Stronger evidence

Drug Class	Bone Mineral Density (BMD)	Fracture risk
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	↓	?

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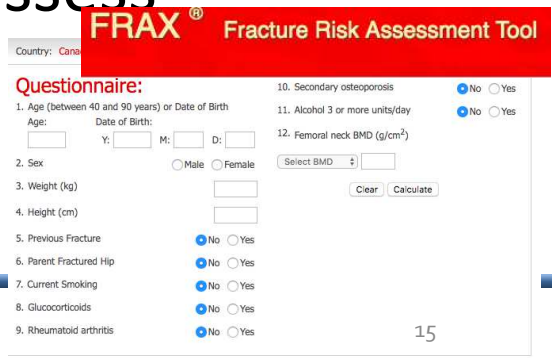
Screen for Drugs that Impact Bone Health

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 <u>not</u> 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.

HANT et al. *Cleveland Clinic Journal of Medicine*. 2016;83(4):281–288

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Glucocorticoids

- 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)

1. Albaum et al *Popul Ther Clin Pharmacol*. 2014;21(3):e486–504

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

1. Albaum et al *Popul Ther Clin Pharmacol*. 2014;21(3):e486–504, 2 Buckley et al *Arthritis Care Res*. 2017;69(8):1095–1110

Glucocorticoids

How to manage:

- Get bone density, assess fracture risk
- Reduce dose of glucocorticoid to lower dose if possible <u>or</u> 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 <u>≥</u>2.5 mg/day <u>and</u> moderate to high risk of fractures)

Buckley et al *Arthritis Care Res*. 2017;69(8):1095–1110, Papaioannou A et al. CMAJ 2010;182:1864-1873

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®)

1. Hadji P, et al *J Bone Oncol*. 2017;7:1–12

Aromatase Inhibitors

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

1. Hadji P, et al *J Bone Oncol*. 2017;7:1–12, 2. Amir E et al J Natl Cancer Inst 2011;103:1299-1309

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

1. Hadji P, et al *J Bone Oncol*. 2017;7:1–12, 2. Amir E et al J Natl Cancer Inst 2011;103:1299-1309

Aromatase Inhibitors

Options for Treatment:

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

Hadji P, et al *J Bone Oncol*. 2017;7:1–12, Trémollieres et al *Maturitas*. 2017;95:65–71

Androgen Deprivation Therapy (ADT) For Prostate Cancer

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

Types	Medications
GnRH Agonists	Leuprolide (Eligard®) Goserelin (Zoladex®)
Androgen receptor blockers	Enzalutamide (Xtandi®) Bicalutamide (Casodex®)
Androgen synthesis inhibitors	Abiraterone (Zytiga®)

Androgen Deprivation Therapy (ADT)

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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]

1. Alibhai et al *Clin Oncol*. 2017;29(6):348–355

Proton Pump Inhibitors (PPI)

Types
Proton pump inhibitors: omeprazole, esomeprazole, lansoprazole, deslanzoprazole, pantoprazole, rabeprazole

- Role: acid suppression
- Mechanism of effect on bones: not known[1]
  - Theory: PPI suppress acid secretion, ↓ calcium absorption
  - Possibly direct action on osteoclasts

1. Panday et al. *Therapeutic Advances in Musculoskeletal Disease*. 2014;6(5):185–20, 2. Hussain S, et al *Rheumatology International*. 2018:1–16

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.

1. Hussain S, et al *Rheumatology International*. 2018:1–16 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

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

- Mechanism not well understood
  - May increase breakdown of vitamin D in body
- Fractures may also be associated with seizures[3]

1. Panday et al. *Therapeutic Advances in Musculoskeletal Disease*. 2014;6(5):185–20, 2. Vestergaard et al. Acta Neurol Scand 2005:112;277-286, 3 PSAP

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.

1. Panday et al. *Therapeutic Advances in Musculoskeletal Disease*. 2014;6(5):185–20, 2. Vestergaard et al. Acta Neurol Scand 2005:112;277-286, 3 PSAP

Selective Serotonin Reuptake Inhibitors (SSRI)

Types

SSRI's:

fluoxetine,
paroxetine,
citalopram,
escitalopram,
sertraline,
fluvoxamine

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

Warden et al *Curr Osteoporos Reports*. 2016;14(5):211–218

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

Warden et al *Curr Osteoporos Reports*. 2016;14(5):211–218

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

HANT et al. *Cleveland Clinic Journal of Medicine*. 2016;83(4):281–288

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.