Drug-Induced Osteoporosis

Beyond the Break Webinar

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Conflicts of Interest

- I have been on Advisory Boards/Speakers Bureau’s for Pfizer Canada and Merck Canada
Objectives

1. To appreciate the effects of drug induced osteoporosis.
2. To consider the assessment of drug induced osteoporosis.
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 including glucocorticoids, aromatase inhibitors, ADT, PPI, anticonvulsants and SSRI’s.
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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 experience an osteoporotic fracture.
- Prescription drugs present a potentially modifiable risk factor.
- There are no reliable estimates of the overall incidence of drug induced osteoporosis.
Introduction

- In Canada, ~40% of Canadians take at least one prescription medication, and this rises to ~80% when looking at ages 65 years and over.\(^1\)
  - 70% take at least 2 medications, while 30% are on at least 5 medications

- Many classes of drugs have been shown to adversely effect BMD and/or increase fracture risk.\(^2\)
  - With variable levels of evidence and sometimes with uncertain causality.

Introduction

- Awareness is limited, therefore preventative measures are not always taken.

- Care gap continues to exist even in populations at highest risk, for both screening and preventative measures.

- Increasing our awareness of the effects of drugs on bone health will help risk stratify patients.  
  - Careful screening and assessment by clinicians is required.

- Some have well established guidelines ie glucocorticoid-induced, but for many guidelines do not exist.
Drugs that Affect Fracture Risk

Munson et al, 2016 Retrospective cohort
n=168,133 Medicare beneficiaries with fragility fracture

Munson et al, JAMA Internal Med 2016;176(10):1531-38
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Considerations When Assessing Drugs That Impact Bone

- Causality has not been well established for all.
- Causal relationships for following:
  - Glucocorticoids, aromatase inhibitors, androgen deprivation therapy, GnRh agonists
- Uncertain plausibility regarding mechanism of action of effects on bone for many drugs.
- Most evidence is observational in nature.
- Complex interplay of multiple factors.
Considerations When Assessing Drugs That Impact Bone

Need to consider confounding factors:

- Effect of the underlying disease on bone health.
- Effect of other concomitant drugs used to treat the underlying disease.
- Effect of the medication on falls.
- Possibility of other comorbid conditions.
- Effect of lifestyle behaviors when assessing studies.
Assessing Drugs that Impact Bone Health

- What is the affect on bone density and/or fractures?
- What is the level of evidence?
- What is the mechanism of action on bone loss or fractures? How plausible is this evidence?
- Does it have a dose response? Is it duration dependent?
- How quick is the response? When is the maximum response?
- Are the effects on BMD and fracture risk reversible when it is discontinued? How quickly does this happen?
Assessing Drugs that Impact Bone Health

- How should we screen patients at greatest risk?
- Are there alternate medications available?
- Are there guidelines to guide us in decision making?
- If preventative measures required, which have been most evidence to support use?

Considerations in assessment:
FRAX, CAROC – the only drug induced osteoporosis drugs evaluated is glucocorticoids
## Drugs Shown to Impact Bone Health

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<thead>
<tr>
<th>Drug Class</th>
<th>Bone Mineral Density (BMD)</th>
<th>Fracture risk</th>
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<td>Aromatase Inhibitors</td>
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<td>Androgen Deprivation Therapy</td>
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<td>GnRH Agonists (women)</td>
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<td>Anticonvulsants</td>
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<td>Certain antiretrovirals</td>
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Managing Drugs That Affect Bone Health

General recommendations

Balance the benefits of treatment to risk of bone loss/fractures.
Reassess need for medication if possible
Use lowest dosage, shortest duration
Adequate calcium and vitamin D
Counsel patients on lifestyle measures
Lifestyle Considerations

Education on lifestyle and risk factors

- Exercise – 30 minutes physical activity most days of the week, weight bearing
- Smoking cessation
- Limit alcohol intake (<2 drinks per day)
- Limit caffeine (<400 mg daily, ~4 cups of coffee)
- Reducing fall risk – including medications that increase risk of falls

Papaioannou A et al. CMAJ 2010;182:1864-1873,
Screening Patients At Risk for Drug Induced Osteoporosis

Importance:

1) To identify patients at high risk of bone loss/fracture at baseline

2) To introduce interventions to those at higher risk of fracture

Fracture Risk Assessment:

- FRAX/CAROC is not designed to assess fracture risk for all drugs
- Secondary osteoporosis option (FRAX) may underestimate the effect of drugs on fracture risk
Managing Prevention of Drug Induced Osteoporosis

Preventative strategies include:

1. Initiate osteoporosis medication to prevent bone loss and fractures.

2. Screen patients with BMD/FRAX assessment, initiate osteoporosis medications when patients at high risk.

3. Consider switching to alternate medication if possible.

4. No additional action, lifestyle measures only. Counsel on bone health.
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Glucocorticoids

- Glucocorticoids (GC) are the most common cause of secondary osteoporosis.

- Despite the availability of guidelines, low level of management for GC induced osteoporosis\(^1\)
  - In a recent SR, <40% of chronic GC users had BMD testing or osteoporosis medications for prevention\(^1\)

- Mechanism: Both an increase in bone resorption and reduction in bone formation
  - Inhibition of osteoblast differentiation
  - Increased osteoclast activity

Glucocorticoids

- Decrease BMD and increase in fractures.
  - Greater effect on trabecular bone

- Rapid affect on bones – bone loss at 6 – 12% within first year, with the highest rate of BMD loss the first 3 – 6 months\(^1,2\)

- Fracture risk increases within 3 months

- Risk is reversible, both on BMD and fracture risk

Glucocorticoids

- Dose dependent and duration dependent.\(^1\)
  - Chronic defined for 3 months or longer.
  - Daily ie >2.5 - 7.5 mg

- High cumulative doses of >5 gm also correlates with BMD loss

- Guidelines:
  - American College of Rheumatology (ACR)\(^2\), IOF
  - General guidelines also address: Osteoporosis Canada, National Osteoporosis Foundation, etc.

Glucocorticoids

- Fracture risk assessment should be completed within the first 6 months
- Reduce dose to minimally effective dose or discontinue if possible
- Osteoporosis medication options for prevention and treatment:
  - Oral bisphosphonates as first choice
  - Others:
    - IV zoledronic acid
    - denosumab
    - teriparatide

Glucocorticoids

- Prevention considerations:
  - Osteoporosis Canada guidelines:\(^1\)
    - 7.5 mg or more prednisone equivalent if planned for 3 months or longer of therapy
  - ACR guidelines:\(^2\)
    - 2.5 mg or more if planned for 3 months or longer of therapy if patient is at moderate to high risk of fracture (based on FRAX).
    - Very high dose of GC’s (\(\geq 30\) mg day of prednisone or equivalent or >5 gm cumulative dose in past year)

Note: FRAX can underestimate risk with high doses, ACR guidelines include FRAX adjustment

Aromatase Inhibitors (AI)

Aromatase inhibitors: letrozole, anastrozole, exemestane

- Role: adjuvant treatment for breast cancer
- Mechanism for bone loss: decrease in estrogen levels by inhibiting aromatase enzyme responsible for conversion of androgens to estrogen.
- Marked increase in bone resorption, 2 – 4 fold increase compared to physiologic bone loss (postmenopause).¹
- Few studies compare different AI (likely similar effect).

Aromatase Inhibitors (AI)

- Decrease in BMD and increase fracture risk.
  - Absolute fracture risk 10% in studies (5 years), longer duration associated with greater risk\(^1,2\)

- Most bone loss occurs in first year

- After discontinuing AI, bone turnover normalizes however, BMD partially recovers

- FRAX assessment: “secondary osteoporosis” may underestimate the effect of AI in breast cancer patients

Aromatase Inhibitors

- Several guidelines exist to guide approach:
  - Joint statement IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG 2017
  - EMAS, ESMO, ASCO

- Who to treat?
  - Evaluate clinical risk factors for fractures
  - BMD (DXA) measurement baseline, CAROC/FRAX assessment
  - Consider treatment if T score $< -2$ or $> 2$ risk factors for fractures
  - Consider treatment if high risk on CAROC/FRAX

Aromatase Inhibitors

Patient with cancer receiving endocrine treatment known to accelerate bone loss (Al, GnRH and TAM in premenopausal women)

- T-score > -2.0 and no additional risk factors
  - Exercise
  - Calcium and vitamin D if necessary
  - Monitor risk and BMD at 1–2 year intervals

- Any 2 of the following risk factors:
  - Age > 65 years
  - T-score < -1.5
  - Smoking (current or history)
  - BMI < 20
  - Family history of hip fracture
  - Personal history of fragility fracture > 50 years
  - Oral glucocorticoid use for > 6 months

- T-score < -2.0
  - Exercise
  - Calcium and vitamin D
  - Denosumab or Bisphosphonate therapy (zoledronic acid, alendronate, risedronate, ibandronate)

- Monitor BMD every 2 years
  - Check compliance with oral therapy
Aromatase Inhibitors

Options for Treatment:
- Oral or IV bisphosphonates (zoledronic acid q6 – 12 months)
- Denosumab

- Duration for prevention: continue until AI is finished (adjuvant breast cancer program is complete)

Androgen Deprivation Therapy (ADT)

ADT for prostate cancer includes:

- Gonadotropin-releasing hormone agonists (leuprolide, goserelin, triporelin)
- Gonadotropin-releasing hormone antagonists (ganirelix, cetrorelix, degarelix)
- Oral anti-androgens (flutamide, bicalutamide, nilutamide)

- Mechanism in bone loss: decrease levels of both estrogen and testosterone in men; antagonist to androgen receptors

- Decrease in BMD and increase in fractures:
  - ADT may increase the relative risk of any fracture by 50% during 5 – 10 year follow-up

- Greatest BMD decline in first year, up to 10% decline
  - BMD decline can be seen within months of starting.
  - Reversible on discontinuation

Androgen Deprivation Therapy (ADT)

- Studies have shown that men on ADT for prostate cancer are insufficiently screened and treated.\(^1,2\)

- Guidelines: Cancer Care Ontario (CCO)\(^3\)

- Who to treat?
  - Estimate patients absolute fracture risk: evaluation of clinical risk factors
  - BMD (DXA) measurement baseline
  - CAROC/FRAX assessment
  - If high risk of fracture then consider treatment

*Note: recommendations are for non-metastatic prostate cancer*

Androgen Deprivation Therapy (ADT)

- Options for treatment:
  - Oral or IV bisphosphonates
  - Denosumab

Note: Each agent has been shown to improve BMD in patients on ADT, denosumab shown to reduce vertebral fractures in this population

Cancer Care Ontario (CCO) guidelines

Recommend denosumab first line in patients with prostate cancer on ADT at high risk of fracture
If denosumab is not available or contraindications, then consider bisphosphonates

Proton Pump Inhibitors (PPI)

PPI: omeprazole, esomeprazole, lansoprazole, deslanzoprazole, pantoprazole, rabeprazole

- Mechanism of effect on bones: not known
  - Theory: PPI suppress acid secretion, therefore ↓ GI calcium absorption
  - Possibly direct action on osteoclasts proton pumps, ↑ bone resorption

- PPI increase in fracture risk (observational studies, meta-analysis (RR 1.26 hip))

- Studies looking at PPI and BMD decline have found no clear association,
  - BMD in men affected, not in women – though fracture increased in both

Proton Pump Inhibitors

- Dose dependent and duration dependent.
  - Higher doses compared to lower doses (though difficult to quantify in studies)
  - Fracture effect is dependent on duration of use\textsuperscript{1,2}

- Same response on fracture risk has not been seen with H2 antagonists\textsuperscript{3}

- Fracture risk reduces when PPI discontinued\textsuperscript{1}

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

- Patients on bisphosphonates taking PPI may have further increase in risk.\textsuperscript{1-3}

- Confounders: long term PPI use has been associated with falls

- No guidelines to guide for fracture risk and PPI.

Proton Pump Inhibitors

- **Bottom line:**
  - Use PPI only if clearly indicated.\(^1\)
  - Consider deprescribing\(^2\)
    - Use lowest dose, shortest duration, use “on-demand” as needed
    - Assess need for continued use.
    - Consider switching to H2 antagonists
- Recommend calcium citrate if patient on any acid suppression agent to avoid issues with absorption with calcium carbonate

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

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

- Mechanism not well understood
  - Initial theories: cytochrome P450 enzyme inducing AED accelerate vitamin D inactivation
  - Possibly direct effect on osteoblast proliferation (ie phenytoin in animal studies)
  - Valproic acid, fractures due to hypophosphatemia

- Decrease BMD and increase in fractures
  - Risk of fractures may double (meta-analysis RR 2.2)

- Fractures may also be associated with epilepsy or associated with the trauma during seizure activity

Anticonvulsants

Bottom line:

- Evidence based strategies (i.e. screening, prevention) with anticonvulsants are limited.

- If on cytochrome P450 enzyme inducing AED evaluate vitamin D level (baseline, 6 – 12 months after). May require higher vitamin D doses 2000 – 4000 IU

- Screen patients with risk factors for osteoporosis, counsel patients on bone health.

- Consider alternative anticonvulsant if risks outweigh benefits.

Selective Serotonin Reuptake Inhibitors

SSRI’s: fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine

- Mechanism not clearly established, may be multifactorial.
  - Possibly direct effects on bone formation.
  - May be direct effect of serotonin on serotonin receptors on bone. Serotonin from GI, inhibits bone formation, while serotonin from brain stimulates bone formation and inhibits bone resorption.

- Several meta-analysis have reported increased risk of fracture with SSRI RR 1.7, increased risk shown with SSRI but not with TCA antidepressants.
  - All observational studies

Selective Serotonin Reuptake Inhibitors

- Confounders:
  - Depression is independently associated with increased fractures.
  - Falls may also be a contributing factor, both with the use of SSRI as well as depression itself.

- Dose dependent response with SSRI’s and fractures.
  - This is also seen with falls, as increased SSRI doses are associated with increase in falls.

- Fracture risk increase is seen within 2 – 3 weeks of starting and continues until 3 months after stopping.
  - Note that falls may be the initial reason for increase

Selective Serotonin Reuptake Inhibitors

- Bottom line:
  - use lowest doses
  - counsel on bone health
  - consider alternate agents at patients at high risk of fracture

- No guidelines exist to guide.
Final Points

- Adequate monitoring of bone health, when drugs with adverse bone safety profiles are used, and consider interventions as appropriate.

- Potential effects on bone loss and fractures in the individual patient, must be taken into account when assessing the balance of benefits and risks.

- Also consideration of other factors that increase fracture risk, such as the effect of medications on falls.

- The impact of multiple drugs at the same time on bone health is unknown.
- This webcast will be archived within 1-3 business days.
- Find all our archived sessions at http://bit.ly/2Flqekd
- If you haven’t done so already, please complete an evaluation survey at http://bit.ly/2H4fP2S
- If you have questions about Beyond the Break, please contact Kevin at kn@osteoporosis.ca or Arlene at arlene.silverstein@wchospital.ca
References


References con’t

- Hant FN, Bolster. Drugs that may harm bone: Mitigating the risk. Cleveland Clinic Journal of Medicine. 2016;83(4):281–288