Clinical Question 9

- When patients are treated with Selective Serotonin Receptor Inhibitors, do they have an increase in the risk of fracture?

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Learning Objectives

Upon completion of this module, participants will be better able to:

- Explain the impact of SSRIs on the risk profile of patients with osteoporosis
- Explain how to mitigate the impact of SSRI associated bone loss with osteoporosis medications
- Describe why chronic SSRI treatment is associated with increased fragility fracture risk
- Mitigate the impact of medication-related factors which may increase the risk of bone loss and fragility fractures

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Clinical Question 9

When patients are treated with SSRI, do they have an increase in the risk of fracture?

Patients on chronic SSRI have increases in fragility fracture risk from numerous studies and are a potent risk factor; patients on SSRI are appropriate candidates for bone health evaluation and follow-up.

SSRI = Selective Serotonin Receptor Inhibitors

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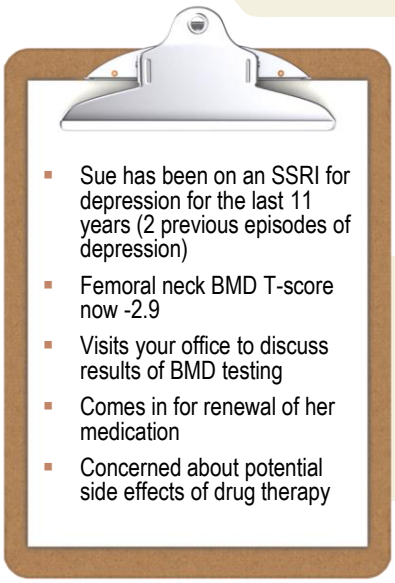
Clinical Vignette



- Sue has been on an SSRI for depression for the last 11 years (2 previous episodes of depression)
- Femoral neck BMD T-score now -2.9
- Visits your office to discuss results of BMD testing
- Comes in for renewal of her medication
- Concerned about potential side effects of drug therapy

Sue
66 years old

What is Anna's risk of osteoporotic fracture?

1. Low
2. Moderate
3. High

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Clinical Vignette

Sue
66 years old

- Sue has been on an SSRI for depression for the last 11 years (2 previous episodes of depression)
- Femoral neck BMD T-score now -2.9
- Visits your office to discuss results of BMD testing
- Comes in for renewal of her medication
- Concerned about potential side effects of drug therapy

What would you discuss with her regarding her BMD results and current meds?

1. Discuss her bone density results and fracture risk
2. Ensure she is taking adequate calcium and vitamin D
3. Explain to her that the SSRI has increased her risk of fragility fracture and start her on a bisphosphonate or denosumab
4. Explain to her that the SSRI has increased her risk of fragility fracture and wean her off of it
5. 1, 2 & 3

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Selective Serotonin Reuptake Inhibitors (SSRIs)

- SSRIs are commonly used antidepressants
  - → First-line treatment for major depressive disorder in Canada[1]
  - → ~69% of all antidepressants prescribed in Canada in 2013 were SSRIs/SNRIs[2]
- SSRIs selectively block the serotonin transporter (5-HTT) in the CNS to increase extracellular levels of serotonin (5-HT) and relieve symptoms of depression[3]
- SSRIs also act on 5-HT receptors, thus modulating the release of 5-HT directly[4]
- Serotonin (5-HT) receptors have been identified on osteoclast, osteoblast and osteocyte cell lines[4]

SNRI = Serotonin-Norepinephrine Reuptake Inhibitor

1. Kennedy SH et al. (2016) *Can J Psychiatry*, 61(9), 540-560.; 2. IMSB, Compuscript (Feb'14). 3. Chau K et al. (2012) *J Osteoporos*, 2012, 323061.
4. Tsapakis EM et al. (2012) *Eur Psychiatry*, 7, 156-169.

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Selective Serotonin Reuptake Inhibitors and Serotonin- Norepinephrine Reuptake Inhibitors

- Serotonin is a monoamine produced in the duodenum and in brainstem neurons
- Serotonin receptors present on bone cells
- Effect on bone complex- poorly understood
- Gut production of serotonin is the major source of circulating serotonin and may inhibit osteoblast
- SSRI increase RR of any fracture
- Meta-analysis of 34 observational studies demonstrated increased relative risk for any fracture in patients on SSRI compared to no SSRI (RR 1.39 (95% CI 1.32-1.47).

Rabenda V. et al. Osteoporos Int. 2013 Jan;24(1):121-37.

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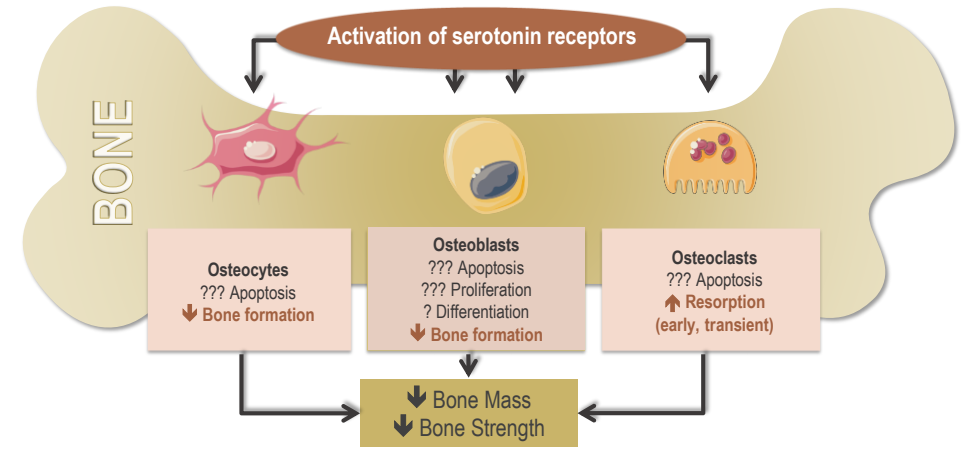
Selective Serotonin Reuptake Inhibitors and Serotonin- Norepinephrine Reuptake Inhibitors



- Serotonin (5-HT) receptors have been identified on osteoclast, osteoblast and osteocyte cell lines[2]
- Effects on bone formation and resorption may be governed by the activation of a number of 5-HT receptors on osteoblasts and osteoclasts via endocrine, autocrine/paracrine and neuronal pathways[2]

Adapted from: 1. Bliziotes, M. (2010) *J Clin Endocrinol Metab*. 95(9), 4124-4132. 2. Tsapakis EM, et al. (2012) *Eur Psychiatry*, 27, 156–169.

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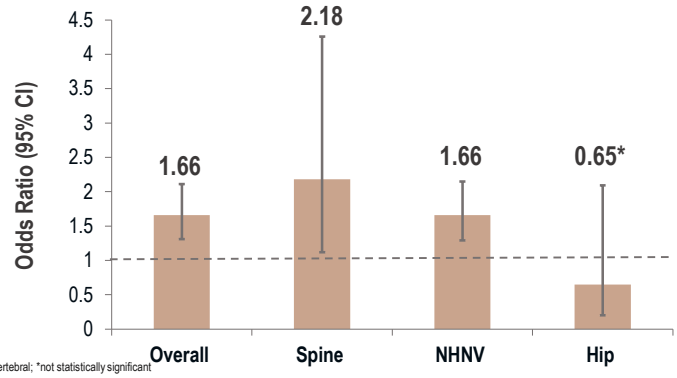
SSRI Use Associated with an Increased Risk of Overall, Clinical Spine and Non-Hip/Non-Vertebral Fractures

Global Longitudinal Study of Osteoporosis in Women (GLOW)
Multivariable regression model predicting Year 3/Year 5 fracture.
(n=1,149)



NHNV = non-hip-non-vertebral; *not statistically significant

Adachi JD, et al. (2013) *ASBMR*, Oral presentation; OP 1049.

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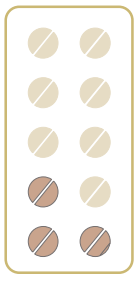
SSRI/SNRI Use Associated with Increased Fragility Fracture Risk Over 10 Years

Canadian Multicentre Osteoporosis Study (CaMos)
Prospective cohort study (N=6,645, n=192)



Among the 6,645 CaMos subjects included,

2.9%

(192) were **USING SSRIs OR/AND SNRIs** at baseline

- SSRI/SNRI use was associated with increased risk of fragility fracture: **HR, 1.88; 95% CI, 1.48–2.39**
- After controlling for multiple risk factors, the adjusted HR for current SSRI/SNRI use remained elevated: **HR, 1.68; 95% CI, 1.32–2.14**

Moura C et al. (2014) *Osteoporos Int.*, 25, 1473–1481.

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SSRI/SNRI Product Monographs Warn about Fracture Risk*

- Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs/SNRIs.
- Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal.
- Until further information becomes available, a possible effect on bone mineral density with long-term treatment with SSRIs/SNRIs cannot be excluded and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

*Accessed March 17, 2017.
Product Monographs of Prozac® (fluoxetine), Zoloft® (sertraline), Celexa® (citalopram), Cipralex® (escitalopram), Paxil® (paroxetine), Effexor XR® (venlafaxine), Cymbalta® (duloxetine), Pristiq® (desvenlafaxine), Trintellix® (vortioxetine)

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Recommendations for Patients on SSRI

- Reassess ongoing need for medication
- Use lowest dosage and shortest duration needed
- Counsel patients on lifestyle changes: encourage weight bearing exercise, cessation of tobacco use, and limiting alcohol use
- Supplement calcium and vitamin D
- Consider screening and monitoring bone density with dual-energy absorptiometry (DXA)
- Initiate osteoporosis treatment if indicated

Adapted from: Hant FN and Bolster MB. (2016) *Cleve Clin J Med.*, 83, 281-288.

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Discussion: Clinical Takeaways

1. SSRI/SNRIs are a first-line treatment for major depressive disorders in Canada[1]
2. Serotonin (5-HT) receptors have been identified on osteoclast, osteoblast and osteocyte cell lines[2]
3. Effects on bone formation and resorption may be governed by the activation of a number of 5-HT receptors on osteoblasts and osteoclasts via endocrine, autocrine/paracrine and neuronal pathways[2]
4. SSRI/SNRI use is associated with an increased risk of hip, spine and non-vertebral fractures[3]

1. Kennedy SH et al. (2016) *Can J Psychiatry*, 61(9), 540-560. 2. Tsapakis EM, et al. (2012) *Eur Psychiatry*, 27, 156–169.
3. Rabenda V et al. (2013) *Osteoporos Int*., 24, 121-137.

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