Secondary Causes of Osteoporosis and Low Bone Density

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Bone Density Report

T-score = -2.6 at the Lumbar Spine: “The Patient Has Osteoporosis”
Low BMD on DXA Does Not Equal “Postmenopausal Osteoporosis”

![Graph showing BMD on DXA and osteoporosis]

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD (g/cm²)</th>
<th>YA T-Score</th>
<th>AM Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>0.881</td>
<td>-2.7</td>
<td>-0.9</td>
</tr>
<tr>
<td>L2</td>
<td>0.828</td>
<td>-3.1</td>
<td>-1.3</td>
</tr>
<tr>
<td>L3</td>
<td>0.866</td>
<td>-2.8</td>
<td>-0.9</td>
</tr>
<tr>
<td>L4</td>
<td>0.947</td>
<td>-2.1</td>
<td>-0.3</td>
</tr>
<tr>
<td>L1-L2</td>
<td>0.814</td>
<td>-2.8</td>
<td>-1.0</td>
</tr>
<tr>
<td>L1-L3</td>
<td>0.832</td>
<td>-2.8</td>
<td>-1.0</td>
</tr>
<tr>
<td>L1-L4</td>
<td>0.865</td>
<td>-2.6</td>
<td>-0.8</td>
</tr>
<tr>
<td>L2-L3</td>
<td>0.848</td>
<td>-2.9</td>
<td>-1.1</td>
</tr>
<tr>
<td>L2-L4</td>
<td>0.864</td>
<td>-2.6</td>
<td>-0.8</td>
</tr>
<tr>
<td>L3-L4</td>
<td>0.903</td>
<td>-2.4</td>
<td>-0.6</td>
</tr>
</tbody>
</table>
Low BMD on DXA or X-ray Does Not Equal Postmenopausal Estrogen-deficiency Induced Osteoporosis

- Osteoporosis due to other secondary disorders
- Ostemalacia- decreased mineralization with normal or increased osteoid
- Osteitis Fibrosa Cystica- hyperparathyroidism-stimulated bone resorption with replacement by fibrous elements
- Combination of Above
Secondary Osteoporosis

• Secondary osteoporosis is defined as osteoporosis or low bone density for which there is an identifiable causal factor other than menopause and aging.
Evaluating for Secondary Causes of Osteoporosis

• Just because a woman is postmenopausal and has osteoporosis doesn’t mean that she has postmenopausal osteoporosis

• Failure to identify underlying disorders may result in inadequate or inappropriate treatment
Secondary Causes of Osteoporosis

- Drugs
- Endocrinopathies
- GI diseases
- Renal Osteodystrophy (CKD-MBD)
- Marrow-based and neoplastic disorders
- Inherited disorders of collagen metabolism
- Rheumatic inflammatory disorders
- Osteomalacia
Endocrinopathies Associated with Osteoporosis

- Hypogonadism
- Primary Hyperparathyroidism
- Diabetes
- Hyperthyroidism
- Hypercortisolism
- Hypercalciuria with or without renal stones
Gastrointestinal Disorders Associated with Osteoporosis

- Celiac disease (Sprue)
- Gastrectomy
- Intestinal bypass surgery
- Primary biliary cirrhosis
- Pancreatic insufficiency
Marrow-based and Neoplastic Disorders Associated with Osteoporosis

- Multiple myeloma
- Lymphoma
- Systemic Mastocytosis
Rheumatic Inflammatory Disorders Associated with Osteoporosis

- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Systemic Lupus
Genetic Disorders Associated with Osteoporosis

Collagen/Metabolic

- **Collagen Disorders**
  - Osteogenesis imperfecta
  - Ehlers-Danlos syndrome
  - Marfan syndrome

- **Metabolic Disorders**
  - Hypophosphatemia
  - Homocystinuria
How Often are Secondary Causes Found?
Laboratory Yield-
Secondary Causes of Osteoporosis

• Cross-sectional chart review study of 664 postmenopausal women (≥ 45 yrs) referred with BMD T-score < -2.5

• Analyzed screening strategies for cost and diagnostic yield

### Secondary Causes of Osteoporosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 new diagnosis (n=55)</td>
<td>32.4%</td>
</tr>
<tr>
<td>Vitamin D deficiency, &lt;20 ng/mL (n=7)</td>
<td>4.1%</td>
</tr>
<tr>
<td>Hypercalciuria (n=17)</td>
<td>9.8%</td>
</tr>
<tr>
<td>Renal (n=7)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic (n=6)</td>
<td></td>
</tr>
<tr>
<td>Undefined (n=4)</td>
<td></td>
</tr>
<tr>
<td>Malabsorption (n=14)</td>
<td>8.1%</td>
</tr>
<tr>
<td>Relative calcium malabsorption (n=11)</td>
<td></td>
</tr>
<tr>
<td>Celiac sprue (n=3)</td>
<td></td>
</tr>
<tr>
<td>Hyperparathyroidism (n=12)</td>
<td>6.9%</td>
</tr>
<tr>
<td>Primary (n=1)</td>
<td></td>
</tr>
<tr>
<td>Secondary (n=11)</td>
<td></td>
</tr>
<tr>
<td>Exogenous hyperthyroidism (n=4)</td>
<td>2.3%</td>
</tr>
<tr>
<td>Cushing’s disease (n=1)</td>
<td>0.6%</td>
</tr>
<tr>
<td>Hypocalciuriic hypercalcemia (n=1)</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Tannenbaum C et al, *J Clin Endocrinol Metab* 2002;87:4431-4437
Basic LabTests When Considering Secondary Causes of Low Bone Mass

- Serum calcium (chemistry screen)
- 25-OH Vitamin D
- 24 hour urine calcium
- TSH (in women receiving thyroid supplementation)
- These tests identify 92% of patients with 2nd causes
- Cost of $ 118 per patient

24 Hour Urine Calcium

- Low urine calcium = malabsorption
- High urine calcium = renal calcium wasting

- Lab reference range 100-300 mg/day (1-4 mg/kg/day)

Should be collected when vitamin D is adequate and calcium intake is within target of 1200-1500 mg daily
When Should Additional Lab Tests for Secondary Causes of Osteoporosis be Performed?

• When the Z-score is below –2.0
• When the T-score is out of proportion with what we suspect based on clinical risk factors alone
• Guided by the history and physical, and initial lab testing
Additional Lab Tests for Secondary Causes of Osteoporosis

- Intact PTH (if serum calcium is high)
- Celiac Panel
- SPEP, UPEP
- Serum Tryptase/Urine Histamine (mastocytosis)

- Total and Free Testosterone in Males

- Bone Biopsy in CKD-MBD
- Skin Biopsy for Collagen Disorder
Differential Diagnosis of Hypercalcemia

- Primary hyperparathyroidism
- Malignancy
- Hypervitaminosis D
- Thiazides
- Sarcoid, granulomatous disorders
- Lithium
- Hypervitaminosis A
- Milk alkali syndrome
Primary Hyperparathyroidism - Definition

- Persistent hypercalcemia in the presence of elevated or “inappropriately normal” levels of PTH.
iPTH - Calcium Relationship

- Primary hyperparathyroidism
- Hypercalcemia of malignancy
- Hypoparathyroidism
- Normal
BMD Recovery Following Parathyroidectomy for Primary Hyperparathyroidism

Celiac Disease

- One of the most common genetic disorders
- Clinically evident in 1% of northern Europeans
- May be found in up to 3.4% of patients with osteoporosis
- Present in 5-20% of first-degree relatives of known celiac patients

# Antibodies Associated with Celiac Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (Range)</th>
<th>Specificity (Range)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA anti-tTG antibodies</td>
<td>&gt;95.0 (73.9–100)</td>
<td>&gt;95.0 (77.8–100)</td>
<td>Recommended as first-level screening test</td>
</tr>
<tr>
<td>IgG anti-tTG antibodies</td>
<td>Widely variable (12.6–99.3)</td>
<td>Widely variable (86.3–100)</td>
<td>Useful in patients with IgA deficiency</td>
</tr>
<tr>
<td>IgA antiendomysial antibodies</td>
<td>&gt;90.0 (82.6–100)</td>
<td>98.2 (94.7–100)</td>
<td>Useful in patients with an uncertain diagnosis</td>
</tr>
<tr>
<td>IgG DGP</td>
<td>&gt;90.0 (80.1–98.6)</td>
<td>&gt;90.0 (86.0–96.9)</td>
<td>Useful in patients with IgA deficiency and young children</td>
</tr>
</tbody>
</table>

Celiac Disease Diagnostic Testing Algorithm

High probability (>5 percent)

- Duodenal biopsy
  - TTGA IgA
    - Both negative
      - Celiac disease unlikely
    - Both positive
      - Celiac disease
    - Biopsy/serology disagreement
      - HLA DQ2 and DQ8 genotyping
      - Measure IgA level ± TTGA/DGP IgG
      - Work-up for other causes of villous atrophy

Low probability (<5 percent)

- TTGA IgA ± IgA level
  - Positive TTGA
    - Duodenal biopsy
      - TTGA IgG ± DGP IgG
        - Any positive
          - Celiac disease unlikely
        - All negative
  - Negative TTGA Low IgA
  - Negative TTGA Normal IgA

DGP: deamidated gliadin peptide; HLA: human leukocyte antigen; Ig: immunoglobulin; TTGA: tissue transglutaminase antibody.

Disease Associations with Celiac Disease

- Dermatitis Herpetiformis (high correlation)
  - Most with DH have celiac disease
- 3% of CD patients have Selective IgA deficiency
- 10% of patients with IgA deficiency have CD
- Patients with symptomatic iron deficiency anemia (10-15%)
- Type 1 diabetes (3-6%)
- Downs syndrome (5-12%)

Summary- Celiac Disease

- Serologic and biopsy testing must be done on a gluten-containing diet
- Both a positive serologic test and intestinal biopsy are necessary to make a presumptive diagnosis
- Definitive Dx requires a + response of symptoms and/or signs of CD on gluten-free diet
- Beware of patients with IgA deficiency
BMD Recovery on Gluten Free Diet

Duerksen DR. Journal of Clinical Densitometry. 2012;1515, no. 1, 120-123,

81% increase

60% increase
Drug-induced Osteoporosis

- Glucocorticoids
- Aromatase inhibitors
- Proton pump inhibitors (PPIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Antiseizure medicines
- Thiazolidinediones
- Long-term Heparin
- Tamoxifen (premenopausal use)
- Gonadotropin releasing hormone agonists (GnRH)
- Thyroid hormones in excess
- Antiretroviral Therapy
- Lithium
- Chemotherapeutic / immunosuppressives (MTX, CsA, Tacrolimus)
- Medroxyprogesterone acetate for contraception
Drug-induced Osteoporosis

- Glucocorticoids
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Glucocorticoid-Induced Osteoporosis: Epidemiology

- GIOP is the most common iatrogenic cause of osteoporosis
- Approximately 1% of the adult population is receiving oral glucocorticoids at any given time (up to 3% of patients over age 70)
Fractures Are the Most Common Serious Adverse Event of Glucocorticoids

<table>
<thead>
<tr>
<th>Adverse Events (AEs)</th>
<th>User (112)</th>
<th>Nonuser (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>21 (19%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Serious Infection</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>GI Bleed or Ulcer</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Diabetic Complication</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Dose Relationship of Fracture Risk With Glucocorticoids

- Chart review from General Practice Database in UK
- Steroid users matched by age, gender, and clinical practice to non-users
- ~60% female, mean age 57 years

van Staa et al, J. Bone and Mineral Res. 2000;15(6);993-1000
Fracture Risk is increased even at Doses < 2.5 mg Prednisolone

Fracture Risk in GIOP

Adapted from van Staa et al, JBMR. 2000;15(6)
Treatment of Glucocorticoid-induced Osteoporosis

- Ensure adequate Ca and Vitamin D
- Reduce fall risk
- Pharmacologic therapies
  - Teriparatide
  - Bisphosphonates
    - Alendronate
    - Risedronate
    - Zoledronic Acid
ACR Recommendations for Postmenopausal Women and Men >50 years Using Glucocorticoids for > 3 Months

Risk assessed by FRAX; **Low risk** = <10% 10-year risk of Major Osteoporotic Fractures, **Medium risk** = 10-19%, **High risk** >20%

- **Low Risk***
  - Prednisone dose > 7.5 mg/day
    - Alendronate OR risedronate OR zoledronic acid
- **Medium Risk***
  - Any dose of GC
    - Alendronate OR risedronate
  - Prednisone dose > 7.5 mg/day
    - Zoledronic acid
- **High Risk***
  - Any dose of GC
    - Alendronate OR risedronate OR zoledronic acid OR teriparatide
Aromatase Inhibitors for Breast Cancer

- Aromatase inhibitors therapy for postmenopausal, ER+ women with advanced disease
  - Anastrazole (Arimidex)
  - Letrazole (Femara)
  - Exemestane (Aromase)
ATAC: Effects on BMD

ATAC: Bone Fractures

RR = relative risk.


### Fractures in the Major Randomized Aromatase Inhibitor Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N/n</th>
<th>F/U, mo</th>
<th>Treatment</th>
<th>Clinical fracture rate, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AI vs TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>9366/609</td>
<td>100</td>
<td>ANA vs TAM</td>
<td>11.0 vs 7.7 [p&lt;0.001]</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>4922/352</td>
<td>51</td>
<td>LET vs TAM</td>
<td>8.6 vs 5.8 [p&lt;0.01]</td>
</tr>
<tr>
<td><strong>AI after 2-3 years of TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>4724/277</td>
<td>58</td>
<td>EXE vs TAM</td>
<td>7.0 vs 5.0 [p = 0.003]</td>
</tr>
<tr>
<td>ABCSG8/ARNO</td>
<td>3224/50</td>
<td>28</td>
<td>ANA vs TAM</td>
<td>2.0 vs 1.0 [p = 0.015]</td>
</tr>
<tr>
<td><strong>AI after 5 years of TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA-17</td>
<td>5187/256</td>
<td>30</td>
<td>LET vs Placebo</td>
<td>5.3 vs 4.6 [p = 0.25]</td>
</tr>
</tbody>
</table>

ANA: anastrozole; TAM: tamoxifen; EXE: exemestane; LET: letrozole;

Pant S, Shapiro CL. Drugs 2008;68:2591

Risk of Bone Fracture Correlates with Undetectable Estrogen Levels
Z-FAST: Up-front vs Delayed Bone Protection with IV Zoledronic Acid (ZA)

Adjuvant breast cancer
- ER/PgR+
- Postmenopausal
- No prior ET
- No prior bisphosphonate

Stratification
- Adjuvant CT
- T score
- Induced postmenopausal*

**Up-front**

Letrozole 2.5 mg/d + ZA 4 mg IV q6mo

**Delayed**

Letrozole 2.5 mg/d

Delivered ZA (4 mg IV q6mo) if
- BMD T score -2 SD
- Or clinical fracture
- Or asymptomatic fracture at 36 mo

- Primary end point: LS BMD at 12 mo
- Z-FAST: N=602 (North America)

Z-FAST: Mean Percent Change in BMD with Zoledronic Acid

Randomized Trial of Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors for Nonmetastatic Breast Cancer

Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors

2003 ASCO Guidelines for Treating Bone Loss in Breast Cancer

Provide lifestyle advice
Begin calcium and vitamin D

- BMD T score > -1
  - Provide reassurance

- BMD T score between -1 and -2.5
  - Consider drug therapy on an individualized basis

- BMD T score ≤ -2.5
  - Begin drug therapy
    - Alendronate
    - Risedronate
    - Zoledronic acid

Proton Pump Inhibitors and Increased Fracture Risk: 2010 FDA Warning

• Revised warning for PPI: possible increased risk of hip, wrist, & spine fractures.
• Based on 7 epidemiologic studies & claims database analysis (no randomized trials)
• Increased risk after 1-7 years of treatment
  – (note: OTC label for 14 days treatment)
• Risk include age >50, “high dose”, longer duration
• Calcium carbonate absorption?

www.fda.gov  safety communication 5/25/10
The effect of Proton Pump Inhibitors on Calcium Carbonate Absorption

- Double-blind study using 45Ca-labeled calcium carbonate
- 1 week course of Omeprazole 20 mg daily
- Lowered fractional calcium absorption from 9.1% to 6.5%

PPIs and Hip Fractures

• PPI therapy 1st linked to an increased risk for hip fractures in 2006

• UK General Practice Research Database
  – Cases included all patients with an incident hip fracture (n = 13,556), and 135,386 controls

• The strength of the association between hip fracture and PPI therapy increased with increasing duration of PPI therapy.
  
• Adjusted OR=
  
  – 1 year, 1.22 [95% C I, 1.15 - 1.30];
  
  – 2 years, 1.41 [95% C I, 1.28 - 1.56];
  
  – 3 years, 1.54 [95% C I, 1.37 - 1.73]; and
  
  – 4 years, 1.59 [95% C I, 1.39 - 1.80]; (P < .001)

PPIs and Hip Fractures

• Retrospective, case–control study matched 15,792 cases of osteoporosis-related fractures with 47,289 controls

• Long-term exposure to PPI therapy, (7 or more years), was significantly associated with an increased risk of any osteoporosis-related fractures (OR 1.92 [1.16–3.18], $P = 0.011$)

• Hip fracture risk was increased after only 5 years of continuous use

Targownik et al CMAJ 2008;179(4):319
Northern California Kaiser database identified patients with a hip fracture (cases, n = 33,752) and matched these 4:1 to controls (n = 130,471)

Cases were 30% more likely than controls to have taken PPIs for at least 2 years (odds ratio [OR] 1.30 [95% CI 1.21–1.39])

The greatest relative risk of hip fractures in patient 50-59 on PPI >2 years (OR 2.31)

Risk declines after discontinuation
PPIs and hip fracture in the WHI

• The Women’s Health Initiative, with more than 1 million person-years of follow-up, found no association between PPI use and hip fracture

• There was a modest association between PPI use and spine, arm, wrist and total fractures

Proton Pump Inhibitors and Risk of Fractures: A Meta-Analysis of 11 International Studies


![Graph showing relative risk of fractures with 95% confidence intervals for various studies and outcomes.](image-url)
Proton Pump Inhibitor Use and the Antifracture Efficacy of Alendronate

Abrahamsen B, et al.
Proton Pump Inhibitor Use and the Antifracture Efficacy of Alendronate

- Population-based, national register–based, open cohort study of 38,088 new alendronate sodium users (mean duration of follow-up 3.5 yrs).
- The hip fracture risk reduction associated with complete refill compliance to alendronate was a 39% risk reduction [HR], 0.61; 95% [CI], 0.52-0.71; *P*.001) in patients who were not PPI users.
- The risk reduction in concurrent PPI users was non-significant (19%; HR, 0.81; 95% CI, 0.64-1.01; *P*.06).

PPI Use and the Risk Reduction in Hip Fractures on Alendronate

Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people

Liu et al.
Lancet 1998;351 (9112). 1303-1307
Odds Ratio for Hip Fracture by Timing of Exposure to Anti-depressant

<table>
<thead>
<tr>
<th>Exposure</th>
<th>n</th>
<th>Odds ratio (95% CI) Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>891</td>
<td>3.3 (2.9–3.8)</td>
<td>2.4 (2.0–2.7)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>326</td>
<td>2.3 (1.8–2.9)</td>
<td>1.8 (1.4–2.3)</td>
</tr>
<tr>
<td>Former</td>
<td>471</td>
<td>1.6 (1.3–2.0)</td>
<td>1.2 (0.9–1.5)</td>
</tr>
<tr>
<td><strong>Secondary-amine TCA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>400</td>
<td>3.0 (2.4–3.7)</td>
<td>2.2 (1.8–2.8)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>104</td>
<td>1.7 (1.1–2.6)</td>
<td>1.2 (0.8–2.0)</td>
</tr>
<tr>
<td>Former</td>
<td>169</td>
<td>2.2 (1.6–3.1)</td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td><strong>Tertiary-amine TCA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1715</td>
<td>1.8 (1.6–2.0)</td>
<td>1.5 (1.3–1.7)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>733</td>
<td>1.2 (1.0–1.5)</td>
<td>1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>Former</td>
<td>1029</td>
<td>1.2 (1.0–1.4)</td>
<td>1.0 (0.8–1.2)</td>
</tr>
</tbody>
</table>

*For comorbidity and previous drug exposures.

Table 3: Estimated unadjusted and adjusted odds ratios for hip fracture by timing of exposure

Depression-induced Structural Impairment of Mice Exposed to Chronic Mild Stress for 4 Weeks

Serotonin, SSRIs and Bone Density

- Serotonin is a critical regulator of bone mass that fulfills different functions depending on its site of synthesis.
  - Brain-derived serotonin (Tph2) promotes osteoblast proliferation
  - Duodenal-derived serotonin (Tph1) suppresses osteoblast proliferation and bone formation.
- Hence, increasing levels of duodenum-derived serotonin may lead to osteoporosis and fractures.
Bone – Gut Connection

**Mechanism**

**Duodenum**

**Enterochromaffin Cell**

**LRP5**

**Tph1**

**Serotonin**

**Osteoblast**

**Htr1b**

**Creb**

**Bone**

Decreased Osteoblast Proliferation

Abbreviation: Creb, cyclic AMP-responsive element-binding protein.

SSRIs and Fracture: Canadian Multicenter Osteoporosis Study

Prospective cohort of 5008 adults 50 years old or greater, followed over 5 years for fractures

• 137 were on SSRIs
• Risk of fracture was 2.1 times higher in people ≥50 on SSRIs
• Odds of falling for people on SSRIs is 2.2 times greater
• BMD in the hips of SSRI users 4% lower than for non-users
• Effects among SSRI users are dose-dependent

Fracture-free Survival by SSRI Use

Fracture Risk From Psychotropic Medications
A Population-Based Analysis

Leslie W, et al.
J Clin Psychopharmacol
2008;28:384–391
### Table 2: Odds Ratios for Osteoporotic Fractures

<table>
<thead>
<tr>
<th></th>
<th>Partially Adjusted OR* (95% CI)</th>
<th>Fully Adjusted OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current medication use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>1.84 (1.69–2.00)</td>
<td>1.45 (1.32–1.59)</td>
</tr>
<tr>
<td>Other monoamine antidepressants</td>
<td>1.36 (1.27–1.46)</td>
<td>1.15 (1.07–1.24)</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.90 (0.62–1.30)</td>
<td>0.63 (0.43–0.93)</td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>1.46 (1.26–1.69)</td>
<td>1.01 (0.86–1.19)</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>1.79 (1.49–2.14)</td>
<td>0.96 (0.79–1.17)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1.21 (1.15–1.28)</td>
<td>1.10 (1.04–1.16)</td>
</tr>
<tr>
<td><strong>Mental disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td>NA</td>
<td>1.72 (1.53–1.95)</td>
</tr>
<tr>
<td>Depression</td>
<td>NA</td>
<td>1.12 (1.03–1.20)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>NA</td>
<td>1.61 (1.27–2.04)</td>
</tr>
<tr>
<td>Dementia</td>
<td>NA</td>
<td>1.41 (1.29–1.54)</td>
</tr>
</tbody>
</table>

Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case–control studies

Wu Q et al.
Risk of Fracture Associated with SSRI Use

Anticonvulsant-induced bone loss

- Some, not all, anticonvulsants induce hepatic cytochrome P$_{450}$ activity and accelerate catabolism of 25-OH vitamin D
- Low 25-OH vitamin D levels
- Inhibition of calcium absorption
- 2$^{nd}$ hyperparathyroidism
- Osteomalacia
Anticonvulsant Use and Fractures

*Unadjusted model; † fully adjusted model.

Risk Factors for Anticonvulsant Bone Disease

- High-dose, multiple drug regimen
- Long-term therapy
- Low vitamin D intake
- Limited sunlight exposure
- Elderly or institutionalized patients
Treatment of Anticonvulsant Bone Disease

- Calcium 1200 mg QD
- **Vitamin D** in dosages necessary to maintain normal 25-OH vitamin D level
- **Mean 2400 mg/day** *
- Consider switching to other anticonvulsants which do not cause this problem

* A prospective study to evaluate the dose of vitamin D required to correct low 25-hydroxyvitamin D levels, calcium, and alkaline phosphatase in patients at risk of developing antiepileptic drug-induced osteomalacia.

Collins N; Maher J; Cole M; Baker M; Callaghan N. Q J Med 1991;78(286):113-22
Drug-induced Osteoporosis

- Glucocorticoids
- Aromatase inhibitors
- Medroxyprogesterone acetate for contraception
- Proton pump inhibitors (PPIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Antiseizure medicines
- Thiazolidinediones
- Long-term Heparin
- Tamoxifen (premenopausal use)
- Gonadotropin releasing hormone agonists (GnRH)
- Thyroid hormones in excess
- Antiretroviral Therapy
- Lithium
- Chemotherapeutic / immunosuppressives (MTX, CsA, Tacrolimus)
"I feel a lot better since I ran out of those pills you gave me."