Breaking News in Osteoporosis
Long-term Bisphosphonate Therapy: Helpful or Harmful?

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May 9, 2012

Bisphosphonates for Osteoporosis---- Where Do We Go from Here?

Marcea Whitaker, MD, Jia Guo, PhD, Theresa Kehoe, MD and George Benson, MD

The New York Times

"New Cautions About Long-Term Use of Bone Drugs" May 9, 2012

An X-ray shows a fracture in the femur of a woman who used Fosamax for seven years

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The New York Times

"New Cautions About Long-Term Use of Bone Drugs" May 9, 2012

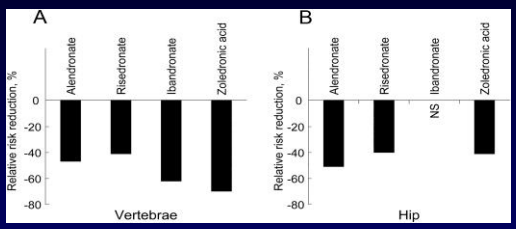
"The concern is that after years of use, the drugs may in rare cases actually lead to weaker bones in certain women, contributing to "rare but serious adverse events," including unusual femur fractures, esophageal cancer and osteonecrosis of the jaw, a painful and disfiguring crumbling of the jaw bone."

FDA-Approved Indications for BPs

	Postmenopausal Osteoporosis		Glucocorticoid-Induced Osteoporosis		Men
	Prevention	Treatment	Prevention	Treatment	
Alendronate (1995)	√	√		√	√
Risedronate (2000)	√	√	√	√	√
Ibandronate (2005)	√	√			
Zoledronate (2007)	√	√	√	√	√

Watts *et al.* J Clin Endocrinol Metab 2010.

RRR in fractures after three years of treatment



Khosla S et al. JCEM 2012;97:2272-2282

FDA Review of Long-Term Efficacy Trials

- 3 long-term extension trials (1496 pts)
  Alendronate (FLEX) 10 yrs
  Risedronate (VERT-MN) 7 yrs
  Zoledronic Acid (HORIZON-PFT) 6 yrs
- FDA reanalysis of data : composite end point of all fractures (vertebral and nonvertebral)
- Conclusion: little benefit beyond 5 yrs

FDA Labeling Change
"Important Limitations of Use"

"The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis"

Whitaker et al, NEJM, May 2012

FDA Labeling Change
"Important Limitations of Use"

"Patients at low risk for fracture (e.g. younger patients without a fracture history and with a bone mineral density approaching normal) may prove to be good candidates for discontinuation..after 3 to 5 years,

.....whereas patients at increased risk (e.g. older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy."

Whitaker et al, NEJM, May 2012

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Continuing Bisphosphonate Treatment for Osteoporosis: For Whom and for How Long?

Dennis Black, MD; Douglas Bauer, MD, Ann Schwartz, PhD, Steven Cummings, MD and Clifford Rosen, MD

FLEX: Alendronate Long-term extension trial

Characteristic	NNT for 5 yrs to prevent one Clinical Vertebral Fracture
No Vertebral Fracture	
T-score ≤ -2.5	24
T-score > -2.5 and ≤ -2.0	63
T-score >-2.0	102
+Vertebral Fracture	
T-score ≤ -2.5	17
T-score > -2.5 and ≤ -2.0	17
T-score >-2.0	51

What happened to the placebo group in FLEX trial?

- 21% of postmenopausal women fracture in 5 years after stopping alendronate

Bauer, ASBMR Oct 2010

Incidence of Fracture by Treatment Group: FLEX Trial

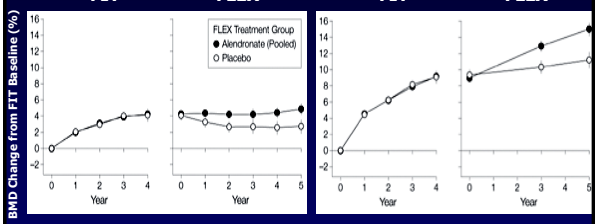
Table 3. Incidence of Fracture by Treatment Group

Fractures	Placebo, No. (%) (n = 437)	Pooled Alendronate, No. (%) (n = 662)	Relative Risk (95% Confidence Interval)*
Vertebral			
Clinical	23 (5.3)	16 (2.4)	0.45 (0.24-0.85)
Morphometric	46 (11.3)	60 (9.8)	0.86 (0.60-1.22)
Clinical			
Any	93 (21.3)	132 (19.9)	0.93 (0.71-1.21)
Nonspine	83 (19.0)	125 (18.9)	1.00 (0.76-1.32)
Hip	13 (3.0)	20 (3.0)	1.02 (0.51-2.10)
Forearm	19 (4.3)	31 (4.7)	1.09 (0.62-1.96)

*Adjusted for clinic and stratum.

Black, D. M. et al. JAMA 2006;296:2927-2938.

BMD Change in FLEX Participants



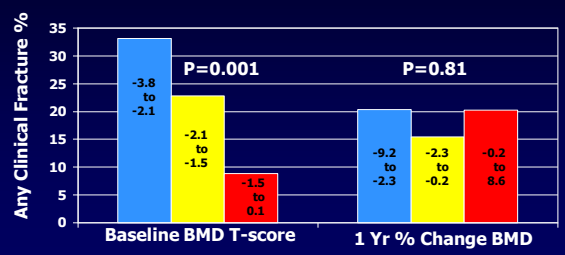
Black, D. M. et al. JAMA 2006;296:2927-2938.

What predicts fracture after discontinuation in FLEX trial?

- Strongly related to total hip BMD at baseline
- May not be related to change in total hip BMD at 1 yr and 2 yr
- But cannot rule out an increased fracture risk among women with substantial BMD loss after discontinuation

Bauer, ASBMR Oct 2010

Predicting fractures in the 5 years after discontinuing alendronate (FLEX)



437 women in placebo group of FLEX trial; BMD at total hip

Bauer, ASBMR, Oct 2010

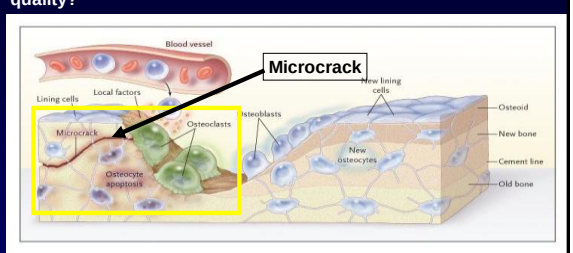
Are atypical fractures a risk of long-term therapy?

Femoral Neck

Subtrochanteric

The Bone Remodeling Cycle

•Does long-term use of bisphosphonates impair the repair of microcracks and replacement of old bone leading to poor bone quality?



Seeman E and Delmas P. N Engl J Med 2006;354:2250-2261

If bisphosphonates were not offered to postmenopausal women with osteoporosis:

10-29 osteoporotic fractures would occur for each subtrochanteric fracture avoided

This is likely to be a low estimate (over a 5 year period)

Abrahamson, ASBMR 2010

Osteonecrosis of the Jaw

after tooth extraction in a patient taking zoledronic acid for metastatic breast cancer

- Over 90% of cases are in cancer patients
- 60% of cases occur after tooth manipulation
- 40% likely related to periodontal disease and trauma
- Under-reported side effect
- *Prevention*
  - Remove foci of infection before initiating a bisphosphonate
  - Regular dental exams

Woo, S.-B. et. al. Ann Intern Med 2006;144:753-761

Bisphosphonates: Weighing the Risks

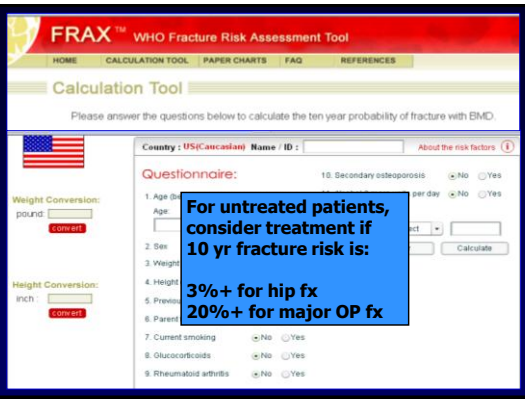
Benefits	Risks
Vertebral Fracture Absolute Risk Reduction 1000-2300/100K pt yrs	Atypical Femur Fractures 60-100/100K pt yrs
Nonvertebral Fracture Absolute Risk Reduction 700-1000/100K pt yrs	Osteonecrosis of Jaw Incidence: 20-28/100K pt yrs Prevalence: 10-14/100K users

Abrahamson, 2010
Jan de Beur, ASBMR, 2012

WHO Fracture Risk Assessment Tool: FRAX™

http://www.shef.ac.uk/FRAX/index.htm

Risk Factors Included in the FRAX™ Tool	
Current Age	Use of glucocorticoid therapy
Gender	Secondary osteoporosis/RA
Personal history of a fracture	Parental hip fracture
Femoral neck BMD	Current smoking
Low body mass index	Alcohol use ≥ 3 drinks/day



Expert Opinion Regarding Duration

Fracture Risk	Suggested Duration of Rx	Suggested Duration of Drug Holiday
Low	Rx rarely needed	N/A
Mild	3-5yrs	Off BP until BMD decreases significantly or fracture occurs
Moderate	5-10yr	Off BP for 2-3+ yrs (or less if BMD decreases or fracture)
High	10yr	Off BP for 1-2+ yrs (or less if BMD decreases or fracture occurs); consider alternate medications during BP holiday

Watts and Diab, JCEM, 2010

What are the options?

- Continued drug holiday
  - Continue adequate calcium, vitamin D, physical activity, avoidance of falls
- Reinitiate bisphosphonate therapy
- Denosumab
- Teriparatide
- Raloxifene

Not all bisphosphonates are the same

- Half-life is long but varies
- Zoledronate>Alendronate>Risedronate

Case 1

- 56yo WF, no fracture history, menopause 2008
  LS -2.0 (-6.6% vs 2007)
  FN -2.1 (-2.2% NS vs 2007)
- Oral alendronate Dec 2008: leg cramps
- FRAX Risk: Major OP: 5.3%; Hip 0.3%
- Recommend: No pharmacologic treatment

Case 2

- 56yo WF, temodar for pituitary macroadenoma resulting in menopause 2009; hx ankle fx 2008
  LS -0.8
  FN -1.9 (-8.1% vs 2010)
- FRAX Risk: Major OP 23%; Hip 2.5%
- Recommend: Oral bisphosphonate for 3 years

Case 3

- 81yo WF hx femur fx 2003; tib-fib fx 1998
  LS -2.2
  FN -3.8 (+3.8% vs 2004)
- Oral bisphosphonates 2003-2010
- FRAX Risk: Major OP 34%; Hip 17% but not valid after treatment + T-score <-2.5
- Recommend: continued drug holiday vs teriparatide

Case 4

- 60yo WF no fracture history
  LS -2.6
  FN -3.4 (-7.2% vs 2010)
- Oral bisphosphonates 2007-2010
- FRAX Risk: Major OP 7.6%; Hip 0.7% but not valid after treatment + T-score <-2.5
- Offered: continued drug holiday, restart bisphosphonate therapy vs teriparatide

Recommendations

- No rationale to withhold BP therapy from patients with osteoporosis
- Use FRAX to determine need to start a BP in a pt with osteopenia
- Continued use of BPs beyond a treatment period of 3-5 years should be re-evaluated annually based on pertinent medical history & medication regimen
- Consider drug holidays; restart BP or another agent if loss of BMD or fracture
- Ask about thigh & groin pain in pts on long-term BP therapy