
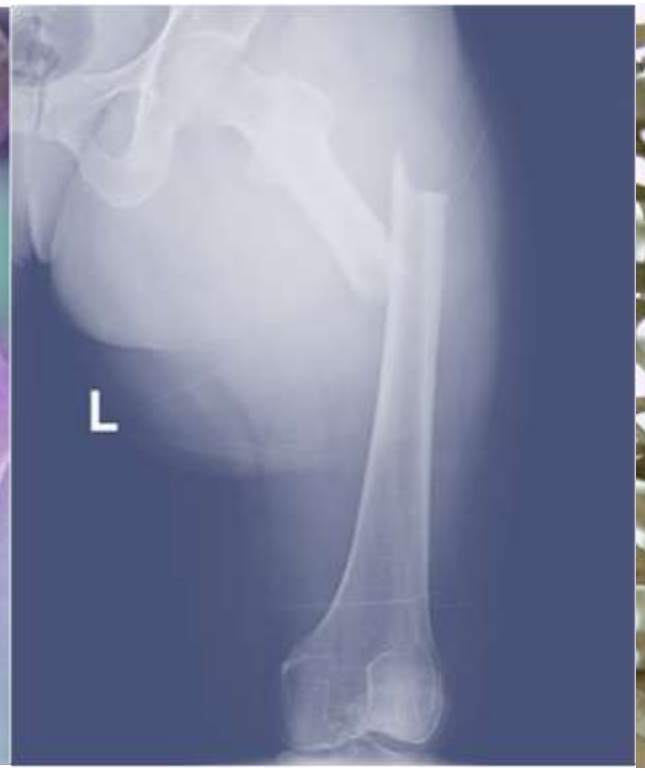

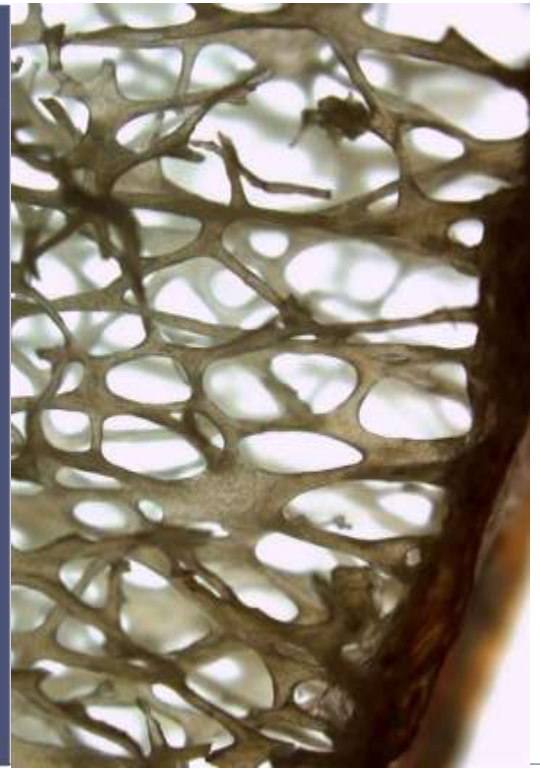

Long-term drug therapy and drug discontinuation for fracture prevention

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Annual Refresher Course for Family Physicians, McGill; October 2019

Disclosures

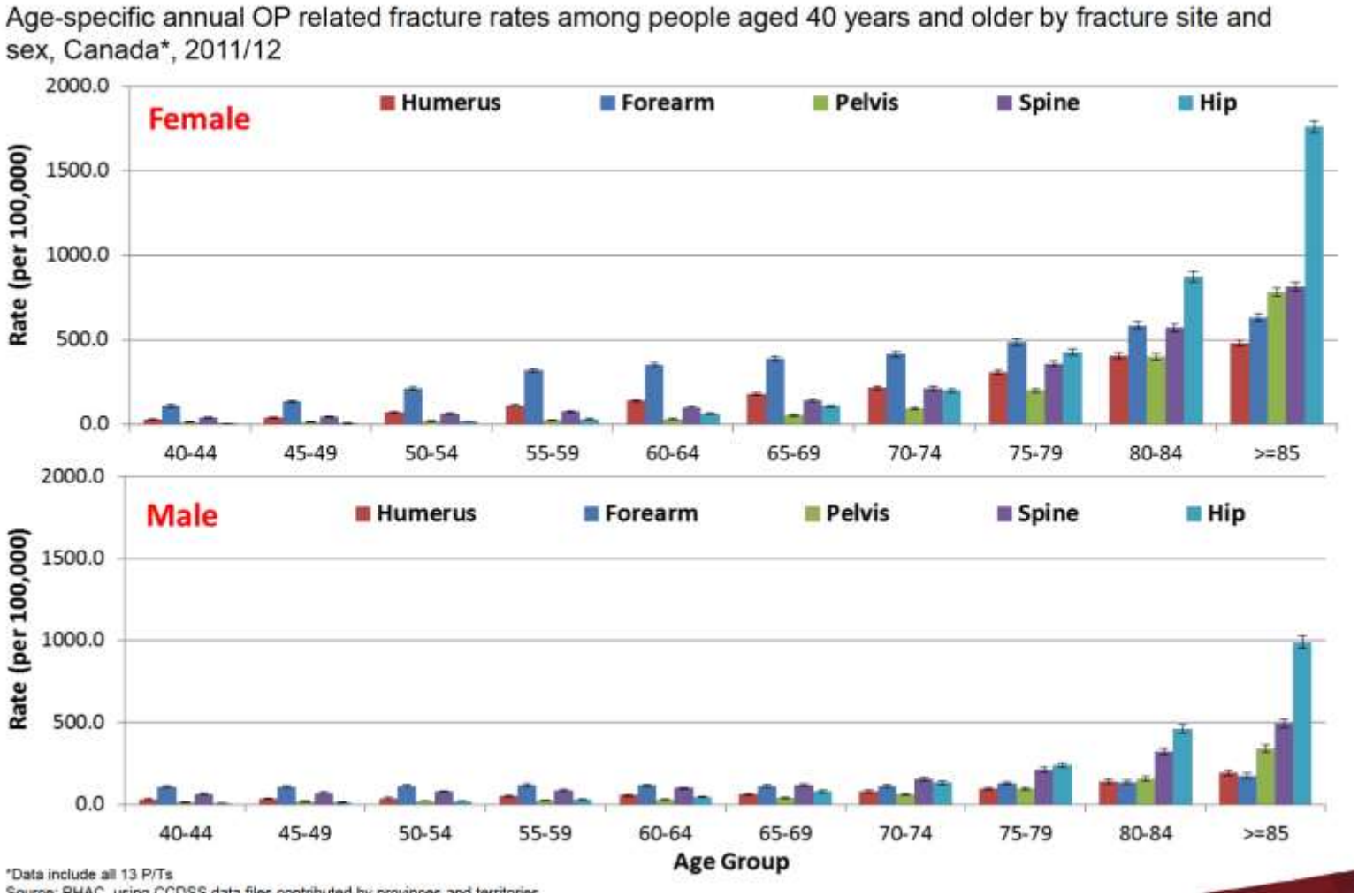
- Research Grants:
  - Industry partnership grant with CIHR, GreyBox and Amgen
    - HIP MOBILE study

Objectives

As a result of attending this session, participants will be able to:

- Discuss the benefits and harms associated with longer term anti-osteoporosis pharmacotherapy
- Discuss the effects of stopping anti-osteoporosis pharmacotherapy (drug holiday)on fracture risk
- Integrate monitoring strategies for patients who are on pharmacotherapy or off pharmacotherapy (drug holiday) for fracture prevention

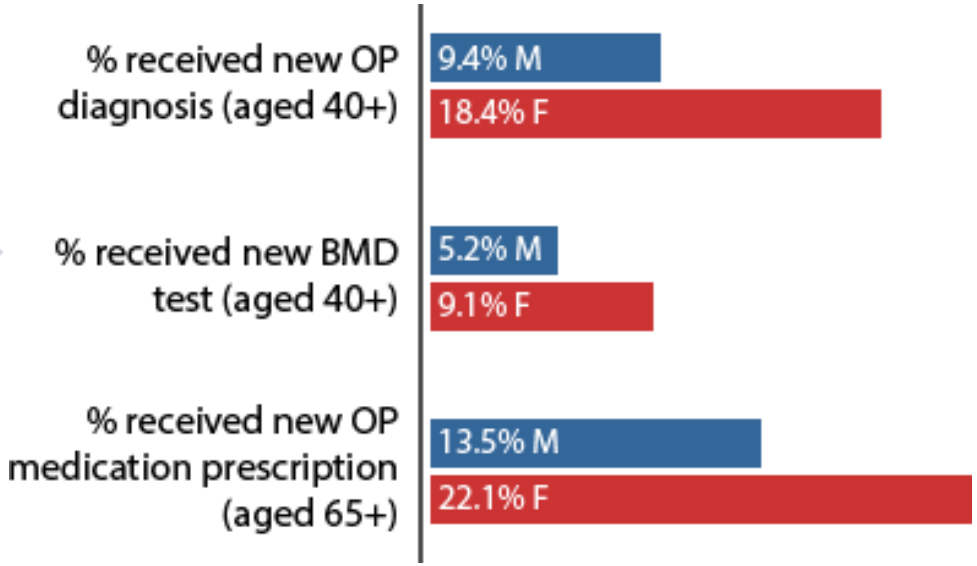
Osteoporotic Fractures: A Canadian Perspective- Public Health Agency of Canada



Morin SN et al ASBMR 2018

In Canada in 2014-15:

136,000
fractures* among Canadians aged 40+, of which



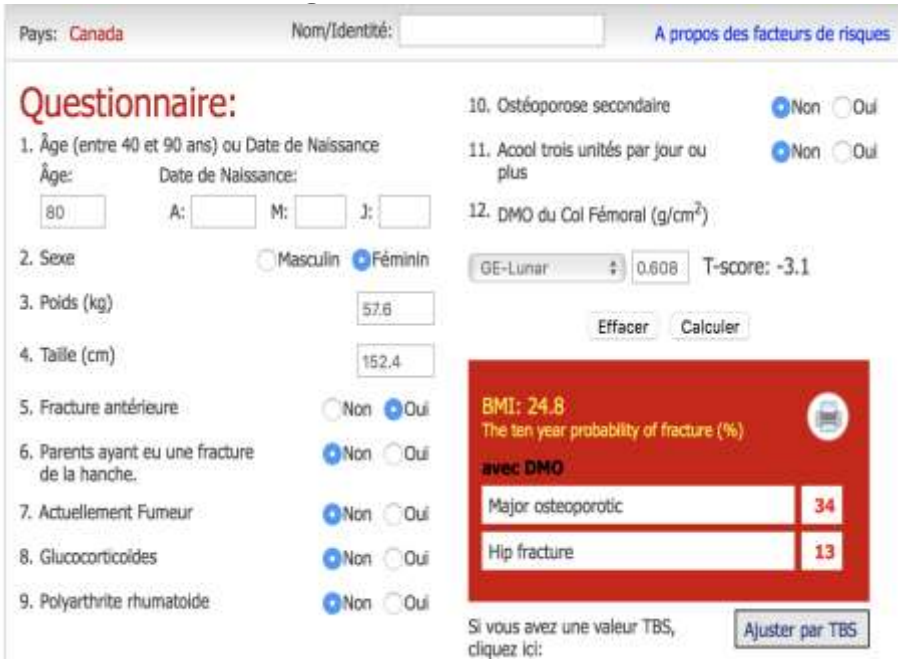
*Fracture includes hip, forearm, spine, humeral or pelvis.
Data were not available from: YT for fractures; YT and SK for new OP diagnosis; YT, NU, SK, and NS for new BMD test; and YT, NT, SK, and NB for new OP medication prescription.
Source: Public Health Agency of Canada using Canadian Chronic Disease Surveillance System data files contributed by provinces and territories, July 2018.

- Morin SN et al ASBMR 2018

Ms FFx

- 80 y old
- HBP controlled; Remote CVA – no residual deficit
- Long standing seizure disorder; well controlled with carbamazepine
- Previous wrist fractu
-

L2-L4	25/Sep/2013
Neck	25/Sep/2013



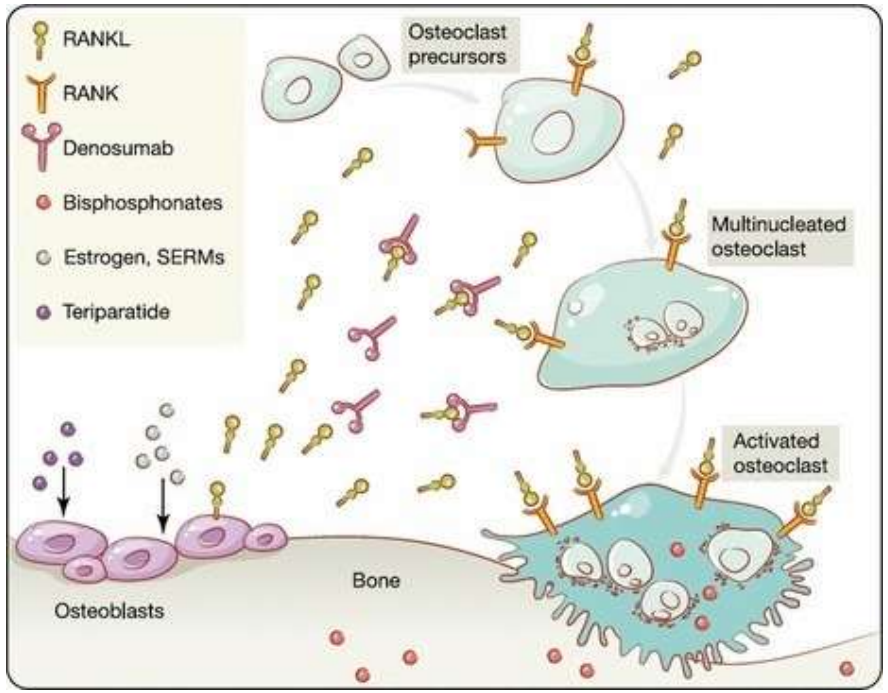
Antiresorptive and Anabolic Bone Drugs for OP

Bisphosphonates:
ALN, RSN, ZOL
RANKL inhibitor:
Denosumab
SERMs:
Raloxifene

Benefits
Inhibit osteoclastic activity
Decrease BTM
Increase BMD
Reduce Fractures (all sites)
Generally well tolerated

Adverse effects
GI
Acute phase reaction
Muscle cramps

Thromboembolic events
Atypical Femur Fractures
Osteonecrosis of the Jaw



Bisphosphonates: slow offset
Denosumab rapid offset
Raloxifene: rapid offset

Teriparatide: rapid offset
Romozosumab: rapid

PTH analogues:
Teriparatide
Sclerostin AB:
Romozosumab

Benefits
Activates osteoblastic activity
Increase BMD
Reduce Fractures
Generally well tolerated

Adverse effects
Hypercalcemia
Hyperuricemia
Muscle cramps

BlackBox warning:
T: Osteosarcoma
*approved for max **24** months
R: CVD
*approved for max **12** months

Efficacy of Approved Anti-resorptive Medications for the Treatment of Osteoporosis in women (RCT)

RCT[1] of alendronate vs. pbo for 3y in 2027 PM women aged 55-81 with RVF and T-score ≤−1.6			
Fracture Type	Relative and Absolute Risk Differences (95% CI)		
RVF	Lower risk	RR 0.53 (0.41 to 0.68)	ARD −12% (−15% to −10%)
Clinical fracture	Lower risk	HR 0.72 (0.58 to 0.90)	ARD −5% (−8% to −1%)
Nonvertebral fracture	No significant difference	HR 0.80 (0.63 to 1.01)	ARD −2.8% (−5.7% to 0.2%)
Hip fracture	Lower risk	HR 0.49 (0.23 to 0.99)	ARD −1.1% (−2.2% to 0.0%)
RCT[2] of alendronate vs. pbo for 4y in 1631 PM women aged 54-81 without RVF and T-score ≤−2.5 (subgroup analysis)			
Fracture Type	Relative and Absolute Risk Differences (95% CI)		
RVF	Lower risk	RR 0.50 (0.31 to 0.82)	ARD −3% (−5% to −1%)
Clinical fracture	Lower risk	HR 0.64 (0.50 to 0.82)	ARD −7% (−10% to −3%)
Hip fracture	Lower risk	HR 0.44 (0.18 to 0.97)	ARD −1.2% (−2.4% to 0.0%)
RCT[3] of risedronate vs. pbo for 3y in 5445 PM women aged 70-79 with T-score <−4.0 or T-score <−3.0 plus 1 nonskeletal risk factor			
Fracture Type	Relative and Absolute Risk Differences (95% CI)		
Hip fracture	Lower risk	HR 0.60 (0.60 to 0.90)	ARD −1.0% (−1.8% to −0.2%)
RCT[4] of risedronate vs. pbo for 3y in 2458 PM women aged <85 with ≥2 RVF or 1 RVF and T-score ≤−2.0			
Fracture Type	Relative and Absolute Risk Differences (95% CI)		
RVF	Lower risk	RR 0.59 (0.43 to 0.82)	ARD −6% (−9% to −2%)
Nonvertebral fracture	Lower risk	HR 0.60 (0.39 to 0.94)	ARD −2% (−5% to 0%)
RCT[5] of zoledronate vs. pbo for 3y in 3889 PM women aged <85 with T-score ≤−2.5 or ≥2 RVF and T-score ≤−1.5			
Fracture Type	Relative and Absolute Risk Differences (95% CI)		
RVF	Lower risk	RR 0.30 (0.24 to 0.38)	ARD −8% (−9% to −6%)
Clinical fracture	Lower risk	HR 0.67 (0.58 to 0.37)	ARD −4% (−5% to −3%)
Nonvertebral fracture	Lower risk	HR 0.75 (0.64 to 0.87)	ARD −3% (−4% to −1%)
Hip fracture	Lower risk	HR 0.59 (0.42 to 0.83)	ARD −0.9% (−1.5% to −0.3%)

RCT[7] of denosumab vs. pbo for 3y in 7868 PM women aged 60-90 with T-score ≤−2.5			
Fracture Type	Relative and Absolute Risk Differences (95% CI)		
RVF	Lower risk	RR 0.32 (0.26 to 0.41)	ARD −5% (−6% to −4%)
Nonvertebral fracture	Lower risk	HR 0.80 (0.67 to 0.95)	ARD −1.4% (−2.5% to −0.3%)
Hip fracture	Lower risk	HR 0.60 (0.37 to 0.97)	ARD −0.4% (−0.8% to 0.0%)
RCT[8] of raloxifene vs. pbo for 3y in 7705 PM women aged 31-80 with T-score ≤−2.5 or RVF			
Fracture Type	Relative and Absolute Risk Differences (95% CI)		
RVF	Lower risk	RR 0.70 (0.50 to 0.80)	ARD −4% (−5% to −2%)
Nonvertebral fracture	No significant difference	HR 0.90 (0.80 to 1.10)	ARD −0.8% (−2.2% to 0.6%)

RVF: radiographic vertebral fractures
ARD Absolute risk difference
RR Relativerisk
HR: Hazard ratio

Ensrud K and Crandall CJ. *JAMA* October 17 2019

Osteoporosis Duration of Treatment: debate unique among chronic disease management

- How well does a specific drug maintain its anti-fracture efficacy with long term use?
- How does the duration of medication influence the risk of rare side effects such as atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ)
- How persistent is the anti-fracture efficacy of a specific drug after it is discontinued?

Longer term therapy (> 3years)

- Efficacy: Anti-Fracture Benefits:
- Alendronate vs PBO x 4 years
  - Lower risk in RVF HR 0.56 (95% CI: 0.39-0.80)
  - No difference in clinical fractures, hip fractures
- Zoledronic Acid vs PBO x 6 years
  - Clinical fractures: HR 0.73 (95% CI: 0.60-0.90); ARD: 5%
  - Non vertebral fractures: HR: 0.66 (95% CI: 0.51-0.85); ARD 5%
  - Clincal vertebral fractures: 0.41 (95% CI: 0.22-0.75) ; ARD 2%
- Raloxifene vs PBO 4 to 8 years
  - Clinical vertebral fractures: RR 0.58 (95% CI: 0.43-0.79); ARD 2%
- Extension studies:
  - Alendronate (FLEX): 10 y, Zoledronic Acid: 9 years
  - Denosumab 10 years
- Harms:
  - RCTs: AFF and ONJ too few
  - Cohort studies:
    - AFF and ONJ incidence increases with duration of therapy.
    - AFF: ++ Bisphosphonates (110 per 100,00 person years with treated for 9 years+); + Denosumab
    - ONJ: very rare in OP population

- Fink HA *Ann Int Med* 2019. 171(1):37-50

Duration of Therapy
What do Guidelines currently Recommend ?

- Osteoporosis Canada Individuals at high risk for fracture should continue osteoporosis therapy without a drug holiday--Guidelines currently being updated, to be published in 2020
- The ACP guidelines (2017) recommend therapy with bisphosphonates or denosumab for 5 years to reduce hip and vertebral fractures – but suggest that high risk patients may benefit from longer treatment
- The NOF guidelines (2014) recommend an initial treatment with bisphosphonates of 3 to 5 years and those at high risk should continue treatment
- An ASBMR task force (2016) recommends an initial 5 years of oral bisphosphonate therapy or 3 years of iv therapy followed by continued therapy up to 10 years (oral) or 6 years (IV) in those at high risk (low hip T-score, previous MOF or fracture while on therapy or older women)


OSTEOPOROSIS
BONE DENSITY
POTENTIAL FRACTURE SITES
+65 AGE
HIP FRACTURE
CAFEINE
SPINE
CALCIUM
YOGURT
SMOKING
SUN
EXERCISE
AVOID ALCOHOL
VITAMIN D
M
BONE MATRIX
OSTEOPOROSIS
OSTEOPENIA
NORMAL
-3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0
T-SCORE
LOST OF HEIGHT
BACK PAIN

Mrs FFx

- 83 y old
- Tolerating bisphosphonate well
- Usually does not forget to take her medication
- Walks when the weather is nice and attends an exercise class twice a week
- She has fallen twice in the last 6 months- no injuries
- Her weight is stable

L2-L4	19/Apr/2016	83.4	Osteoporosis	-3.0	0.843 g/cm²	2.2%	-
Neck	19/Apr/2016	83.4	Osteoporosis	-3.2	0.601 g/cm²	-2.6%	-

Objective 2_Drug Holiday (temporary discontinuation)

- Interruption of therapy after initial treatment: to reduce risk of Harms
  - Who- When- For how long - ?
  - What would be the criteria for resuming therapy

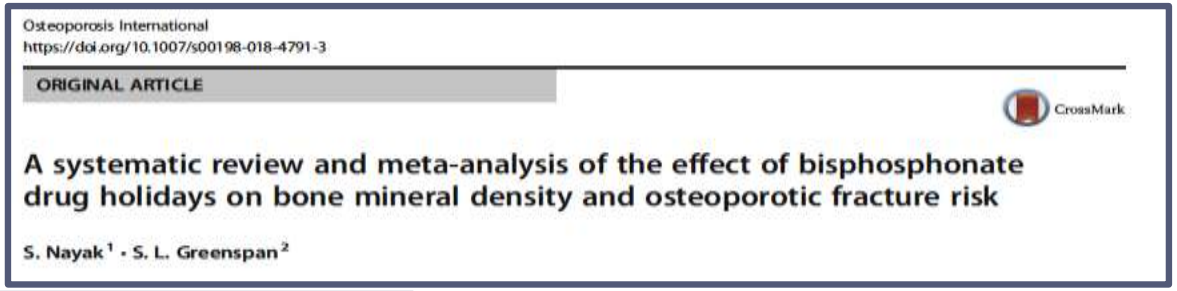
Annals of Internal Medicine

REVIEW

Long-Term Drug Therapy and Drug Discontinuations and Holidays for Osteoporosis Fracture Prevention

A Systematic Review

Howard A. Fink, MD, MPH; Roderick MacDonald, MS; Mary L. Forte, PhD, DC; Christina E. Rosebush, MPH; Kristine E. Ensrud, MD, MPH; John T. Schousboe, MD, PhD; Victoria A. Nelson, MSc; Kristen Ullman, MPH; Mary Butler, PhD, MBA; Carin M. Olson, MD, MS; Brent C. Taylor, MPH, PhD; Michelle Brasure, PhD, MSPH, MLIS; and Timothy J. Wilt, MD, MPH



Osteoporosis International

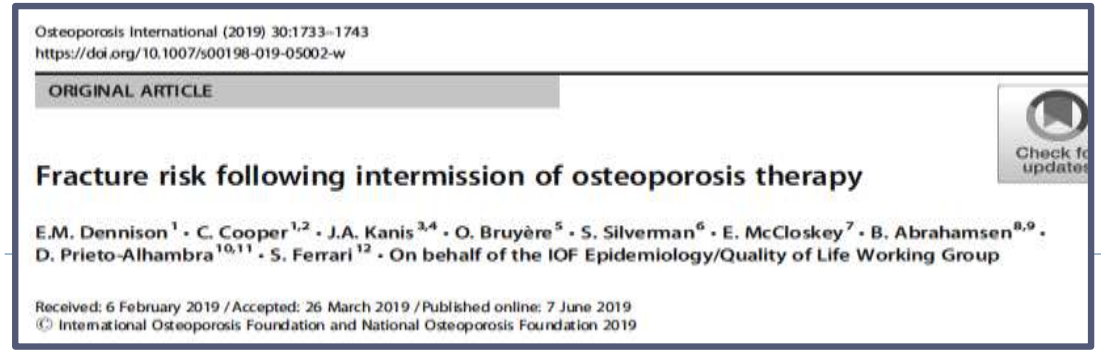
https://doi.org/10.1007/s00198-018-4791-3

ORIGINAL ARTICLE

CrossMark

A systematic review and meta-analysis of the effect of bisphosphonate drug holidays on bone mineral density and osteoporotic fracture risk

S. Nayak[1] · S. L. Greenspan[2]



Osteoporosis International (2019) 30:1733–1743

https://doi.org/10.1007/s00198-019-05002-w

ORIGINAL ARTICLE

Check for updates

Fracture risk following intermission of osteoporosis therapy

E.M. Dennison[1] · C. Cooper[1,2] · J.A. Kanis[3,4] · O. Bruyère[5] · S. Silverman[6] · E. McCloskey[7] · B. Abrahamsen[8,9] · D. Prieto-Alhambra[10,11] · S. Ferrari[12] · On behalf of the IOF Epidemiology/Quality of Life Working Group

Received: 6 February 2019 / Accepted: 26 March 2019 / Published online: 7 June 2019

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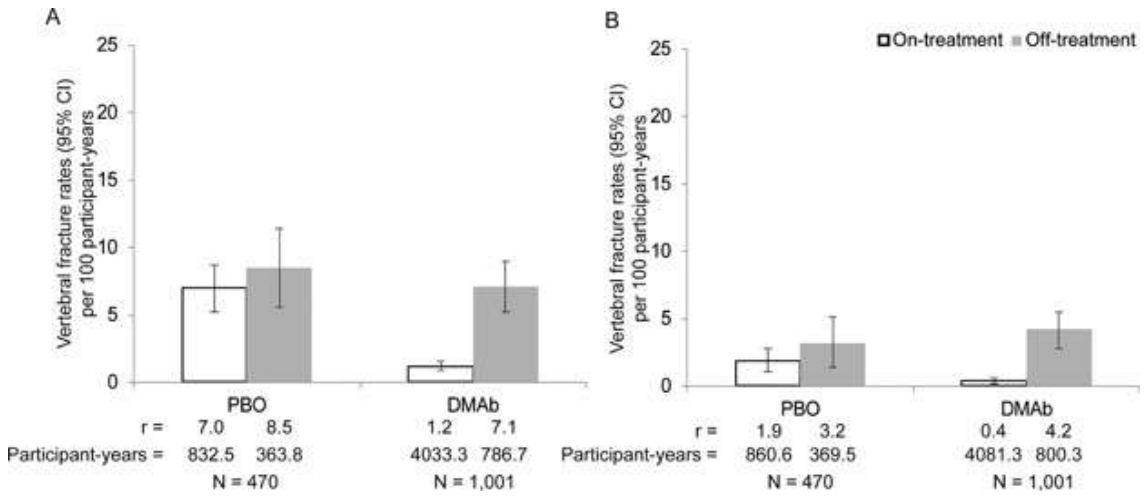
Effects of Bisphosphonate Discontinuation vs Continuation on Incident fractures

Drug: Continuation vs Discontinuation	Fracture outcome	Relative Risk (95% CI)	Absolute Risk Difference	Strength of Evidence
Alendronate (N=1099) (10 y vs 5y+ 5y PBO)	Clinical	0.93 (0.71-1.21)	-1% (-6- 4%)	moderate
	Non vertebral	1.00 (0.76-1.32)	-1% (-5 - 5%)	moderate
	Clinical Vertebral	**0.45 (0.24-0.85)**	**-3% (-5- -0.5%)**	moderate
	R Vertebral	0.86 (0.60-1.22)	-1% (-5- 2%)	moderate
Zoledronic Acid (N=1233) (6 y vs 3y +3y PBO)	Clinical	1.04 (0.71-1.54)	NA	moderate
	Non vertebral	0.99 (0.7- 1.5)	-0.3% (-3- 35)	moderate
	Clinical Vertebral	1.81 (0.53- 6.2)	NA	insufficient
	R Vertebral	**0.51 (0.26-0.95)**	**-3% (-6- -1%)**	low

- Fink HA *Ann Int Med* 2019. 171(1):37-50

Denosumab Discontinuation and Rebound-associated Vertebral Fractures

Vertebral Fractures After Discontinuation of Denosumab:
A Post Hoc Analysis of the Randomized
Placebo-Controlled FREEDOM Trial and Its Extension



KEY POINTS

- Denosumab, a well-tolerated, injectable inhibitor of osteoclast-mediated bone resorption, has been shown in randomized controlled trials to reduce significantly the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.
- Recent evidence shows that patients previously treated with denosumab who discontinue the drug have an increased risk for rebound vertebral fractures, which are often multiple and may occur as soon as eight months after the last injection of the drug.
- When prescribing denosumab, clinicians should consider the patient's ability to adhere to regular dosing and counsel the patient against discontinuation without medical consultation.

Important to review risk and benefits of use upon initiation
Preliminary data supporting that one year of alendronate or iv zoledronic acid is protective of rebound bone loss

- Cummings S et al *JBMR* 2018
  Symonds C et al *CMAJ* 2018

Predicting Fracture Risk during a bisphosphonate holiday in the FLEX study

- BP therapy reduces fractures but to minimize risk of rare side effects, drug holidays (temporary stopping of BP) have been proposed. However, no specific tools are available to quantify fracture risk following BP discontinuation and therefore selection for drug holidays remains subjective.
- FLEX was a randomized trial for an alendronate (ALN) drug holiday after 5 years of initial ALN in the FIT trial. To develop a fracture risk equation after stopping ALN, we used data from the 408 patients randomized to placebo in FLEX.
- A predictive model was created
- Potential risk factors included age, BMD, bone turnover markers (BTM) and fracture history all measured before, during and after the initial 5 year ALN treatment. We compared the results of our risk prediction model to results that could be achieved using FRAX (10-yr MOF) **at FLEX baseline.**
- **Significant predictors in the final FLEX multivariate (MV) model included BMD, age and vertebral fracture status all measured at FLEX baseline.**
- **Factors that were not significant included BTMs (at any time), BMD change and fractures during FIT and other factors.**
- FRAX MOF risk to be equal or superior to the FLEX equation for predicting risk for clinical vertebral and as well as non-spine and hip fracture.

- **After 5 years of alendronate individuals with FRAX 10 year MOF risk above about 23% identifies a high risk group that will likely benefit from an additional 5 years of ALN.**

Black D et al ASBMR annual meeting September 2019

Objective 3_Monitoring while on therapy

- Does monitoring, **while on therapy**, lead to a change in **fracture** outcomes within the treated population?

- Risk factors (FRAX risk score)
- BMD
- Bone turnover markers
  - Formation (osteocalcin)
  - Resorption (C-telopeptide)
- OC: BMD between 1 to 3 years
- ACP: No monitoring while on therapy
- NOF: BMD every 2 years, BTMs may be helpful

BMD Change and Fracture Risk

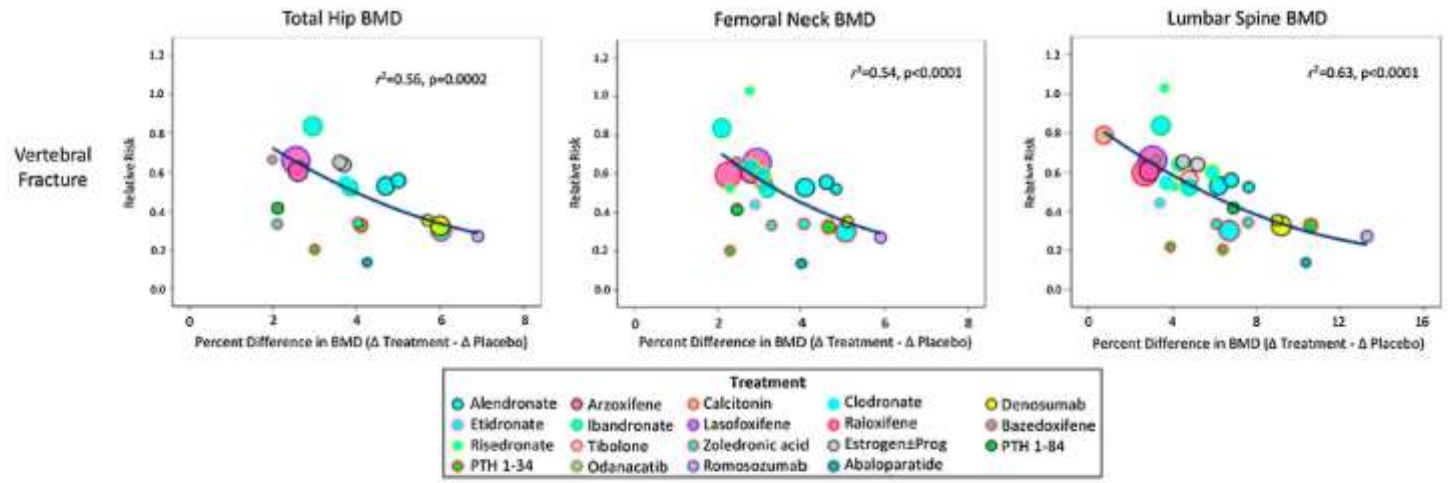


Fig. 1. Association between treatment-related differences in BMD (Active-Placebo, in %) and reduction in vertebral fracture risk. Individual trials are represented by circles with areas that are approximately proportional to the number of fractures in the trial. Drugs of the same class are represented by the symbols of the same color.

Table 5. Estimated Fracture Risk Reduction Associated With BMD Improvement

	Vertebral fracture	Hip fracture	Nonvertebral fracture
Δ Total hip BMD			
2%	28%	16%	10%
4%	51%	29%	16%
6%	66%	40%	21%
Δ Femoral neck BMD			
2%	28%	15%	11%
4%	55%	32%	19%
6%	72%	46%	27%
Δ Lumbar spine BMD			
2%	28%	22%	11%
8%	62%	38%	21%
14%	79%	51%	30%

BMD = bone mineral density.

Bouxsein M et al *JBMR* 2019

BTMs Change and Fracture Risk

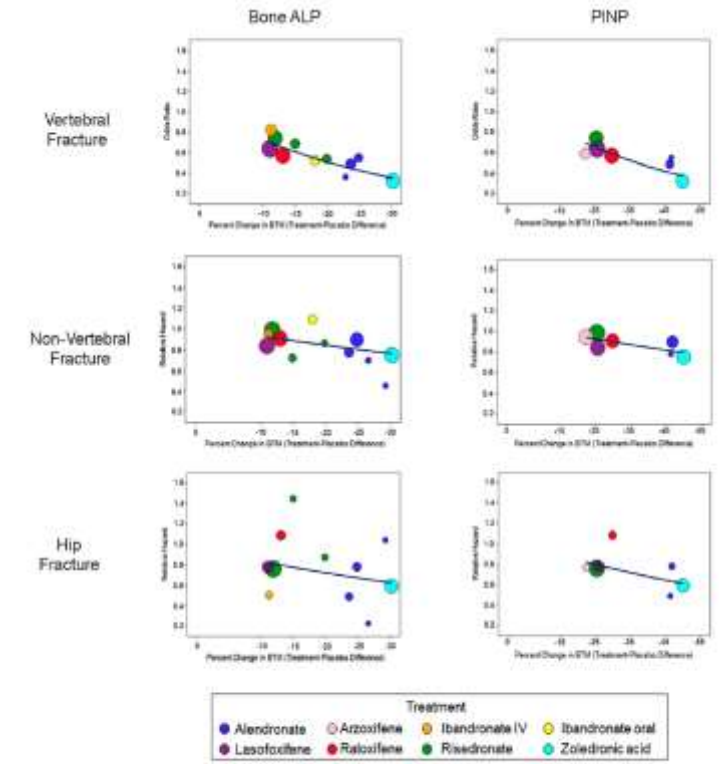


Fig. 1. The relationship between the odds ratio (for vertebral fracture) or the relative hazard (for nonvertebral and hip fracture) and the difference between treatment and placebo group in percentage change in BTM for the two bone formation markers. Larger circles indicate studies with more fractures, and the line represents log relative risk plotted against percent change.

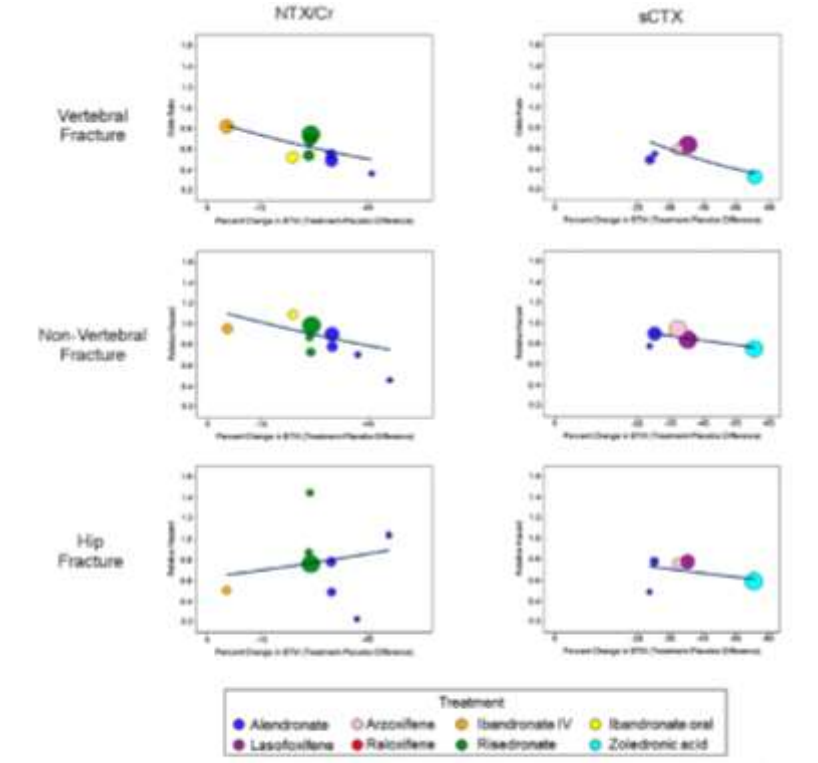


Fig. 2. The relationship between the odds ratio (for vertebral fracture) or the relative hazard (for nonvertebral and hip fracture) and the difference between treatment and placebo group in percentage change in BTM for the two bone resorption markers. Larger circles indicate studies with more fractures, and the line represents log relative risk plotted against percent change.

Bauer DC et al *JBMR* 2018

Monitoring while Off Therapy

- Does an observed increase/decrease (vs stability) in a monitoring parameter **during the drug holiday** following bisphosphonate therapy predict a difference in **fractures**?
- Risk factors (FRAX risk score)
- BMD
- Bone turnover markers
  - Formation (osteocalcin)
  - Resorption (C-telopeptide)

Short-term (1 and 2 years) monitoring during drug holiday (OFF Rx) with BMD and BTMs

Doug Bauer, 2014, FLEX trial, 437 Women, Alendronate 4 or 5 years to PBO

Tertile with greatest change vs other 2 tertiles	Risk of Fracture HR (95% CI) 2 years off Rx
BMD decrease	
F Neck	1.51 (0.93- 2.44)
Total Hip	1.56 (0.97-2.52)
≥3% decrease	
F Neck	1.45 (0.90-2.35)
Total Hip	**1.68 (1.05-2.72)**
BTM increase	
Resorption marker (NTx)	1.14 (0.70-1.86)
Formation marker (BAP)	1.03 (0.63-1.67)

BMD and older age at the time of discontinuation of alendronate were associated with the risk of fracture after discontinuation
BTMs at the time of discontinuation of alendronate were not associated with subsequent fracture risk

Bauer DC et al *JAMA Int Med* 2014

Mrs FFx

- 86 y old
- Has stopped taking her bisphosphonate 2 years ago
- Continues to walk and go to her class.
- No new medications or health issues
- Takes a vitamin D supplement
- She has gained 1 kg in the last year

L2-L4	30/Apr/2019	86.4	Osteoporosis	-6.5	0.425 g/cm²	-36.0%	Yes
Neck	30/Apr/2019	86.4	Osteoporosis	-3.1	0.608 g/cm²	-2.6%	-

Key Learning Points: Evidence

- There is moderate-high strength evidence that longer term use (>3 years) of bisphosphonates and denosumab reduces fractures
- There is moderate strength evidence that longer term use (>5 years) of bisphosphonates associates with increased harm, namely AFF (rare) and ONJ (very rare)
- There is low to moderate strength evidence that drug holidays do not increase fracture risk in women who do not have very low BMD or have a high FRAX score at end of treatment period (5 years of alendronate or 3 years of zoledronic acid)
- There is low to moderate strength evidence that supports monitoring patients with BMD while on therapy at an interval of 2- 3 years
- There is insufficient evidence to recommend a monitoring strategy for patients while on drug holiday or as to when anti-osteoporosis treatment might be resumed

Key Learning Points: Recommendations for Fracture Prevention

- Objective 1: *Discuss the benefits and harms associated with longer term anti-osteoporosis pharmacotherapy*
- Treatment should be initiated promptly in patients (50+) deemed to be at higher for fractures based on a fracture risk assessment tool (FRAX or CAROC): post-fracture, initiation of high dose glucocorticoids, older frail patients using a bisphosphonate or denosumab
- Duration of initial treatment should be 5 years
- A multi-faceted approach including exercise, balance-gait training and nutrition recommendations MUST be part of the management plan with referral to experts as required
- AFF and ONJ are very, very rarely seen in patients who have been ≤ 5 years of bisphosphonates

Key Learning Points: Recommendations for Fracture Prevention

- Objective 2 : *Discuss the effects of stopping anti-osteoporosis pharmacotherapy (drug holiday)on fracture risk*
- Drug holiday from bisphosphonates should be considered after 3 to 5 years on therapy if the “bone health markers” have stabilized or improved.
- In those who have very low femoral neck BMD, have sustained a recent (< 5 years) major osteoporotic fracture (hip, spine, humerus, pelvis), or who have a FRAX MOF risk of 23% or more, treatment should be prolonged with periodic evaluation for harms
- Drug holiday should last 2 to 3 years, assuming no recurrence in fractures or major change in clinical risk profile
- Standard drug holiday is for bisphosphonate treatment not for denosumab.

Key Learning Points: Recommendations for Fracture Prevention

- Objective 3: *Integrate monitoring strategies for patients who are on pharmacotherapy or off pharmacotherapy (drug holiday) for fracture prevention*
- While on **therapy**, patients can be monitored with a BMD ~ 24 months following initiation of treatment
- While on **drug holiday**, monitoring BMD or BTMs change is NOT helpful in predicting those who will fracture
- Fracture risk should be reassessed after 2 or 3 years after discontinuation. Treatment can resume with a bisphosphonate, if no contraindication.

QUESTIONS?

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