5 – 5:45 pm

Controversies in Osteoporosis Prevention and Management

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- M. Susan Burke, MD, FACP: Speakers Bureau for Merck & Co., Inc.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

- Review the guidelines and controversies regarding screening and benefits and adverse effects of therapy
- Discuss the controversies regarding duration of therapy and monitoring of therapy

The Situation

- 1 in 2 postmenopausal women and 1 in 5 older men will have an osteoporosis-related fracture in their lifetimes.
- Because of the aging of the U.S. population, the number of hip fractures in the U.S. is expected to double or triple by 2040.
- 53.6 million older US adults have osteoporosis or low bone mass at the femoral neck or lumbar spine.

USPSTF, Ann Intern Med 3/1/2011; Schneider and Guralnik 1990; Wright et al JBMR 2014

Osteoporosis Definition
NIH Consensus Conference

A skeletal disorder characterized by compromised *bone strength* predisposing to an increased risk of fracture

Bone strength = Bone density + Bone quality[1]

1. NIH Consensus Conference, 2000. Available at: http://consensus.nih.gov/2000/2000Osteoporosis111html.htm. Accessed 12-16-05.

Whom to screen → Which test → How to diagnose

Whom to treat → Benefits and risks of therapy → Monitoring → Treatment duration

Screening Guidelines: Women

- Women 65 years or older (USPSTF 2011, NOF 2014)
- Postmenopausal women aged 50-64:
  - Fracture during adulthood
  - Condition (e.g., rheumatoid arthritis) or medication associated with low bone mass or bone loss (NOF)
  - Women < 65 y/o whose 10-year risk of osteoporotic fracture is ≥ that of a 65-year-old white woman who has no additional risk factors (i.e. ≥ 9.3%) (USPSTF)

USPSTF, Ann Intern Med 3/1/2011
National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis 2014 www.nof.org

FRAX: Practical Considerations

- Not validated for spine bone mass
  - If normal hip bone mass with low spine bone mass, FRAX underestimates fracture risk
- Not validated for:
  - Patients treated with osteoporosis pharmacotherapy past 1-2 years
- Underestimates fracture risk in patients with:
  - Recent or multiple fractures
  - Those at increased risk for falling

National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis 2014 www.nof.org

Screening Guidelines: Men

- Current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.

USPSTF Ann Intern Med 3/1/2011

Screening Guidelines: Men

- Considerations:
  - Potential preventable burden is increasing due to aging U.S. population
  - Potential harms are likely to be small
  - Men most likely to benefit from screening have a 10-year risk for osteoporotic fracture equal to or greater than that of a 65-year-old white women without risk factors (which is ≥ 9.3%)

USPSTF, Ann Intern Med 3/1/2011

Whom to screen → **Which test** → How to diagnose

Whom to treat → Benefits and risks of therapy → Monitoring → Treatment duration

Which Test?

- Current diagnostic and treatment criteria rely on dual-energy x-ray absorptiometry (DXA) measurements of lumbar spine and hip ONLY
- T-scores from other technologies cannot be used according to the WHO diagnostic classification because they are not equivalent to T-scores derived from DXA

USPSTF Ann Intern Med 3/1/2011
National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis 2014 www.nof.org

WHO Diagnostic Classification

Classification	BMD	T-score
Normal	Within 1 SD of a young adult reference population	T-score at -1.0 and above
Low Bone Mass (Osteopenia)	Between 1.0 and 2.5 SD below that of a young-adult reference population	T-score between -1.0 and -2.5
Osteoporosis	2.5 SD or more below that of a young-adult reference population	T-score at or below -2.5
Severe or Established Osteoporosis	2.5 SD or more below that of a young- adult reference population	T-score at or below -2.5 with one or more fractures

National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis 2014 www.nof.org

Whom to screen → Which test → **How to diagnose**

Whom to treat → Benefits and risks of therapy → Monitoring → Treatment duration

Clinical Diagnosis: NOF

- Diagnosis is by either:
  - BMD T-score ≤ -2.5 at lumbar spine or hip by dual-energy x-ray absorptiometry, or
  - Adulthood hip or vertebral fracture in the absence of major trauma (such as motor vehicle accident or multiple story fall) - without BMD criteria

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New Focus: Vertebral X-rays or Vertebral Fracture Assessment (VFA)

- Vertebral fxs detected incidentally by x-ray confer dx of osteoporosis
- So, √ vertebral x-rays or VFA (can be done at same time as DXA) in:
  - All women ≥ 70 and all men ≥ 80 if BMD T-score at spine, total hip or femoral neck is < -1.0.
  - Women 65-69 and men 70-79 if T-score at the spine, total hip or femoral neck is < -1.5
  - Postmenopausal women and men ≥ 50 with specific risks:
    - Low trauma fracture during adulthood (age 50)
    - Historical height loss of ≥ 1.5 inches (4 cm)
    - Prospective height loss ≥ 0.8 inches (2 cm)
    - Recent or ongoing long term glucocorticoid treatment

NOF, 2014

Whom to screen → Which test → How to diagnose

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Whom To Treat: NOF 2014

- Postmenopausal women and men age ≥50 if:
  - Hip or vertebral (clinical or asymptomatic) fracture
  - T-score ≤ -2.5 femoral neck, total hip, or lumbar spine
  - Low bone mass (T-score between -1.0 and -2.5 at femoral neck, total hip, or spine) if:
    - 10-yr probability of hip fracture ≥3% or
    - 10-yr probability of major osteoporosis-related fracture ≥20% **based on U.S. WHO FRAX**

National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis 2014 www.nof.org

Whom to screen → Which test → How to diagnose

Whom to treat → **Benefits and risks of therapy** → Monitoring → Treatment duration

Benefits of Therapy: Systematic Review

- High-strength evidence that the following drugs reduce fractures compared with placebo:
  - Bisphosphonates
  - Denosumab
  - Teriparatide
  - Risk reductions 40-64% for vertebral fractures, 20-40% for nonvertebral fractures
- Raloxifene reduces only vertebral fractures
- Demonstrated hip fracture reduction: bisphosphonates, denosumab

Crandall et al. Annals of Internal Medicine 2014

Adverse Effects of Therapy: Systematic Review

- Mild upper GI symptoms:
  - Bisphosphonates
  - Denosumab
  - Teriparatide
- Influenza-like symptoms:
  - Zoledronic acid
- Serious infections:
  - Denosumab (cellulitis, infectious arthritis, endocarditis)
- VTE, fatal stroke:
  - raloxifene
- Atypical subtrochanteric fx:
  - Bisphosphonates
  - 2-100 per 100,000 women
- Osteonecrosis of the jaw:
  - Bisphosphonates
  - 0.03%-4.3% (pending new standardized case definitions)

Crandall et al. Annals of Internal Medicine 2014

Atypical Subtrochanteric (Femoral) and Diaphyseal Femoral Fractures (AFF)

2nd Report of Task Force, American Society for Bone & Mineral Research

- Reported in patients taking BPs, and in patients on denosumab
- Also occur in patients with no exposure to these drugs
  - Probably associated with glucocorticoid use
- Absolute risk with BPs is low, 3.2 to 50 cases per 100,000 person-years
- Long-term use may be associated with higher risk (~100 per 100,000 person-years)
- MRI : Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh

Shane et al. JBMR 2013

Dx & Management of Osteonecrosis of the Jaw:
A Systematic Review and International Consensus

- Vast majority of cases (>90%) have occurred in cancer patients receiving six-fold to 10-fold higher doses of BPs than those used to treat osteoporosis
- In patients taking lower-dose BPs for osteoporosis, the risk of ONJ is extremely low (1 in 10,000 to 1 in 100,000 patients, compared with 1% to 2% per year for cancer patients receiving higher doses of BPs)
- Risk factors: Invasive oral surgery procedures, glucocorticoids, DM, poor oral hygiene

Khan et al JBMR 2015

Osteonecrosis of the Jaw:
Am. Assoc. of Oral and Maxillofacial Surgeons 2014

- Risk of ONJ among patients exposed to oral bisphosphonates following tooth extraction is 0.5%
- Antiangiogenic agents, when given with antiresorptive medications, are associated with an increased risk of ONJ
- Occurs in pts not exposed to antiresorptive agents
- There is currently no evidence that interrupting bisphosphonate therapy alters the risk of ONJ in patients following tooth extraction

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

Osteonecrosis of the Jaw:
Am. Assoc. of Oral and Maxillofacial Surgeons 2014

- Pts taking antiresorptive for osteoporosis generally have less severe manifestations, respond more readily to rx
- Individuals receiving monthly IV bisphosphonates or denosumab for treatment of oncologic disease have an increased risk of developing ONJ following tooth extraction and thus these procedures should be avoided if possible

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

Bisphosphonates and ONJ:
Am. Assoc. of Oral and Maxillofacial Surgeons 2014

- 3 scenarios:
  - Scenario 1: oral bisphosphonate for < 4 years and have no clinical risk factors
  - Scenario 2: oral bisphosphonate for < 4 years and corticosteroids or antiangiogenic meds concomitantly
  - Scenario 3: oral bisphosphonate > 4 years

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

Bisphosphonates and ONJ

- Scenario 1: Oral bisphosphonate for < 4 years and no clinical risk factors
  - No alteration or delay in planned surgery is necessary
  - This includes any and all procedures common to oral and maxillofacial surgeons, periodontists
  - If dental implants are placed, give informed consent related to possible long-term implant failure and the low risk of developing osteonecrosis of the jaw if the patient continues to take an antiresorptive agent

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

Bisphosphonates and ONJ

- Scenario 2: Oral bisphosphonate for < 4 years and corticosteroids or antiangiogenic meds concomitantly
- Or
- Scenario 3: Oral bisphosphonate > 4 years
  - Prescribing provider should be contacted to consider discontinuation of oral bisphosphonate (drug holiday) for at least 2 months prior to oral surgery, if systemic conditions permit
  - The antiresorptive should not be restarted until osseous healing has occurred

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

Choice of Therapy: What To Do?

"The harms of bisphosphonates, the most commonly prescribed therapies, are no greater than small."
USPSTF, Ann Intern Med 3/1/2011

What do I do?

- Balance risk of serious AEs with risk of fracture if untreated
  - Likely benefits outweigh risks:
    - Preexisting vertebral or hip fracture
    - L-spine or hip BMD T-score ≤ -2.5
  - Unlikely benefits outweigh risks:
    - Absolute 10-year risk of fracture ≤3% at hip or ≤20% for major osteoporotic fracture

Calcium and Vitamin D: Institute of Medicine

Group		Dose	
Sex	Age	Calcium	Vitamin D
Women	51-70	1,200 mg/d	600 IU/d
Men	51-70	1,000 mg/d	600 IU/d
Women and Men	>70 y/o	1,200 mg/d	800 IU/d

http://www.iom.edu/reports/2010/dietary-reference-intakes-for-calcium-and-vitamin-d.aspx

Vitamin D Levels

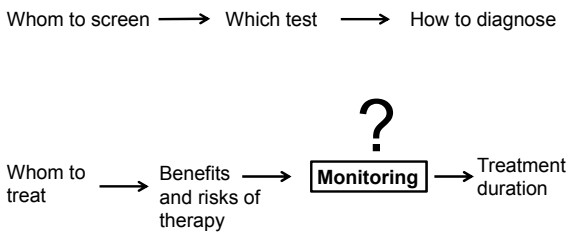
- For individuals with osteoporosis, vitamin D supplements should be recommended in amounts sufficient to bring the serum 25(OH)D level to approximately 30 ng/ml (75 nmol/L)
- Many patients with osteoporosis will need more than the general recommendation of 800-1,000 IU per day
- Consider checking 25(OH) D levels annually, especially if initial level was low

National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis 2014 www.nof.org

Calcium and CHD
Meta-analysis of RCTs

- Total 63,563 participants
- No significant associations with:
  - CHD events
  - All-cause mortality
  - Secondary outcomes: MI, angina pectoris and acute coronary syndrome, chronic CHD
- Current evidence does not support the hypothesis that calcium supplementation with or without vitamin D increases coronary heart disease or all-cause mortality risk in elderly women

Lewis et al J Bone Miner Res 2015



Monitoring: Serial Testing
USPSTF

- Evidence is lacking about optimal intervals
- Because of limitations in the precision of testing:
  - Minimum of 2 years to reliably measure a change in BMD
  - Longer intervals may be necessary to improve fracture prediction. Measurement error of the machine!
- Changes in BMD of < 3-6% at hip and 2-4% at spine from test to test may be due to the precision error of the test itself!

Ann Intern Med 3/1/2011
2014 www.nof.org

Monitoring: Untreated Older Women

Study of Osteoporotic Fractures postmenopausal women ≥ 65 y/o

If baseline T-score is….	then the time period required for 10% of women to progress to osteoporosis BMD was:
-1.01 to -1.49	15 years
-1.50 to -1.99	5 years
-2.00 to -2.49	1 year

Gourlay et al NEJM 2012

Monitoring: Untreated Younger Postmenopausal Women

- Women's Health Initiative study
- In women without osteoporosis at baseline, the time for 1% of women to have hip or clinical vertebral fx was:
  - 12 years if 50-54 y/o
  - 7 years if 60-64 y/o
  - (Vs. 3 years in women with osteoporosis at baseline)
- Thus, women aged 50-64 years without osteoporosis on first BMD test are unlikely to benefit from frequent rescreening before age 65 yrs

Gourlay et al Menopause 2014

Monitoring <u>During</u> Treatment: Systematic Review

- RCTs were not designed to show that monitoring BMD during therapy decreases hip fractures.
- For patients receiving antiresorptive therapy for whom serial BMD measurements have not shown an increase, or who have decreases in BMD, statistically significant benefits are still obtained in terms of fracture reduction

Crandall et al Annals of Internal Medicine 2014

Whom to screen → Which test → How to diagnose

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Treatment Duration: Systematic Review

- RCTs were not specifically designed to compare shorter with longer duration of therapy
  - post-hoc analyses only
- Optimal duration of therapy unknown
- FDA review post-hoc data:
  - h/o fx, BMD T-score that remains ≤ - 2.5 may benefit from continued rx

Crandall et al Annals of Internal Medicine 2014
Whitaker NEJM 2012 (see post-hoc data Black NEJM 2012 & JBMR 2012

Treatment Duration: NOF Guidelines

- After the initial 3-5 years' treatment, check:
  - Interval fractures, new chronic diseases/meds
  - BMD testing
  - Vertebral imaging if height loss during rx
- If used, what is duration of a drug holiday? No data!

National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis 2013 <u>www.nof.org</u>

Summary

- <u>Remember</u>: only 2 in 10 fractures are followed up with testing or treatment!
- After hip fracture:
  - Only 40% fully regain their pre-fracture level of independence
  - Only 1 in 3 are treated within 12 months of d/c
- Women ≥ 65 y/o: screen, re✓ based on initial T-score:
  - T-score -1.0 to -1.9: wait 5 years
  - T-score -2.0 to -2.4: wait 1-2 years
- Women aged 50-64: screen with FRAX, secondary causes

Summary (cont'd)

- Men: <u>consider</u> screening if 10-year risk for osteoporotic fracture ≥ 9.3%, secondary causes
- Measure height yearly ≥ 50 y/o
- Don't ignore incidentally-detected vertebral fx
- Treatment candidates: hip or vertebral fracture or BMD T-score ≤ -2.5
- Use FRAX to aid treatment decisions ≥ age 50 with low bone density (not in osteoporotic range) and
  - 10 year hip fx probability <u>≥</u> 3%
  - 10 year major osteoporotic fx probability <u>≥</u> 20%

Summary (cont'd)

- To decrease hip fracture, use bisphosphonates or denosumab (use bisphosphonates 1st line)
- When rechecking BMD on rx, don't forget about the measurement error of the machine
  - Changes in BMD of < 3-6% at hip and < 2-4% at spine from test to test may be due to the precision error of the test itself
- Counsel about low absolute risk of serious AEs with bisphosphonates, balance against fx risk without therapy

Give All Your Patients the Best Fighting Chance Against Osteoporosis

References

- Ruggiero et al, Medication-Related Osteonecrosis of the Jaw-2014 Update, American Association of Oral and Maxillofacial Surgeons Position Paper, 2014, available at http://www.aaoms.org/members/resources/aaoms-advocacy-and-position-statements/
- Shane et al, Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research, J Bone Miner Res. 2014 Jan;29(1):1-23
- Eisman et al, ASBMR Task Force on Secondary Fracture Prevention. J Bone Miner Res. 2012 Oct;27(10):2039-46.