2016 AACE/ACE POSTMENOPAUSAL OSTEOPOROSIS GUIDELINES:
Practical Applications

Pauline M. Camacho, MD, FACE
Professor of Medicine
Loyola University Medical Center
Director of Loyola University Osteoporosis and Metabolic Bone Disease Center

Steven M. Petak MD, JD, MACE, FACP
Associate Clinical Professor
Weill-Cornell Medical College
Division Head and Chief of Endocrinology
Houston Methodist Hospital  Houston, Texas
Outline

- Diagnosis
- Workup and evaluation
- Treatment choices
- Rare adverse events
- Drug holidays
- Sequential and combination therapy
- Treatment Algorithm
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY —
CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS —2016

Co-Chairs: Pauline M. Camacho, MD, FACE; Steven M. Petak, MD, MACE, FACP, JD

Committee:
Neil Binkley, MD; Bart L. Clarke, MD, FACP, FACE;
Steven T. Harris, MD, FACP Daniel L. Hurley, MD, FACE;
Michael Kleerekoper, MBBS, MACE; E. Michael Lewiecki, MD, FACP, FACE;
Paul D. Miller, MD; Harmeet S. Narula, MD, FACP, FACE;
Rachel Pessah-Pollack, MD, FACE; Vin Tangpricha, MD, PhD, FACE;
Sunil J. Wimalawansa, MD, PhD, MBA, FCCP, FACP, FRCP, DSc, FACE;
Nelson B. Watts, MD, FACP, MACE
The Process

- 2 years of work
- 14 authors
- 313 references
- 42 recommendations
- At least 20 versions of the manuscript
- 7 versions of the algorithm!
NEW CLINICAL DEFINITION
Osteoporosis Diagnosis

Osteoporosis should be diagnosed based on:

▪ Presence of fragility fractures in the absence of other metabolic bone disorders

▪ T-score of $-2.5$ or lower in the lumbar spine (AP), femoral neck, total hip, and/or $33\%$ (1/3) radius even in the absence of a prevalent fracture
Osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX country-specific thresholds.
NBHA Position Statement: Clinical Diagnosis of Osteoporosis

In postmenopausal women and men age 50 years and older, osteoporosis may be diagnosed by:

- T-score ≤ -2.5 at the LS, TH, or FN
- Low trauma hip fracture regardless of BMD
- Osteopenia with low trauma vertebral, proximal humerus, pelvis or some distal forearm fractures
- FRAX MOF risk ≥ 20% or HF risk ≥ 3%

NBHA Position Statement: Clinical Diagnosis of Osteoporosis

In postmenopausal women and men age 50 years and older, osteoporosis may be diagnosed by:

- T-score ≤ -2.5 at the LS, TH, or FN
- Low trauma hip fracture regardless of BMD
- Osteopenia with low trauma vertebral, proximal humerus, pelvis or some distal forearm fractures
- FRAX MOF risk ≥ 20% or HF risk ≥ 3%
Implications of the New Clinical Definition

- More patients will be labeled with the diagnosis
- Increased capture of high risk patients
- Increased coverage for DXA/labs and medications
- More accurate government cost appropriation for osteoporosis
Workup and Evaluation
Evaluation for Secondary Osteoporosis

- Complete blood cell count
- Serum chemistry, including calcium, phosphate, total protein, albumin
- Liver enzymes, alkaline phosphatase, serum creatinine, and electrolytes
- 24-h collection for calcium, sodium, and creatinine excretion
- Serum 25-hydroxyvitamin D
- Intact PTH
- TSH
- Tissue transglutaminase
- SPEP and free light chains
- Serum tryptase
- Urinary free cortisol
- Bone biopsy
# Causes of Secondary Osteoporosis

<table>
<thead>
<tr>
<th>Endocrine or metabolic causes</th>
<th>Nutritional/GI conditions</th>
<th>Drugs</th>
<th>Disorders of collagen metabolism</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td>Alcoholism</td>
<td>Antiepileptic drugs⁶</td>
<td>Ehlers-Danlos syndrome</td>
<td>AIDS/HIV ⁸</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Anorexia nervosa</td>
<td>Aromatase inhibitors</td>
<td>Homocystinuria due to cystathionine deficiency</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Type 1</td>
<td>Calcium deficiency</td>
<td>Chemotherapy/immunosuppressants</td>
<td>Marfan syndrome</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Type 2</td>
<td>Chronic liver disease</td>
<td>Depo-Provera</td>
<td>Osteogenesis imperfect</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn’s disease, and gastric resection or bypass)</td>
<td>Glucocorticoids</td>
<td></td>
<td>Hemophilia</td>
</tr>
<tr>
<td>Hypercortisolism</td>
<td>Total parenteral nutrition</td>
<td>Gonadotropin-releasing hormone agents</td>
<td>Hypercalciumia</td>
<td></td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Vitamin D deficiency</td>
<td>Heparin</td>
<td>Immobilization</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
<td>Lithium</td>
<td>Major depression</td>
<td></td>
</tr>
<tr>
<td>Hypogonadism</td>
<td></td>
<td>Proton pump inhibitors</td>
<td>Myeloma and some cancers</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td></td>
<td>Selective serotonin reuptake inhibitors</td>
<td>Organ transplantation</td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
<td>Thiazolidinediones</td>
<td>Renal insufficiency/failure</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td>Thyroid hormone (in supraphysiologic doses)</td>
<td>Renal tubular acidosis</td>
<td></td>
</tr>
</tbody>
</table>

b Antiepileptic drugs are used in the treatment of osteoporosis due to their ability to decrease bone resorption. ⁶ Includes anticonvulsants such as carbamazepine, phenytoin, and valproic acid. ⁸ HIV-related causes of osteoporosis include chronic infections, immune suppression, and medications such as glucocorticoids and antiretroviral agents.
Causes of Secondary Osteoporosis

- Recommend all patients with osteoporosis undergo evaluation
- Present in up to 40% of patients who are tested

    Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. J Clin Endocrinol Metab 87:4431-4437 [EL 3; CSS]
INITIAL CHOICE OF AGENT
# Current Medications for Osteoporosis

## Inhibit Bone Resorption

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Fosamax, generic</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Actonel, Atelvia, generic</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Boniva, generic</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Reclast, generic</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Prolia</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Evista, generic</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Miacalcin, Fortical</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Various</td>
</tr>
<tr>
<td>Strontium</td>
<td>(dual effect)</td>
</tr>
</tbody>
</table>

## Stimulate Bone Formation

- Teriparatide (Forteo)
## FDA Approved Agents and Effect on Fracture Risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertebral Fracture</th>
<th>Nonvertebral Fracture</th>
<th>Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin (Miacalcin®, Fortical®)</td>
<td>✔</td>
<td>No effect demonstrated</td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Raloxifene (Evista®)</td>
<td>✔</td>
<td>No effect demonstrated</td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Ibandronate (Boniva®)</td>
<td>✔</td>
<td>No effect demonstrated</td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>✔</td>
<td>★</td>
<td>✔</td>
</tr>
<tr>
<td>Risedronate (Actonel®, Atelvia®)</td>
<td>✔</td>
<td>✔</td>
<td>★</td>
</tr>
<tr>
<td>Zoledronic acid (Reclast®)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Denosumab (Prolia™)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>✔</td>
<td>✔</td>
<td>No effect demonstrated</td>
</tr>
</tbody>
</table>
Recommendations on initial choice of agent

- Approved agents with efficacy to reduce hip, non-vertebral, and spine fractures including alendronate, risedronate, zoledronic acid and denosumab, are appropriate as initial therapy for most patients at high risk of fracture.

- Teriparatide, denosumab or zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at especially higher fracture risk.

- Raloxifene or ibandronate may be appropriate initial therapy, in some cases, for patients requiring drugs with spine-specific efficacy.
Risk Stratification

▪ **Moderate fracture risk**: Alendronate, risedronate, denosumab, or zoledronic acid

▪ **Higher fracture risk**: Denosumab, teriparatide or zoledronic acid
Higher fracture risk category:

- Older age
- Prior fractures
- Very low T score
- High fall risk
- Glucocorticoids
RARE ADVERSE EVENTS
Rare but Serious Adverse Events (SAEs), namely Atypical Femoral Fractures (AFF) and Osteonecrosis of the Jaw (ONJ), have raised concerns regarding the prolonged use of such drugs.

The long term retention of BPs in bone, and the serious AEs, led to the concept of drug holiday, to maximize benefits and minimize harms.
Bisphosphonate-Associated Osteonecrosis of the Jaw
Report of a Task Force of the ASBMR*

• Osteonecrosis of the jaw (ONJ) definition
  ▫ The presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a healthcare professional

▪ ONJ rarely associated with oral bisphosphonates
  ▫ Estimated between 1 in 10,000 and 1 in 100,000 patient-years

▪ The ASBMR report recommends:
  “Patients should be informed that the risk of developing bisphosphonate-associated ONJ with routine oral therapy for osteoporosis or Paget's disease seems to be low, ranging between 1/10,000 and 1/100,000 [per year]...”

*ASBMR = American Society for Bone and Mineral Research

SUBTROCHANTERIC FRACTURES OF THE FEMUR

Watts NB and Diab D, J Clin Endocrinol Metab 2010;95:1555-1555
How common are these fractures?

- Preliminary estimates of atypical femoral fracture incidence based on an HMO database (2.6 M people > 45)
- Progressive increase from 2 per 100,000 cases per year for 2 years of BP use to 78 per 100,000 cases per year for 8 years of BP use.

Bonus Features!

- Section on patient communication of rare adverse events
- Printable materials (www.empoweryourhealth.org) illustrating benefit/risk of treatment
DURATION OF THERAPY
Evidence used for recommendations

▪ FLEX trial
▪ HORIZON study extension
▪ Clinical experience
Recommendations on Optimum Duration of Therapy

- For oral bisphosphonates, consider a “bisphosphonate holiday” after 5 years of stability in lower-risk (or moderate risk) patients
- For oral bisphosphonates, consider a “bisphosphonate holiday” after 6 to 10 years of stability in higher-risk patients
- Treatment with teriparatide should be limited to 2 years
For IV zoledronic acid, consider a drug holiday after 3 annual doses in lower-risk (moderate risk) patients and after 6 annual doses in higher-risk patients.

Teriparatide or raloxifene may be used during the “bisphosphonate holiday” period for higher-risk patients.
A drug “holiday” is not recommended with denosumab
ON COMBINATION THERAPY
AACE does not recommend concomitant use of antiresorptive agents for prevention or treatment of postmenopausal osteoporosis – (no fracture data)

If estrogen is being given for treatment of menopausal symptoms or raloxifene is being given to reduce the risk of breast cancer, an additional agent such as a bisphosphonate, denosumab, or teriparatide may be considered
ON SEQUENTIAL THERAPY
Treatment with teriparatide should always be followed by antiresorptive agents to prevent bone density decline and loss of fracture efficacy.
Several studies on teriparatide discontinuation showed BMD loss (PMO, premenopausal women, men) if not followed by antiresorptive therapy

- Leder 2009, Cohen 2015,
When is the drug holiday over?
- Fracture
- BMD decline
- Rise in bone turnover markers may be a signal that the holiday should be over, but does not apply to those with low BTM’s prior to treatment
Lumbar spine or femoral neck or total hip T-score of \(\leq -2.5\), a history of fragility fracture, or high FRAX® fracture probability

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

No prior fragility fractures or moderate fracture risk

- Alendronate, denosumab, risedronate, zoledronic acid
- Alternate therapy: Ibandronate, raloxifene

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Prior fragility fractures or indicators of higher fracture risk

- Denosumab, teriparatide, zoledronic acid
- Alternate therapy: Alendronate, risedronate

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

Switch to injectable antiresorptive if on oral agent
Switch to teriparatide if on injectable antiresorptive or at very high risk of fracture

Reassess at least yearly for response to therapy and fracture risk

Denosumab

Teriparatide for up to 2 years

Zoledronic acid

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Sequential therapy with oral or injectable antiresorptive agent

If stable, continue therapy for 6 years
If progression of bone loss or recurrent fractures, consider switching to teriparatide

\* 10 year major osteoporotic fracture risk \(\geq 20\%\) or hip fracture risk \(\geq 3\%\). Non-US countries/regions may have different thresholds.

\** Indicators of higher fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.

\*** Medications are listed alphabetically.

\**** Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.
No prior fragility fractures or moderate fracture risk**

- Alendronate, denosumab, risendronate, zoledronic acid***
- Alternate therapy: Ibandronate, raloxifene

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

- Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to teriparatide if on injectable antiresorptive or at very high risk of fracture

Prior fragility fractures

- Denosumab, teriparatide, raloxifene
- Alternate therapy: Alendronate, raloxifene

Reassess at least yearly

Denosumab

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

* 10 year major osteoporotic fracture risk: countries/regions may have different indicators
** Indicators of higher fracture risk include age, frailty, glucocorticoids, etc.
*** Medications are listed alphabetically
**** Consider a drug holiday after 5 years of oral agent and 3 years of IV bisphosphonate therapy. During the holiday, another anti-osteoporotic agent such as raloxifene could be used.
Recommend pharmacologic therapy
Education on lifestyle measures, fall prevention, benefits and risks of medications

Prior fragility fractures or indicators of higher fracture risk**

- Denosumab, teriparatide, zoledronic acid***
- Alternate therapy: Alendronate, risedronate

Reassess at least yearly for response to therapy and fracture risk

Denosumab

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Teriparatide for up to 2 years

Sequential therapy with oral or injectable antiresorptive agent

Zoledronic acid

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.

** Indicators of higher fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.

*** Medications are listed alphabetically.

**** Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.
Conclusions

- Significant advances are happening in the diagnosis, prevention and treatment of osteoporosis
- The 2016 AACE/ACE Postmenopausal Guidelines have updated recommendations on the diagnosis, treatment and long term follow up of patients with osteoporosis
- Be sure to download your copy from aace.com
THANK YOU FOR YOUR ATTENTION