Hot Off the Press: The Latest News in Menopause

Zaher Merhi M.D.
Assistant Professor
University of Vermont College of Medicine
Department of Obstetrics & Gynecology
Division of Reproductive Endocrinology and Infertility
Definitions

- The term “menopause” is derived from Greek Meno (months) and pause (cessation)

- Climacteric which is by dictionary definition is period of life when fertility and sexual activity decline. It is a wide term leading to:
  * Pre Menopause
  * Peri Menopause
  * Post Menopause
Definitions

**Perimenopause:**
- 3-5 years period before menopause
- ↑frequent irregular anovulatory bleeding → amenorrhea and intermittent menopausal symptoms.

**Menopause:**
- Retrospective diagnosis after 12 months of amenorrhea.
- Mean age – 51 years.
## Recommendations of stages of Reproductive Aging Workshop (STRAW) Park City, Utah, USA, July 2001, reprinted with permission.

<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology:</td>
<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late*</td>
<td>Early*</td>
<td>Late</td>
<td></td>
</tr>
<tr>
<td>Duration of Stage:</td>
<td>variable</td>
<td>variable</td>
<td></td>
<td>1 yr</td>
<td>4 yrs</td>
<td>until demise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual Cycles:</td>
<td>variable to regular</td>
<td>regular</td>
<td>variable cycle length (&gt;7 days different from normal)</td>
<td>≥2 skipped cycles and an interval of amenorrhea (≥60 days)</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine:</td>
<td>normal FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stages most likely to be characterized by vasomotor symptoms

↑ = elevated
<table>
<thead>
<tr>
<th>Stage</th>
<th>-5</th>
<th>-4</th>
<th>-3b</th>
<th>-3a</th>
<th>-2</th>
<th>-1</th>
<th>+1a</th>
<th>+1b</th>
<th>+1c</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>REPRODUCTIVE</td>
<td>MENOPAUSAL TRANSITION</td>
<td>POSTMENOPAUSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>variable</td>
<td>variable</td>
<td>1-3 years</td>
<td>2 years</td>
<td>3-6 years</td>
<td>Remaining lifespan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PRINCIPAL CRITERIA**

<table>
<thead>
<tr>
<th>Menstrual Cycle</th>
<th>Variable to regular</th>
<th>Regular</th>
<th>Regular</th>
<th>Subtle changes in Flow/Length</th>
<th>Variable Length</th>
<th>Persistent ≥7-day difference in length of consecutive cycles</th>
<th>Interval of amenorrhea of ≥60 days</th>
</tr>
</thead>
</table>

**SUPPORTIVE CRITERIA**

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>FSH</th>
<th>AMH</th>
<th>Inhibin B</th>
<th>Antral Follicle Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Variable</td>
<td>Low</td>
<td>Variable</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>&gt;25 IU/L**</td>
<td>Low</td>
<td>Variable</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Stabilizes</td>
<td>Low</td>
<td>Stable</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td>Stabilizes</td>
<td>Very Low</td>
<td>Stable</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

**DESCRIPTIVE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Vasomotor symptoms</th>
<th>Vasomotor symptoms</th>
<th>Increasing symptoms of urogenital atrophy</th>
</tr>
</thead>
</table>

* Blood draw on cycle days 2-5  
**Approximate expected level based on assays using current international pituitary standard^67-69

The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.
Ovarian aging

- ↓ quantity and quality of the pool of follicles and oocytes

- By 50 years of age, each ovary would contain 2500 to 4000 primordial follicles

- Follicular depletion accelerates in the last decade of reproductive life

- By age 45 to 46 years, menstrual irregularity occurs

Hertig A. *J Clin Endocrinol Metab* 1944
Bigelow B. *Obstet Gynecol* 1958
HEADACHES AND HOT FLASHES
TEETH LOOSEN AND GUMS REcede
RISK OF CARDIOVASCULAR DISEASE
BACKACHES
BODY AND PUBIC HAIR BECOMES THICKER AND DARKER
HAIR BECOMES THINNER AND LOSES LUSTER
BREASTS DROOP AND FLATTEN
NIPPLES BECOME SMALLER AND FLATTEN
SKIN AND MUCOUS MEMBRANES BECOME DRIER, SKIN DEVELOPES A ROUGHER TEXTURE
ABDOMEN LOSES SOME MUSEL TONE
STRESS OR URGE INCONTINENCE
BONES LOSE MASS AND BECOME MORE FRAGILE
VAGINAL DRYNESS, ITCHING AND SHRINKING
Hot flashes

• The most common symptom: up to 80%
• Only about 20 to 30% of women seek medical attention for treatment
• When occur at night, described as “night sweats”
• **Sudden** sensation of heat centered on the *upper chest and face* that rapidly becomes generalized
• Lasts 2-4 minutes
• Associated with profuse perspiration and occasionally palpitations
Hot flashes

• Sometimes followed by chills and shivering + feeling of anxiety
• Occur several times per day: range from only 1-2/day to as many as 1/hour during the day and night
• Particularly common at night
• > 80% will continue to have them for > 1 year
• Untreated → stop spontaneously within 4-5 years of onset
• Some women have hot flashes that persist for many years (9% after age 70)
# Causes of flushing

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologic</td>
<td>Menopause</td>
</tr>
<tr>
<td></td>
<td>Hot drinks</td>
</tr>
<tr>
<td></td>
<td>Emotional distress</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Drugs</td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Alcohol plus chlorpromazine or disulfuram</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
</tr>
<tr>
<td></td>
<td>Amyl nitrate</td>
</tr>
<tr>
<td></td>
<td>Nicotinic acid</td>
</tr>
<tr>
<td></td>
<td>Levodopa</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Diseases</td>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td></td>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td></td>
<td>Basophilic chronic granulocytic leukemia</td>
</tr>
<tr>
<td></td>
<td>VIPoma</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Medullary carcinoma of the thyroid</td>
</tr>
<tr>
<td></td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Diencephalic seizures</td>
</tr>
<tr>
<td></td>
<td>Postural Orthostatic Tachycardia Syndrome (POTS)</td>
</tr>
</tbody>
</table>
Vaginal dryness

• Prevalence: up to 47%
• Estrogen deficiency → thinning of the vaginal and urethral epithelium
• Vaginal atrophy (atrophic vaginitis) → vaginal dryness, itching, and often dyspareunia
• Symptoms are usually progressive and worsen
• ↓ vaginal lubrication upon sexual arousal (not necessarily during sexual activity)
• **Urinary Symptoms**: urgency, frequency, nocturia
Vaginal dryness

On exam of genitalia:
1. Vagina appears pale, with lack of the normal rugae
2. Scarce pubic hair
3. ↓ elasticity and turgor of the vulvar skin
4. Introital narrowing or ↓ moisture
5. Fusion or resorption of the labia minora
6. Cervix also can atrophy and become flush with the top of the vaginal vault
7. Pelvic floor - relaxation → prolapse
Other Consequences—Probably due to the fluctuations in serum estradiol concentrations

Breast pain:
- Common in the *early* menopausal transition
- Diminish in the *late* menopausal transition

Menstrual migraines:
- Around the onset of each menstrual period
- Worsen in frequency and intensity during the menopausal transition
Other Consequences

Cognitive changes:
• memory loss and difficulty concentrating (? Dementia)
• Estrogen protective to cognitive function
• Anxiety and depression worsen cognitive performance

Joint pain:
• Diffuse joint pain
• ? estrogen deficiency or rheumatologic disorder
• Some relief with combined Hormone replacement therapy

Skin:
• ↓ collagen & thickness → ↓ elasticity of the skin
Other Consequences

**Depression:**
- 2.5 x more likely in the menopausal transition

**Bone loss:**
- Highest during the 1 year *before* through 2 years after the final menstrual period

**Body composition:**
- Gain fat mass and lose lean mass

**Cardiovascular disease:**
- In part due to estrogen deficiency
- In part by changes in lipid profiles during perimenopause
- Diabetes
- Metabolic syndrome (central obesity, dyslipidemia, insulin resistance, and hypertension)
Menopause: Metabolic Syndrome

Tissue-specific abnormalities in steroid and lipid metabolism
Loss of estrogen

- Adipose tissue
- Liver
- Skeletal muscle
- Pancreas
- CNS

Local metabolic abnormalities

Systemic metabolic abnormalities

Metabolic Syndrome
- Visceral obesity
- Insulin resistance
- Glucose intolerance
- Dyslipidemia
- Hypertension

Systemic Disease

Human Disease
- Cardiovascular disease
- Liver disease
- Diabetes
- Cancer
- Other
Diagnosis of menopause: special situations

Women with underlying menstrual cycle disorders (fibroids...):
- FSH

Women taking oral contraceptives:
- Safe in nonsmokers
- Do not develop vasomotor symptoms
- Stop the pill and measure FSH 2-4 weeks later
- FSH $\geq 25$ IU/L : likely in the menopausal transition
- No FSH value for absolute reassurance about postmenopausal
- Stop the pill by age 50 to 51 years

Post-hysterectomy:
- Measure FSH: $> 25$ IU/L + hot flashes $\rightarrow$ late menopausal transition
- Measure FSH: $> 70$-100 IU/L $\rightarrow$ postmenopausal
The **Women's Health Initiative (WHI)** is a major 15-year research program to address the most common causes of death, disability and poor quality of life in postmenopausal women.
More on the WHI

• Launched in 1991
• A set of clinical trials
• One observational study
• Involve more than 161,000 women
• Mostly healthy & postmenopausal
• Average age of 63 at enrollment
Primary outcomes in WHI

• Heart Disease (main)
• Breast Cancer
• Osteoporosis
• Stroke
• Dementia
WHI Hormone Program Design

Hysterectomy

- YES
  - n= 10,739
  - Conjugated equine estrogen (CEE) 0.625 mg/d

- NO
  - n= 16,608
  - CEE 0.625 mg/d + medroxyprogesterone acetate (MDA) 2.5 mg/d
Clinical Outcomes in the WHI Postmenopausal Hormone Therapy Trials
*(JAMA 2002, 2004)*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>E+P Trial</th>
<th>E-Alone Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio 95% CI</td>
<td>Hazard Ratio 95% CI</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.29 1.02 - 1.63</td>
<td>0.91 0.75 - 1.12</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41 1.07 - 1.85</td>
<td>1.39 1.10 - 1.77</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.11 1.58 - 2.82</td>
<td>1.33 0.99 - 1.79</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.26 1.00 - 1.59</td>
<td>0.77 0.59 - 1.01</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63 0.43 - 0.92</td>
<td>1.08 0.75 - 1.55</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.83 0.47 - 1.47</td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66 0.45 - 0.98</td>
<td>0.61 0.41 - 0.91</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>0.92 0.74 - 1.14</td>
<td>1.08 0.88 - 1.32</td>
</tr>
<tr>
<td>Global index</td>
<td>1.15 1.03 - 1.28</td>
<td>1.01 0.91 - 1.12</td>
</tr>
<tr>
<td>Number of women</td>
<td>8506 8102</td>
<td>5310 5429</td>
</tr>
<tr>
<td>Follow-up time, mean (SD), mo</td>
<td>62.2 (16.1) 61.2 (15.0)</td>
<td>81.6 (19.3) 81.9 (19.7)</td>
</tr>
</tbody>
</table>
WHI Results: Heart

• Women on E & P pill **not** protected from heart disease

• E & P: **24% ↑** in heart disease risk

• Highest risk increase in women with high LDL

Manson, et al. NEJM 2003
More WHI Results

• E & P pill: 24% ↑ in breast cancer
• E&P pill: 2x ↑ dementia (Alzheimer’s) (only women 65 and older)
• E&P pill: 31% ↑ in stroke
• E & P pill: 61% ↑ in blood clots
• E&P part of study was cancelled due to increased rates of disease!

Chebowski, et al. JAMA 2002
Good Results

Hormone replacement therapy reduces rates of invasive colorectal cancer

In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with a significant reduction in the cumulative hazard of invasive colorectal cancer (hazard ratio 0.56, unadjusted 95 percent CI 0.38 to 0.81).

In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with significant reduction in hip fracture (five fewer hip fractures per 10,000 person-years, HR 0.7, unadjusted 95% CI 0.4 to 1.0).

Good Results

- E & P pill: 40% decrease in Osteoporosis and Colorectal Cancer

Chebowski, et al. JAMA 2002
Estrogen alone

• No difference in risk for heart attack
• Uncertain effect for breast cancer
• ↑ risk of stroke (like E & P)
• ↑ risk of blood clots (like E & P)
• No difference in risk for colorectal cancer
• Reduced risk of fracture

Chebowski, et al. JAMA 2002
## Summary (WHI Trials)

<table>
<thead>
<tr>
<th>Condition</th>
<th>E + P</th>
<th>E Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast CA</td>
<td><strong>Significant increased risk</strong></td>
<td>Did not detect increased risk</td>
</tr>
<tr>
<td>Coronary heart disease events</td>
<td><strong>Significant increased risk</strong></td>
<td>Did not detect increased risk</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>Decreased risk</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Decreased risk</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Stroke</td>
<td><strong>Increased risk</strong></td>
<td><strong>Increased risk</strong></td>
</tr>
</tbody>
</table>
As of today: Indications for Hormone Replacement Therapy

1. Moderate to severe vasomotor symptoms (hot flashes)
2. Vaginal atrophy
3. Osteoporosis

Short-term therapy: 2-3 years, and not more than five years.
Kronos Early Estrogen Prevention Study (KEEPS) study

• 42-58 years of age
• Menses absent for at least six months and no more than 3 years
• Good general health
• Have not used Hormone Therapy in the last 3 months
• Have not had a hysterectomy
Primary goal of the KEEPS?

- To learn whether menopausal hormone therapy given to healthy women early in the menopause would have an effect on progression of atherosclerosis as indicated by changes over time in arterial imaging (thickening of the walls of the common carotid arteries).
KEEPS study

727 participants

0.45 mg per day of Premarin (an oral conjugated equine estrogen)

50 µg a day of transdermal estradiol (Climara patch)

Placebo

Women on active estrogens received 200 mg of micronized progesterone (Prometrium) for 12 days each month
Most recent guidelines on HT use:

• HRT remains the most effective treatment available for menopausal symptoms, including hot flashes and night sweats. Many women can take it safely.

• If you have had blood clots, heart disease, stroke, or breast cancer, it may not be in your best interest to take HRT. Be sure to discuss your health conditions with your healthcare provider.

• How long you should take HRT is different for E+P and E only. For E+P, the time is limited by the increased risk of breast cancer that is seen with more than 3 to 5 years of use. For E alone, no sign of an increased risk of breast cancer was seen during an average of 7 years of treatment, a finding that allows more choice in how long you choose to use ET.

• Most healthy women below age 60 will have no increase in the risk of heart disease with HRT. The risks of stroke and blood clots in the lungs are increased but, in these younger age groups, the risks are less than 1 in every 1000 women per year taking HRT.

• E alone delivered through the skin (by patch, cream, gel, or spray) and low-dose oral E may have lower risks of blood clots and stroke than standard doses of oral estrogen, but all the evidence is not yet available.
Behavioral interventions:
1. Relaxation-based method, known as paced respiration
2. Weight loss may help reduce hot flashes
3. Exercise
Alternative Measures
Vasomotor Symptoms

• **SSRI (sertraline, Fluoxetine):** one of first choices in women who are not taking estrogen

• **Gabapentin:** effective in reducing the frequency of hot flashes

• **Progestins:** Megestrol acetate (Megace), High-dose depot medroxyprogesterone acetate

• **Clonidine:** transdermally or orally. side effects: dry mouth, dizziness, constipation, and sedation (limit its value)
Alternative Measures
Vasomotor Symptoms

• Complementary and alternative therapies:

1. Many postmenopausal women use soy products, herbal therapies (in particular, **black cohosh**)... for management of their vasomotor symptoms.

2. **50 to 75** percent of postmenopausal women use alternative therapies for management of menopausal symptoms.
Alternative Measures
Vasomotor Symptoms

• Complementary and alternative therapies:

3. Safety and efficacy are **not** well established.

4. Type and **dose** of soy or herbal supplements have been variable across studies.

5. Phytoestrogens (occur naturally in many plants, fruits, soy and vegetables such as soybeans, chickpeas, and lentils) > placebo.

6. Evening primrose oil, Dong Quai.
Alternative Measures
Vasomotor Symptoms

7. Tibolone (synthetic steroid hormone drug for endometriosis)

8. St. John’s Wort: for mild symptoms (questionable efficacy)

9. Others: flaxseed oil, fish oil, omega 3, red clover, ginseng, rice bran oil, wild yam, calcium, gotukola, licorice root, sage, sarsaparilla, passion flower, ginkgo biloba and valerian root (no evidence)

10. Acupuncture
Osteoporosis

• Bone mass reach peak at the end of their 3rd decade of life
• After 40 years bone resorption > bone formation by 0.5% per year
• This negative balance increase after menopause to a lose of 5% of bone per year
Clinical risk factors for fracture

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
</tr>
<tr>
<td>Previous fracture</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
</tr>
<tr>
<td>Parental history of hip fracture</td>
</tr>
<tr>
<td>Low body weight</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)</td>
</tr>
</tbody>
</table>

## Diagnostic categories for osteopenia and osteoporosis based upon bone mineral density measurement by DXA

<table>
<thead>
<tr>
<th>Category</th>
<th>Bone mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>A value for bone mineral density (BMD) within one standard deviation of the young adult female reference mean (T-score greater than or equal to -1 SD).</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>A value for BMD more than one but less than 2.5 standard deviations below the young adult female reference mean (T-score less than -1 and greater than -2.5 SD).</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>A value for BMD 2.5 or more standard deviations below the young adult female reference mean (T-score less than or equal to -2.5).</td>
</tr>
<tr>
<td>Severe (established) osteoporosis</td>
<td>A value for BMD more than 2.5 standard deviations below the young adult female reference mean in the presence of one or more fragility fractures.</td>
</tr>
</tbody>
</table>

Bone Mineral Density (BMD) screening/follow-up

- All women ≥ 65 years of age
- < 65 years if 1 of risk factor is present
- **Not** routinely in premenopausal women
- If normal DXA: follow-up DXA in 10 to 15 years
- Repeat DXA when on therapy or with underlying clinical factors that might lead to accelerated bone loss (approximately every two years)
Prevention of osteoporosis

1. **Diet:**
   - Adequate intake of calories (to avoid malnutrition) and calcium + vitamin D
   - Calcium (generally 500 to 1000 mg/day), in divided doses, at mealtime
   - 800 IU’s of Vitamin D/day
Prevention of osteoporosis

2. Exercise

• At least 30 minutes three times per week (more is not better!)

3. Cessation of smoking

• Smoking cigarettes accelerates bone loss
• Smoking may also negate the beneficial effect of estrogen therapy
Treatment of osteoporosis

1. **Bisphosphonates:**
   - Alendronate (Fosamax) or Risedronate (Actonel), Zoledronic acid (IV) are first line
   - Alone, first thing in the morning, **before breakfast** with at least 240 mL (8 oz) of **water**
   - Remain upright (sitting or standing) for **at least 30 minutes** after to minimize the risk of reflux
   - No food, drink, medications, or supplements for at least one-half hour
   - Should not take if active upper gastrointestinal disease
   - Stop if develop any symptoms of esophagitis
Treatment of osteoporosis

2. Selective estrogen receptor modulators:
   - Raloxifene (Evista)
   - One of the first-line drugs
   - Somewhat less effective than HRT and bisphosphonates
   - ↓ breast cancer risk but ↑ blood clots and hot flashes

3. HRT: no longer a first-line because of ↑ risk of breast cancer, stroke, clots, and perhaps coronary disease
4. **Parathyroid hormone:**
   - Daily injection and expensive
   - Severe osteoporosis when unable to tolerate any of the available bisphosphonates

5. **Others:** Denosumab, Strontium ranelate, Calcitonin, combination therapy

6. Counseling on fall prevention
THANK YOU