Women’s Health PRN Focus Session—Optimizing Care for Perimenopausal Women
Activity Number: 0217-0000-16-139-L01-P, 1.50 hours of CPE credit; Activity Type: A Knowledge-Based Activity

Tuesday, October 26, 2016
1:30 p.m. to 3:00 p.m.
Regency Ballroom 2

Moderator: Brooke L. Griffin, Pharm. D., BCACP
Associate Professor, Midwestern University, Downers Grove, Illinois

Agenda

1:30 p.m. Hot and Dry Perimenopausal Women: New Treatments to Ease the Transition
Sarah M. Westberg, Pharm. D., BCPS
Co-Associate Dean of Clinical Affairs and Associate Professor, University of
Minnesota College of Pharmacy, Minneapolis, Minnesota

Kylie N. Barnes, Pharm. D., BCPS
Clinical Assistant Professor, University of Missouri-Kansas City School of
Pharmacy, Kansas City, Missouri

2:20 p.m. To Give or Not to Give? Prevention and Treatment of Bone Loss in
Perimenopause
Abigail M. Yancey, Pharm. D., BCPS
Associate Professor, St. Louis College of Pharmacy, St. Louis, Missouri

2:45 p.m. Question and Answer Session

Conflict of Interest Disclosures
Kylie N. Barnes: no conflicts to disclose
Brooke L. Griffin: no conflicts to disclose
Sarah M. Westberg: no conflicts to disclose
Abigail M. Yancey: no conflicts to disclose

Learning Objectives
1. Using an evidence based approach, discuss the safety and efficacy of recently approved agents for the
treatment of genitourinary syndrome of menopause and vasomotor symptoms.
2. Evaluate the place in therapy for these recently approved agents.
3. Evaluate the risks and benefits of contraceptive use during perimenopause.
4. Design individualized, evidence-based contraceptive plans using specific clinical scenarios.
5. Describe bone loss prevention measures for perimenopausal women with an emphasis on calcium and
vitamin D supplementation.
6. Design individualized treatment plans for perimenopausal women at risk for medication-induced bone loss.

**Self-Assessment Questions**

Self-assessment questions are available online at [www.accp.com/am](http://www.accp.com/am)
Hot and Dry Perimenopausal Women: New Treatments to Ease the Transition
Sarah M. Westberg, Pharm.D., FCCP BCPS
Co-Associate Dean for Clinical Affairs
Associate Professor, University of Minnesota College of Pharmacy
October 25, 2016

Learning Objectives
• Discuss the safety and efficacy of recently approved agents for the treatment of genitourinary syndrome of menopause.
• Discuss the safety and efficacy of recently approved agents for the treatment of vasomotor symptoms.
• Evaluate the place in therapy for these recently approved agents.

What are SERMs?
• Selective estrogen receptor modulators
• Exhibit tissue-specific estrogen receptor agonist or antagonist activity
  • ERα
  • ERβ
• Theory is that ERβ may antagonize stimulatory growth in tissues by ERα
  • A specific ER subtype drugs not yet available

Relative Activities of SERMS

<table>
<thead>
<tr>
<th>SERM</th>
<th>Bone</th>
<th>Endometrium</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazedoxifene</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Lasofoxifene</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Osaxifene</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

+++ agonist = estradiol
--- antagonist = fulvestrant


New SERM for Genitourinary syndrome of menopause

Conflict of Interest
• I have no conflict of interests to report.
Case Example

- 59 year old postmenopausal female with intact uterus
- Experienced mild vasomotor symptoms during perimenopause; never used hormones and sxns remain manageable
- Now complains of vaginal dryness and dyspareunia
- Has tried vaginal estrogen creams and tablets; struggles with adherence due to discomfort with application

Which of the following steps would you take for this patient?

A. Provide patient-centered education on vaginal estrogen; encourage adherence to vaginal estrogen cream
B. Start treatment with estrogen vaginal ring
C. Start treatment with systemic estrogen with progesterone
D. Start treatment with ospemifene

Vulvovaginal Atrophy (VVA)

- Characterized by changes in the maturation index of vaginal epithelial cells (decreased superficial cells and increased parabasal cells), elevation in vaginal pH
  - Reduction in vaginal moisture and tissue elasticity
- Commonly experienced as vaginal dryness, dyspareunia, and vaginal irritation
- Reported by up to 40-60% of postmenopausal women
- Symptoms typically persist and/or increase with time and absence of treatment

REVIVE (REal Women’s Views of Treatment Options for Menopausal Vaginal ChangEs)

- Online survey; 3046 postmenopausal women with VVA symptoms responded (37.7% of menopausal women)
- Common Symptoms: dryness, dyspareunia, irritation
  - Symptoms affected enjoyment of sex in 59%
- Few women attributed symptoms to menopause (24%) or hormonal changes (12%)
- 56% had discussed with an HCP; 40% currently using topical treatments
- Of those who discussed with HCP, 62% used OTC products

Ospemifene

- FDA indicated for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
- Estrogen agonist/antagonist
- Contraindications & precautions:
  - undiagnosed vaginal bleeding, known estrogen-dependent neoplasia, active or h/o VTE, arterial thromboembolic disease, hypersensitivity, pregnancy
  - Adverse effects: hot flush, vaginal discharge, muscle spasm, hyperhidrosis

Context of Studying VVA

- “Most Bothersome Symptom”
  - Dyspareunia
  - Vaginal Dryness
- Outcomes complicated by high placebo response rate
- Differences in studies in allowance of lubricants and/or placebo vaginal creams
Ospemifene: Phase III Trial for dyspareunia

**PICO**
Portman et al. 2013

**Population**
605 women aged 40-80 with VVA and most bothersome symptom of dyspareunia

**Intervention**
Ospemifene 60 mg daily

**Comparison**
Placebo

**Outcome**
- Co-Primary Endpoints: Change from baseline to Week 12 in: 1) percentage of parabasal cells in the maturation index (MI), 2) percentage of superficial cells in the MI 3) vaginal pH and 4) severity of dyspareunia (4 point scale)

**Results:** Statistically significant improvements in each of the co-primary endpoints: Decrease in patient reported severity (-1.5 vs. -1.2, p = 0.001)


---

Ospemifene: Phase III Trial for vaginal dryness

**PICO**
Portman et al. 2014

**Population**
314 women aged 40-80 with vulvovaginal atrophy (VVA) with vaginal dryness most bothersome symptom

**Intervention**
Ospemifene 60 mg daily

**Comparison**
Placebo

**Outcome**
- Co-Primary Endpoints: Change from baseline to Week 12 in: 1) percentage of parabasal cells in the maturation index (MI), 2) percentage of superficial cells in the MI 3) vaginal pH and 4) severity of vaginal dryness (4 point scale)

**Results:** Stat sig improvements in each of the co-primary endpoints except patient-reported severity (in ITT group);
Symptom severity score was stat sig in per protocol group (-1.6 vs. -1.2; p=0.0004)


---

Ospemifene: Sexual Function

- A sub-analysis of the combined groups in the previous 2 studies, looked at changes from baseline to Weeks 4 and 12 for Female Sexual Function Index (FSFI) total and domain scores
- Statistically significant improvement in total FSFI score at Week 4 and continued through Week 12
  - Mean change in total score at Week 12 (6.69 vs. 4.14; p<0.001)
  - Dyspareunia group had greater change at Week 12 (7.37 vs. 4.00; p<0.001)


---

Ospemifene: Endometrial Safety

- Compilation of results from 6 individual, placebo controlled studies.
  - 1242 women on ospemifene 60 mg day; 924 placebo
  - Endometrial hyperplasia occurred in <1% in treatment groups (12-52 week trials)

Constanze HO, Griffiths BM, Archer DF. Maturitas. 2015;83:69-78

---

Case Example

- 59 year old postmenopausal female with intact uterus
- Experienced mild vasomotor symptoms during perimenopause; never used hormones and sxs remain manageable
- Now complains of vaginal dryness and dyspareunia
- Has tried vaginal estrogen creams and tablets; struggles with adherence due to discomfort with application

---

Which of the following steps would you take for this patient?

A. Provide patient-centered education on vaginal estrogen; encourage adherence to vaginal estrogen cream
B. Start treatment with estrogen vaginal ring
C. Start treatment with systemic estrogen with progesterone
D. Start treatment with ospemifene
Ospemifene: Emerging data

- Animal models have shown that ospemifene may have similar rates of efficacy against breast cancer as tamoxifen.

2016 ACCP Annual Meeting

Ospemifene: Place in Therapy

- A systemic treatment for a condition which can be treated locally
- More side effects
- Data on endometrial risk is for 1 year
- Vaginal estrogen available in creams, tablets & ring
- Cost: ~$200/month
- May be covered at a High Tier or through PA
- May be a good option in patients who prefer not to use vaginal delivery options
- Potential for use in patients with a history of breast cancer.

2016 ACCP Annual Meeting

New TSEC: Conjugated Estrogens and Bazedoxifene

2016 ACCP Annual Meeting

Case Example

- 55 year old postmenopausal women with complaints about hot flashes, trouble sleeping and increased anxiety. LMP was 6 months ago
- Has had improvement of symptoms with estradiol patches
- Developed rash which she believed was caused by micronized progesterone; was inconsistent in using it

2016 ACCP Annual Meeting

Which of the following steps would you take for this patient?

A. Switch micronized progesterone to medroxyprogesterone acetate
B. Rechallenge lower dose of micronized progesterone
C. Stop hormone therapy and start venlafaxine for vasomotor symptoms and anxiety
D. Start CE/bazedoxifene

2016 ACCP Annual Meeting

What is a TSEC?

- Tissue Selective Estrogen Complex
- SERM + 1 or more estrogens
  - Goal is to blend estrogen-receptor agonist activities of estrogen while minimizing negative effects

2016 ACCP Annual Meeting
Conjugated estrogens / bazedoxifene

- Conjugated estrogens 0.45 mg / bazedoxifene 20 mg daily
- FDA indicated for:
  - The treatment of moderate to vasomotor symptoms associated with menopause
  - Prevention of postmenopausal osteoporosis
- Use for shortest duration of time consistent with patient goals
- Contraindications & precautions similar to CEE & SERMS
- Side effects: nausea, diarrhea, dyspepsia, abdominal pain, muscle spasms, neck pain, dizziness
- Not recommended in renal impairment

Efficacy & Safety of Bazedoxifene Alone

<table>
<thead>
<tr>
<th>PICO</th>
<th>Silverman, et al. 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>6847 healthy postmenopausal women ages 55-85 with osteoporosis (per BMD or compression vertebral fractures).</td>
</tr>
<tr>
<td>Intervention</td>
<td>Bazedoxifene 40 &amp; 20 mg for 3 years</td>
</tr>
<tr>
<td>Comparison</td>
<td>Placebo for 3 years</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primary: Incidence of new vertebral fractures at 36 months</td>
</tr>
<tr>
<td></td>
<td>Incidence of new vertebral fractures was significantly lower (p &lt; 0.05) with bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.3%), and raloxifene 60 mg (2.3%) compared with placebo (4.1%).</td>
</tr>
</tbody>
</table>

Efficacy & Safety of CE/Bazedoxifene

SMART (Selective Estrogens, Menopause, and Response to Therapy)

<table>
<thead>
<tr>
<th>PICO</th>
<th>Pinkerton, et al. 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Generally healthy postmenopausal women ages 40-75 years with an intact uterus; Patients in SMART 1 and SMART 3 subgroups into &lt;5 years or ≥5 years since menopause.</td>
</tr>
<tr>
<td></td>
<td>SMART-1 primary outcome was endometrial hyperplasia; women ages 40-75 with an intact uterus (2 years)</td>
</tr>
<tr>
<td></td>
<td>SMART-2 primary outcome was changes in frequency &amp; severity of hot flashes; women ages 40-65 with an intact uterus and ≥7 hot flashes per day</td>
</tr>
<tr>
<td>Intervention</td>
<td>Bazedoxifene 20 mg with CEE 0.45 or 0.625 mg daily</td>
</tr>
<tr>
<td>Comparison</td>
<td>Placebo</td>
</tr>
<tr>
<td>Outcome</td>
<td>Hot-flush frequency and severity, health-related quality of life (HRQoL), sleep, treatment satisfaction, cumulative amenorrhea, and breast tenderness</td>
</tr>
</tbody>
</table>

Efficacy & Safety of CE/Bazedoxifene

SMART-5 (Selective Estrogens, Menopause, and Response to Therapy)

<table>
<thead>
<tr>
<th>PICO</th>
<th>Pinkerton, et al. 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>1843 postmenopausal women aged 40-65 with an intact uterus</td>
</tr>
<tr>
<td>Intervention</td>
<td>Bazedoxifene 20mg with 0.45 or 0.625 CE</td>
</tr>
<tr>
<td>Comparison</td>
<td>Bazedoxifene 20mg, CE 0.45mg/MPA 1.5 mg or Placebo</td>
</tr>
<tr>
<td>Outcome</td>
<td>Primary endpoints: Endometrial hyperplasia and lumbar spine BMD at 12 months</td>
</tr>
<tr>
<td></td>
<td>Endometrial hyperplasia was &lt;1% and similar across groups</td>
</tr>
<tr>
<td></td>
<td>All active treatment groups saw increase in BMD, with CE/MPA better than CE/Bazedoxifene</td>
</tr>
<tr>
<td></td>
<td>CE/Bazedoxifene groups had lower rates of bleeding (more amenorrhea) and breast tenderness compared to CE/MPA</td>
</tr>
</tbody>
</table>

Case Example

- 55 year old postmenopausal women with complaints about hot flashes, trouble sleeping and increased anxiety. LMP was 6 months ago
- Has had improvement of symptoms with estradiol patches
- Developed rash which she believed was caused by micronized progesterone; was inconsistent in using it
Which of the following steps would you take for this patient?

A. Switch micronized progesterone to medroxyprogesterone acetate
B. Rechallenge lower dose of micronized progesterone
C. Stop hormone therapy and start venlafaxine for vasomotor symptoms and anxiety
D. Start CE/bazedoxifene

Conjugated estrogens / bazedoxifene: Place in Therapy

- Likely comparable to other estrogen therapies for vasomotor symptoms
- Data for bone benefit is primarily vertebral; less effective than CEE/MPA
- May be an option for women with an intact uterus unable or unwilling to take a progestin
- May be an option for women with breast pain on traditional HT
- Cost: ~$170/month
  - May be covered at a High Tier; is preferred by some plans (others will require PA)

Future SERMS on the Horizon

- Lasofoxifene
  - Sought approval for osteoporosis; was not approved
  - Was approved in Europe for treatment of postmenopausal osteoporosis but never marketed
- Acolbifene
  - Studied in combination with DHEA for vasomotor symptoms
  - Breast cancer prevention

Questions?

Sarah M. Westberg, Pharm.D., FCCP, BCPS
swestber@umn.edu

Kylie N. Barnes, Pharm.D., BCPS
University of Missouri – Kansas City School of Pharmacy
Kansas City, Missouri
October 25, 2016

Conflict of Interest
• No conflicts of interest to report.

Learning Objectives
1. Evaluate the risks and benefits of contraceptive use during perimenopause.
2. Design individualized, evidence-based contraceptive plans using specific clinical scenarios.

Case
• LD, a 46 year old, is in need of contraception and treatment for severe hot flashes. She has 3 children from her previous marriage, and does not desire to have anymore children. Her PMH is insignificant, however she is obese (BMI = 37 kg/m²), her blood pressure is 132/84 mmHg, and her most recent labs reveal an A1c of 6.2%.
What is the best option for LD?

Perimenopause
• Occurs around age 45
• Menstrual cycle irregularities and menopausal symptoms

<table>
<thead>
<tr>
<th>Menopause Transition</th>
<th>Menstrual Cycle</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early transition</td>
<td>Increased variability (by &gt; 6 days) in cycle length</td>
<td>Variable</td>
</tr>
<tr>
<td>Late transition</td>
<td>Amenorrhea &gt; 60 days; increased variability in cycle length and prevalence of anovulation</td>
<td>1 – 3 years</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>Amenorrhea &gt; 12 months</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Why Contraception?
• Dramatic decrease in fertility
  • Decrease in oocyte quality and ovulation
  • Decrease in coital frequency
  • Male infertility rates increase
Injectable progestins

- Levonorgestrel (implant)

Contraception

- Reversible
- Long acting

- Progestin Method Typical
  - Effectiveness
  - 2016 ACCP Annual Meeting

Why Contraception?

- Women can still conceive

<table>
<thead>
<tr>
<th>Age</th>
<th>Birth Rate in 2014</th>
<th>Change from 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 40-44</td>
<td>10.6 births per 1000 women</td>
<td>2% ↑</td>
</tr>
<tr>
<td>Age 45 and up</td>
<td>0.8 births per 1000 women</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

- Estimated 75% of pregnancies in women > 40 years old are unplanned

2 ACOG. 2011 Women’s Health Stats and Facts


- Natural family planning
  - Not recommended due to unreliable ovulation and cycle length
  - All other methods are available
  - Must consider relative risks of exposure to contraceptive agents vs. potential health risks of a high risk pregnancy

Non-hormonal Methods

- Barrier methods
  - Option for women who have used these successfully and consistently in the past
  - Refit cervical caps and diaphragms after pregnancy, or if have not been used in several years
  - Spermicides
    - Option to consider amongst women with decreased fertility
  - Copper intrauterine device
    - option for women with light or infrequent menses
    - Cost effective

Hormonal Methods

- Progestin Only Products

<table>
<thead>
<tr>
<th>Method</th>
<th>Typical Use Effectiveness %</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestin only pill</td>
<td>9</td>
<td>Highly effective in the perimenopausal population</td>
<td>No relief of VMS</td>
</tr>
<tr>
<td>Long-acting reversible contraception (implant)</td>
<td>0.05</td>
<td>High effectiveness in first 3 years of use</td>
<td>↓ HDL and ↑ LDL</td>
</tr>
<tr>
<td>Levonorgestrel intrauterine system</td>
<td>0.2</td>
<td>↓ heavy menstrual bleeding</td>
<td>↓ Delayed return to ovulation (injectable)</td>
</tr>
<tr>
<td>Injectable progestins</td>
<td>6</td>
<td>↓ abnormal bleeding</td>
<td>↑ BMD (injectable)</td>
</tr>
</tbody>
</table>

- Estrogen + Progestin Products

<table>
<thead>
<tr>
<th>Method</th>
<th>Typical Use Effectiveness %</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined hormonal methods (pill, patch, ring)</td>
<td>9</td>
<td>↓ heavy bleeding</td>
<td>↑ unscheduled bleeding with continuous or extended regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ dysmenorrhea</td>
<td>May mask signs of menopause due to withdrawal bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ risk for ovarian and endometrial cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ bone density</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic relief of hot flashes or vaginal dryness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ acne</td>
<td></td>
</tr>
</tbody>
</table>
Permanent Contraceptive Methods
• Tubal ligation
• Hysteroscopic tubal occlusion
• Vasectomy

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?

How do we manage the risks?

When?
How?
Where?
Who?
Why?
How?
How do we manage the risks?

**Increased Breast Cancer Risk**
- Undiagnosed mass → Category 2
- Should be evaluated as early as possible
- Benign breast disease → Category 1
- Breast Cancer
  - Current → Category 4
  - Past and no evidence of current disease for 5 years → Category 3

**Increased Bone Loss → DMPA**
- Black box warning for bone loss if used > 2 years\(^1\)
- ACOG → potential fracture risk should not limit a woman’s use of DMPA to 2 years\(^2\)
- Concern for perimenopausal women – fewer years to recover BMD after discontinuing contraceptive
- Retrospective cohort (n = 312,295) found no evidence of ↑ fracture risk with DMPA use > 2 years\(^3\)


**When? And for how long?**

- Contraception options should be discussed until menopause can be confirmed
- When to discontinue depends upon:
  - Individual risk for pregnancy
  - Whether using additional non-hormonal methods to prevent pregnancy
  - Whether has developed any risk factors for continued use of estrogen
  - Timing of menopause

**When? And for how long?**

- Withdrawal bleeding or amenorrhea while on contraception does not rule menopause in or out
- Women nearing age 50 may consider discontinuing contraception for one to two months to see if she is still menstruating
  - Recommend non-hormonal backup method during these two months

**Laboratory Values Suggestive of Menopause**

<table>
<thead>
<tr>
<th>Limited Reproductive Potential</th>
<th>No Need for Contraception</th>
<th>Women Using Combined Hormonal Contraceptives</th>
<th>Women Using Injectable Progestin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH ≥ 20 IU/l</td>
<td>Amenorrhea for 12 months</td>
<td>FSH ≥ 30 IU/l on two occasions 6-8 weeks apart obtained beginning at age 50 (7-14 days after use of contraceptive)</td>
<td></td>
</tr>
<tr>
<td>FSH ≥ 30 IU/l</td>
<td></td>
<td>FSH ≥ 30 IU/l on two occasions 10 days apart obtained beginning at age 50 on the day of an injection</td>
<td></td>
</tr>
</tbody>
</table>


Transitioning to HT

• Once diagnosis of menopause has been made switch hormonal contraception → HT
• Even lowest doses of ethinyl estradiol in OC are fourfold higher than equivalent HT doses of estradiol
*Remember – HT will not block ovulation

Where do the guidelines stand?

• CDC, ACOG and NAMS all support recommending LARC for patients first line for women who have mild or no symptoms
• Highly effective
• Safe
• Convenient
• CHC may be prescribed unless contraindicated when desired or needed (i.e., VMS or cycle control)

What about Emergency Contraception?

• Copper IUD
  • Approved for use if placed within 72 hours of unprotected intercourse
  • When placed 120 hours after unprotected intercourse in large multicenter cohort, no pregnancies resulted among almost 2000 women up to age 44
• Levonorgestrel
  • Approved for use within 72 hours of unprotected intercourse
  • Has not been studied specifically in perimenopausal women

Additional Things to Consider

• Protection against sexually transmitted infections is still a concern
  • Keep in mind, oil-based lubricants can weaken the integrity and reduce the efficacy of latex condoms
  • Continuing the discussion of contraception through menopause is crucial

Case

• LD, a 46 year old, is in need of contraception and treatment for severe hot flashes. She has 3 children from her previous marriage, and does not desire to have anymore children. Her PMH is insignificant, however she is obese (BMI = 37 kg/m²), her blood pressure is 132/84 mmHg, and her most recent labs reveal an A1c of 6.2%.
• What is the best option for LD?
  • CHC recommended for contraception due to VMS
To Give or Not to Give?
Prevention and Treatment of Bone Loss in Perimenopause

Abigail M. Yancey, PharmD, BCPS
St. Louis College of Pharmacy
St. Louis, MO
October 25, 2016

Learning Objectives
• Describe bone loss prevention measures for perimenopausal women with an emphasis on calcium and vitamin D supplementation.
• Design individualized treatment plans for perimenopausal women at risk for medication-induced bone loss.

Is Bone Loss a Concern?
• Bone mass for women peaks between 33-40 years of age for the lumbar spine and 16-19 years of age for the hip
  • Bone mass decreases by 3-5% in the 1st few years after the final menstrual period; this rate eventually slows to 1-2%/year
  • Up to 20% of bone mass may be lost within 5-7 years of menopause

Patient Scenario?
• 49yo WF (5'6", 145 lbs) presents to clinic for her annual physical
  • PMH: GERD
  • SH: 3-4 alcoholic beverages/week; smokes 1/2ppd x 24yrs
  • Meds: Pantoprazole 40mg daily, Calcium Carbonate 500mg BID
  • Diet: low fat, low carb diet
  • Exercise: Walks with neighbor 15 min/day, 3x/wk

  • She is concerned about her family history of hip fracture (mother at age 68) and would like information on how to prevent bone loss.

Conflict of Interest
• Abigail M. Yancey has nothing to disclose

Patient Scenario?
• 49yo WF (5’6”, 145 lbs)
  • PMH: GERD
  • SH: 3-4 alcoholic beverages/week; smokes 1/2ppd x 24yrs
  • Meds: Pantoprazole 40mg daily, Calcium Carbonate 500mg BID
  • Diet: low fat, low carb diet
  • Exercise: Walks with neighbor 15 min/day, 3x/wk

  • What can we recommend to our patient to prevent bone loss?
**Lifestyle - Bone Loss Prevention**

### Smoking Cessation
- Active or Passive

### Alcohol Intake
- Moderate intake (<12/week) may be associated with slightly higher BMD and lower fracture risk
- Excessive intake (>2/day) may be detrimental to bone health

### Calcium Intake
- Premenopausal: 1000mg Calcium + 600IU Vitamin D
- Postmenopausal: 1200mg Calcium + 800-1000IU Vitamin D

**Calcium Controversies**

**Pros**
- Healthy Teeth
- Bone Health
- Lower Incidence of Kidney Stones
- CVD

**Cons**
- Lead Toxicity
- Nutritional Risk
- Sufficient
- Lead Nephrotoxicity
- 2013 USPSTF guidelines on CaD and bone health
- Premenopausal women: inadequate evidence to determine the effect of CaD on fracture risk
- Postmenopausal women: acceptable evidence that Ca 1000 mg + VIt D 400 IU does not affect the incidence of fracture

**Assessing Dietary Intake**

- Sufficient dietary calcium intake
- Estimate Dietary Intake

<table>
<thead>
<tr>
<th>Foods</th>
<th>Estimated Ca/Serving</th>
<th>250 mg for non-dairy sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (8 ounces), yogurt (6 ounces)</td>
<td>300 mg</td>
<td></td>
</tr>
<tr>
<td>Cheese (1 ounce or 1 cubic in)</td>
<td>200 mg</td>
<td></td>
</tr>
<tr>
<td>Fortified foods or juices</td>
<td>Can vary</td>
<td></td>
</tr>
</tbody>
</table>

- Sufficient vitamin D intake
  - Sunlight!!! Fortified milk and cereals (40-50IU/serving)
  - Patient at risk, consider serum 25(OH)D level
    - goal >70ng/ml

**Risk of Kidney Stones**

**The WHI CaD study**
- Increased incidence with calcium supplementation
- HR 1.17; 95% CI, 1.02–1.34
- NHU over a 7-year period: 273
- Absolute risk, CaD group 2.5% and 2.1% in the placebo

**Nurses Health Study**
- Lower risk with higher dietary calcium intake
- Supplementation calcium had a 20% higher risk

**Risk of Cardiovascular Disease**

- Multiple studies have shown a possible link
- Others show no change or even a benefit
- What do we know about the studies we do have?
  - No CaD RCTs with a primary outcome of CVD or events
  - Large observational data from RCTs with other outcomes
  - Correlation but not necessarily causation
- WHI (n=36,282 postmenopausal females 50-69yo)
  - Secondary outcome of CVD – no effect of CaD on CVD

**What can we Learn from these studies?**

- Encourage dietary calcium
  - Mean dietary calcium intake of 820mg/day resulted in a reduced risk of MI
- Supplemental only when dietary insufficient
  - Potential link with higher dose supplemental Ca
  - Doses of 700-899mg/day increased risk
  - Higher risk without co-administered Vitamin D

© American College of Clinical Pharmacy
Risk of Lead
• Lead contamination has been a concern for decades
• Calcium carbonate products derived from
  • Dolomite
  • Bone meal
  • Unrefined oyster shell
• Look for USP verified products
  • Voluntarily submitted
  • Products are tested and verified

To Give or Not to Give?
• Vitamin D
  • Can be taken as one dose with or without food
  • Ergocalciferol (D2) vs Cholecalciferol (D3)
    • Studies are mixed, D3 potentially more effective
    • D3 is the more “natural form” from UVB rays
  • Should not exceed >4000IU/day

To Give or Not to Give?
• Multi-vitamin
  • Calcium 500mg
• Vitamin D 400 - 1000IU
• Calcium Carbonate
  • Take with meals
  • 40% elemental Ca+
• USP Verified
• Calcium Citrate
  • Fasting State
  • 20% elemental Ca+
  • Better for patients on PPI or H2RAs

For absorption purposes 500mg elemental Ca+ per dose
Don’t exceed >2000mg/day

Learning Objectives
• Describe bone loss prevention measures for perimenopausal women with an emphasis on calcium and vitamin D supplementation.
• Design individualized treatment plans for perimenopausal women at risk for medication-induced bone loss.

Drug Induced Bone Loss
• Aromatase Inhibitors
  • Proton Pump Inhibitor
  • Glucocorticoids
  • SSRIs
  • AEDs
  • DMPS

Glucocorticoids
• American College of Rheumatology Guidelines
  • Prior to starting long-term therapy (>3-4 months) assess:
    • 25(OH)D, Height, Fall Risk, Fragility fracture history
  • All patients should received 1200-1500mg of Calcium and 800-1000IU Vitamin D
  • Decision for Pharmacological Treatment is based on:
    • Dose and duration of therapy, history of fragility fracture, and childbearing potential

© American College of Clinical Pharmacy
Drug Induced Bone Loss

- American College of Rheumatology Guidelines

Drug Induced Bone Loss

Proton-Pump Inhibitors

- FDA Warning - March 2011 (updated from May 2010) - Increased risk of fractures of the hip, wrist or spine – risk higher in older patients, higher dose, and longer duration of therapy.
- Using data from the SWAN study
- Mean age of 50 years; follow for a median 9.9 years
- No difference in annualized BMD change between groups
- Patients should use lowest dose and shortest duration
- Supplement of choice – Calcium Citrate

Drug Induced Bone Loss

Antidepressants

- SSRIs and TCAs – 2 fold increase in risk of fracture
- However not homogenous throughout the class
- Possibly depends on the agents affinity for the serotonin transporter
- When generated in the periphery: Serotonin inhibits bone formation
- Increased risk diminishes within a year of stopping therapy

Drug Induced Bone Loss

Aromatase inhibitors

- Anastrozole and letrozole
- Standard of care in adjuvant treatment of HER+
- Prevent the conversion of androgens to estrogen = bone loss
- Calcium 1200mg + Vitamin D 800-1000 IU
- Denosumab: FDA approved for AI induced bone loss
- Zoledronic acid: off label, but significantly reduced BMD loss at 3 yrs
- Bisphosphonates: established data for early stage breast cancer
- Studies focused on preserving BMD and not incidence of fractures

Drug Induced Bone Loss

Antiepileptic Drugs (AEDs)

- Mechanism of why remains in question for many agents
- Which agents are more likely to increase risk is also in question
- Fracture risk is higher for P450 enzyme-inducing compared to non-inducing drugs?
- Vitamin D requirements differ between agents
- Non-enzyme inducing AED: 1000-1200IU/day
- Enzyme inducing AED: 2000-4000IU/day

Drug Induced Bone Loss

Depot-Medroxyprogesterone (DMPA)

- Black Box Warning (11/2004) – limit use to 2 years
- WHO (2005) no restrictions on use for women 18-45 years
- Bone loss most rapid in 1st few years of therapy
- BMD substantially of fully reversible with discontinuation

Carolyn M. Hant Ph.D. 2010.02.1333.26

FDA.gov/downloads/Drugs/NewsEvents/UIUCF99545.pdf

Solomon DM. J Bone Miner Res. 2015 Feb;30(2):232-8

Hant FN. Cleve Clin J Med 2016;83:281-8


Razzel R. Bone 2012;15:696-11

Treatment Concerns - Childbearing Potential

- Bisphosphonates
- Safety data is limited –
  - Case reports have shown increased risk of spontaneous abortion, low birth weights, and earlier delivery (38 vs 40 weeks)
- Use in premenopausal patients should be reserved for special circumstances

Bone Loss Prevention

- Smoking Cessation
- Moderate Alcohol Consumption
- Exercise
- Adequate dietary intake
  - Calcium 1000mg/day
  - Vitamin D 600IU/day
- Multivitamin
- Calcium Carbonate or Calcium Citrate
- Cholecalciferol (D3)

To Give or Not to Give?
Prevention and Treatment of Bone Loss in Perimenopause

Abigail M. Yancey, PharmD, BCPS
St. Louis College of Pharmacy
St. Louis, MO
October 25, 2016