Management of the Perimenopause
What is new?

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Conflict of Interest Disclosure

Beth M. Lalande, MD has no significant relationships with industry to report.
OBJECTIVES

• Define menopause and associated terms
• Review absolute risks/benefits for five years of hormone therapy in younger postmenopausal women
• Discuss symptoms of menopause
• Choose the most appropriate hormone therapy to manage an individual’s menopausal symptoms.
• Utilize non-hormonal medications to treat menopausal symptoms
Menopause

• Menopause is the final menstrual period (FMP) and is usually confirmed when a woman has missed her period for 12 consecutive months (in the absence of other obvious causes).

• It reflects complete or near complete depletion of ovarian follicles and absence of ovarian estrogen secretion. It marks the permanent end of fertility.

• Average age is 51, but age ranges from 40 to early 60s. (Occurs after age 55 in 5% and between 40-45 in 5%.

• Age of menopause influenced by genetics, ethnicity, smoking, and reproductive history.
Diagnosis of Menopause

- Diagnosis of menopause is based on clinical history
- Measurement of FSH and estradiol is not required in women ≥ 45 yrs
- In women s/p hysterectomy or have inadequate menstrual history to ascertain menopause status, measurement of an elevated FSH and low estradiol (<20 pg/ml) on several occasions supports but does not confirm diagnosis
Definitions

**Perimenopause**
- Physical signs of menopause begin many years before the final menstrual period.
- Transition phase is called perimenopause “around menopause”
- It can last 6 years or more and ends 1 year after the final menstrual period.

**Postmenopause**
- All the years beyond menopause

**Induced Menopause**
- when the menstrual periods stop due to a medical intervention, such as surgical removal of both ovaries or chemotherapy.
Definitions

Premature Menopause

- When menopause occurs before the age of 40 and is not medically induced.
- Potential resumption of menses, conception and pregnancy
- Women with premature ovarian insufficiency (premature ovarian failure) should undergo complete evaluation.
  Causes include: idiopathic, autoimmune (PGA), metabolic, genetic (Fragile X premutation)
- Prevalence approx 1%
- Because women with premature menopause spend more years without the benefit of estrogen, they are at greater risk of health problems later in life such as heart disease and osteoporosis.
# Menopause Transition

Adapted from The Stages of Reproductive Aging Workshop for Reproductive Age Women

<table>
<thead>
<tr>
<th>REPRODUCTIVE YEARS</th>
<th>MENOPAUSE TRANSITION</th>
<th>POSTMENOPAUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>Late Reproductive</td>
<td>Early Transition</td>
</tr>
<tr>
<td><strong>Menstrual cycle</strong></td>
<td>Subtle changes in flow</td>
<td>Variable length, &gt;7 day difference in cycle length</td>
</tr>
<tr>
<td>FSH (cycle day 2-5)</td>
<td>variable</td>
<td>↑variability</td>
</tr>
<tr>
<td>AMH</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Vasomotor Symptoms (VMS)</strong></td>
<td>VMS likely</td>
<td>VMS most likely</td>
</tr>
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</table>

**PERIMENOPAUSE**
Menopausal Symptoms

<table>
<thead>
<tr>
<th>GOOD Evidence</th>
<th>FAIR Evidence</th>
<th>POOR Evidence</th>
</tr>
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<tbody>
<tr>
<td>Vasomotor symptoms (60-85%)</td>
<td>Cognitive dysfunction</td>
<td>Body Composition</td>
</tr>
<tr>
<td>Vaginal dryness (30-60%)</td>
<td>Urinary Incontinence</td>
<td>Joint aches and pains</td>
</tr>
<tr>
<td>Sleep disturbances (30-50%) 2-fold increase</td>
<td>Sexual dysfunction</td>
<td></td>
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<tr>
<td>Depressed mood 25-35%: 2-fold increase</td>
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</table>
HOT FLASHES

- 2nd most frequent complaint of perimenopausal women after irregular bleeding
- Prevalence 65-85% of U.S. women
- Can appear in one’s 30’s and 40’s (which doesn’t necessarily mean menopause is early) cluster around menses
- AA (45%) > Hispanics > Caucasians > Japanese, Chinese (17%) Study of Women’s Health Across the Nation (SWAN)
- Worse with higher BMI
- Worse with surgical menopause
- 25% of U.S. women seek help with symptom management
Vasomotor Symptoms: Duration

- 90% of women typically experience VMS for 1-2 yrs around the time of the FMP, then decrease over 8 yrs. Average duration is 4 yrs (Politi 2008)
- 15% have symptoms into their 60’s (Barnabei 2008)
- 9% past age 70 yrs (Huang 2008)
- May recur 10 yrs after menopause
Consequences of Estrogen Deficiency in the Postmenopausal Years

- Increased risk of osteoporosis
- Increased risk of diabetes
- Increased risk of CHD and CVD
- Changes in body composition—increased fat mass and decreased lean body mass
- Skin changes

*Estrogen therapy has long been recognized as the most effective treatment of VMS associated with menopause and historically was thought to reduce risk for heart disease.*

“HRT” was historically used 1950s-2002 routinely for symptom management and disease prevention.
Women’s Health Initiative (WHI)
Does “Hormone Replacement Therapy (HRT)” Prevent Disease?

E+P vs. PBO
- 16,000+ mostly asymptomatic PM women age 50-79 (mean age 63) randomized to continuous, combined estrogen-progestin (CEE 0.625 mg + medroxy-progesterone acetate 2.5 mg vs. placebo)
- Discontinued July 2002 – average follow up 5.2 years due to increased breast cancer, CHD, stroke, VTE

E vs. PBO
- 11,000 PM mostly asymptomatic women
- Unopposed estrogen (CEE 0.625 mg) vs. placebo
- Discontinued Feb. 2004 – average follow up 6.8 years due to increased risk of stroke
NHLBI Stops Trial of Estrogen Plus Progestin
Due to Increased Breast Cancer Risk, Lack of Overall Benefit

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has stopped early a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer. The large multi-center trial, a component of the Women's Health Initiative (WHI), also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit. The study, which was scheduled to run until 2005,
Effects of hormone therapy on event rates: green, placebo; purple, estrogen and progestin. CHD, coronary heart disease; VTE, venous thromboembolic events. (Adapted from Women's Health Initiative. WHI HRT Update. Available at http://www.nhlbi.nih.gov/health/women/upd2002.htm.)
Key Differences: WHI and Observational Studies

<table>
<thead>
<tr>
<th></th>
<th>WHI</th>
<th>Observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Symptoms</td>
<td>No</td>
<td>yes</td>
</tr>
<tr>
<td>Age at HT initiation</td>
<td>63 yrs</td>
<td>52 yrs</td>
</tr>
<tr>
<td>Time since menopause (mean)</td>
<td>12 yrs</td>
<td>2 yrs</td>
</tr>
<tr>
<td>BMI (kg/m2) mean</td>
<td>28-30</td>
<td>24-25</td>
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</tbody>
</table>
Absolute Risks by 10 yr Age Groups in WHI During Intervention Phase

Figure 3. Absolute Risks of Health Outcomes by 10-Year Age Groups in the Women’s Health Initiative Hormone Therapy Trials During the Intervention Phase

- Coronary heart disease
- Invasive breast cancer
- Stroke
- Pulmonary embolism
- Colorectal cancer
- Hip fracture
- All-cause mortality

Cases per 10000 Person-Years

Absolute Risks by 10 yr Age Groups in WHI During Intervention Phase

Conclusions from WHI Extension

- 81.1% of surviving participants of WHI followed through 9/30/10 (8.2 yrs for EPT and 13.2 yrs for ET)
- Post intervention, most risks and benefits were attenuated but persisted in the estrogen plus progestin group
- Most risks and benefits were more neutral in the estrogen alone group
- Neither regimen affected all-cause mortality during intervention, post intervention and during cumulative follow up
Conclusions and Relevance  Menopausal hormone therapy has a complex pattern of risks and benefits. Findings from the intervention and extended postintervention follow-up of the 2 WHI hormone therapy trials do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women.
TIMING HYPOTHESIS

Differential effect on atherosclerosis risk and clinical events according to when HT is initiated
Progression of coronary atherosclerosis by age in postmenopausal women and the ages of women participating in the hormonal trial of the WHI.

Lobo R A JCEM 2013;98:1771-1780
Timing of Exposure

• WHI: no increased risk of CHD in women 50-59 or < 10 yrs postmenopause (2007)
• WHI coronary calcification study (*Manson J, NEJM, 2007*)
• Salpeter meta analysis of clinical trials- CHD, mortality (2006, 2009)
• DOPS: Danish Osteoporosis Prevention Study (2012)
  E2 +progestin vs no treatment
  women <50 yr at study onset, 10 yrs of MHT
  Secondary analysis: reduced risk of composite outcome of mortality, heart failure or MI
  No placebo grp, unusual composite outcome
  *Schierbeck BMJ 2012*
**KEEPS: KRONOS Early Estrogen Prevention Study**

- 727 women within 36 months of LMP
- Age 42-58 (menopause >age 40)
- Baseline low CAC, CIMT and exclusions for CVD, CHD
- CEE 0.45 mg vs. transdermal E2 50 mcg vs. placebo (cyclic micronized P 200 mg x 12 days/month)
- Treatment duration 4 years
- 466 (64%) completed trial and 118 (16%) discontinued study med but were followed through duration of trial
- Endpoints: carotid IMT, coronary artery calcium score-- (Women too young and healthy and study too small to look at MI risk – surrogate markers used)
KEEPS: KRONOS Early Estrogen Prevention Study

KEEPS:  KRONOS Early Estrogen Prevention Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants With CAC Change*, n</th>
<th>Risk Difference vs. Placebo (95% CI), percentage points†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>217 (21.0)</td>
<td>-</td>
<td>0.36</td>
</tr>
<tr>
<td>o-CEE</td>
<td>181 (17.4)</td>
<td>-3.6 (-11.4 to 4.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>t-E2</td>
<td>172 (18.9)</td>
<td>-2.1 (-10.0 to 5.7)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

KEEPS: KRONOS Early Estrogen Prevention Study

*Harman et al Ann Int Med 2014:161;249-260*

- Favorable effects on VMS, mood and anxiety, sexual function, and bone density
- Coronary artery calcium and carotid IMT: no different with HT vs placebo
  - non significant trend of less progression in CAC with estrogen
  - Increases occurred in women who already had some CAC at baseline (5% of women with CAC equal to 0 vs. 67% of women with CAC greater than 0 at baseline had increases of 5 or more units).
  - In women with baseline CAC equal to 0, new development of CAC (defined as 5 units or more) occurred in 10.5% of those on o-CEE, 12.8% on t-E2, and 14.3% on placebo.
  - For women with baseline CAC greater than 0, corresponding values were 63%, 64%, and 73%.
- No statistically significant differences in rates of breast cancer, endometrial cancer, myocardial infarction, TIA, stroke, or venous thromboembolic disease between the three groups.
ELITE: Early vs Late Intervention Trial with Estradiol

- 643 women with LMP <6 or >10 yrs prior to enrollment
- Oral estradiol 1 mg/ day vs. placebo (vaginal progesterone gel 4% 10 days/month
- Launched 2004, treatment duration 6 yrs
- Primary outcome: Carotid IMT
- Presented at AHA 2014 by H Hodi- slowing of CIMT progression in younger women with MHT
WHI Extension Data

CHD Risk in Older Women with ET & EPT

In the 70-79 yr old women with moderate to severe vasomotor symptoms at baseline, had increased CHD risk
HR = 4.34 (95% CI, 1.43-13.14) with ET vs PBO
HR = 5.79 (95% CI, 1.29-25.97) with EPT

Women in the younger age groups with or without severe VMS had no excess risk.

- ET= CEE
- EPT= CEE plus MPA
WHI MEMORY Study in Younger Women

WHIMSY


- 1326 women 50-66 yrs
- Cognitive testing 7.2 yrs after treatment ended at avg age of 67
- HT showed neutral effect on cognitive function
- NO adverse effects as shown in WHIMS starting HT after 65 yr
  - 2 fold increases in dementia risk
  - Worse rates of cognitive decline over time
  - Decreased brain volume on MRI vs placebo
Breast Cancer and Estrogen Therapy


- In WHI, women 50-59 or < 10 yrs after menopause, risk not increased by CEE. 21% reduction of invasive breast cancer in 13-year cumulative follow up was of similar magnitude in each age group. *(Manson J, JAMA, 2013)*

- The risk of breast cancer from estrogen alone, taken for five years, appears to be small
Breast Cancer and Combined EPT

- Studies with combined EPT consistently show increased breast cancer risk. (Endo Soc Sci Statement, JCEM 2010; Chlebowski, R, JAMA 2010)
- In women ages 50-59 in WHI, excess risk of breast cancer during intervention phase persisted for 7 yrs after cessation of EPT with 4.5 excess cases per 1000 over 5 yrs (HR 1.34 (1.03-1.75) (Manson, J, JAMA, 2013)
- Observational studies report greater risk when EPT is started close to menopause (Chlebowski, JNCI, 2013; Prentice, Am J Epidem, 2009; Fournier, J Clin Oncol 2009)
Risk for Breast Cancer by Baseline Hormone Level E+P vs PBO (WHI)

Table. Risk for Breast Cancer by Baseline Hormone Level Among Women Randomized to Estrogen Plus Progesterone or Placebo

<table>
<thead>
<tr>
<th>Hormone Levels at Baseline</th>
<th>Placebo Group</th>
<th>E+P Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio in Highest vs Lowest Quartile</td>
<td>Odds Ratio in Lowest vs Highest Quartile</td>
</tr>
<tr>
<td>Total estradiol</td>
<td>2.52 ($P_{trend}=0.04$)</td>
<td>2.47 ($P_{trend}=0.04$)</td>
</tr>
<tr>
<td>Bioavailable estradiol</td>
<td>2.82 ($P_{trend}=0.03$)</td>
<td>2.35 ($P_{trend}=0.02$)</td>
</tr>
<tr>
<td>Estrone</td>
<td>3.01 ($P_{trend}=0.007$)</td>
<td>3.06 ($P_{trend}=0.02$)</td>
</tr>
</tbody>
</table>

Assess risk of breast cancer and do not treat those at high risk

- High risk (ie 4% chance of breast cancer in 5 years) excess risk 20/1000/5 years (*Santen JCEM 2010*)
- Gail Model
  http://www.cancer.gov/bcrisktoolmobile
- Early menarche, late age at first pregnancy, 2 1st degree relatives with breast cancer, 2 breast biopsies (but no= atypical hyperplasia): 5 yr risk = 4.1%
Considerations Interpreting Data on MHT Effects

- Not full agreement on whether MHT provides benefit or risk in terms of CHD and factors including timing of exposure may impact effect.
- Age, pre-existing conditions, including CVD risk factors
- Prior hormone therapy
- Timing of MHT initiation
- Duration of treatment
- Type of MHT—combined or unopposed, oral or transdermal estrogen
  - CEE metabolism 5-7:1:1 estrone:estradiol
  - vs. transdermal 17β estradiol 1:1 estrone:estradiol
- Progestin used
Estrogen Receptor Activity

- ER-α
  Uterus, breast, liver
- ER-β
  Bone, blood vessels, lungs
- ER-α and ER-β receptors present in ovary and CNS
- 17 beta estradiol binds both receptors
- Phytoestrogens have higher affinity for ER-β
- **ER gene polymorphisms** have been identified and may contribute to individual differences in menopause symptoms and development of osteoporosis, CVD, cognitive dysfunction and breast cancer
Case 1

50 yr old woman whose LMP was 5 months ago has hot flashes and requesting help.
She is awakened at least 5-7 times per night and has frequent episodes during the day that are interfering with her ability to function at work.
No history of VTE, stroke or CHD.
Case 1

What would you recommend to this patient?

- Transdermal estradiol 50 mcg and cyclic micronized progestin
- Oral estradiol 1 mg/d and continuous MPA
- Venlafaxine 75 mg/d
- Soy supplements
Case 1
Is she a good candidate for MHT?

- Women ages 50-59 years or <10 years postmenopause
- Moderate to severe symptoms
- With none of the following contraindications:
  - undiagnosed vaginal bleeding
  - history of estrogen sensitive cancer
  - history of stroke or MI
  - history of DVT or PE
  - liver disease
Approach to the patient with menopausal symptoms

• Provide information on absolute risks, not relative risks
• Put risk in perspective: ≤1 in 1000 is rare
• Discuss goals and potential duration of therapy
• Menopause Map (www.hormone.org)
• North American Menopause Society (www.menopause.org)
• Free app: MenoPro
Santen et al JCEM 2010;95 Suppl1: S1

A

Number of women per 1,000 per 5 years of use

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women ages 50-59 or &lt;10 years of menopausal</td>
<td></td>
</tr>
</tbody>
</table>

- Diabetess
- Breast cancer
- Colorectal cancer
- Overall mortality
- Coronary heart disease
- Endometrial cancer
- Lung cancer
- Veno-thrombotic episodes
- Stroke
- Cholecystitis

Legend:
- E
- E+P
**Anticipated Outcome for 5 years of E+P use in 1000 Women 50-59 years**

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>900+/1000 with VMS improve</td>
<td>No excess CHD (unless CHD history or risk factors)</td>
</tr>
<tr>
<td>5 deaths</td>
<td>1 stroke</td>
</tr>
<tr>
<td>5 fractures</td>
<td>5 VTE</td>
</tr>
<tr>
<td>10 cases type 2 DM</td>
<td></td>
</tr>
</tbody>
</table>

Breast cancer risk drives decision (excess risk depends upon individual’s other risk factors)
Santen et al JCEM 2010;95 Suppl1: S1

B

Number of women per 1,000 per 5 years of use

Symptoms worse

- Fractures
- Diabetes
- Breast cancer
- Colo-rectal cancer
- Overall mortality
- Coronary heart disease
- Endometrial cancer
- Non-small cell lung cancer
- Veno-thrombotic episodes
- Stroke
- Cholecystitis

Symptoms better

- Hot flashes
- Vaginal atrophy

E

E+P

Risks

Benefits
Estrogen for vasomotor symptoms

• E reduces frequency by 80-95% (dose-dependent)
• Low dose estrogen: effective for hot flashes with fewer side effects
• “ultra-low dose” estrogen (0.014 mcg patch approved for prevention of bone loss, but effective for symptoms in many women)
  – Low enough that they don’t need progestin
Effective Low Dose Estrogen Equivalents for Hot Flashes

- 0.5 oral mg micronized 17 beta estradiol
- 25 mcg/day transdermal 17 beta estradiol
- 0.3 mg oral conjugated equine estrogen
- 2.5 mcg oral ethinyl estradiol (most OCPs contain 20-30 mcg EE)
HT: What route of estrogen?

Transdermal 17β estradiol
- Avoids first-pass hepatic metabolism (TG, T)
- Lower risk of stroke in older women (if dose <50 mcg) Renoux BMJ 2010)
- Lower risk of VTE (Canonico et al, BMJ 2007)
  - Meta analysis of all observational studies and RCT oral and transdermal estrogen
  - Oral E2 : 2-3 x increase in VTE, higher in 1st yr
  - Baseline risk 1/1000 woman yrs, additional 1.5 events per 1000 women each year
  - No significant increase in VTE with transdermal E2
Progestin Options

- Medroxy progesterone acetate 2.5 mg daily, 5 mg cyclic
- Micronized progesterone 100 mg daily or 200 mg cyclic
- Appropriate progestin doses for lower E doses unclear

Tolerability issues (vaginal bleeding, mood effects, breast tenderness, breast density)

Women who cannot tolerate them?
- Progestin IUD (levonorgestrel)- (LNG-20 and LNG-14) (Somboonporn Menopause 2011) NOT FDA APPROVED but used in Europe to prevent endometrial hyperplasia
- Selective Estrogen Receptor Modulator (SERMS) (New FDA preferred terminology: Estrogen Agonist/Antagonist with Tissue-Selective Effects
Bazedoxifene Effects

• Prevents bone loss in women with low BMD
• Reduces nonvertebral fractures in women with osteoporosis
• Reduces nonvertebral fractures in high risk women
• Favorable endometrial, ovarian, and breast safety profile in women with osteoporosis

<table>
<thead>
<tr>
<th>TSEC: Tissue Selective Estrogen Complex</th>
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<tbody>
<tr>
<td>• Bazedoxifene (BZA) paired with conjugated estrogens (CE) has been evaluated in multiple phase III trials in &gt; 6000 women</td>
</tr>
<tr>
<td>▪ Selective estrogens</td>
</tr>
<tr>
<td>▪ Menopause</td>
</tr>
<tr>
<td>▪ And Response to</td>
</tr>
<tr>
<td>▪ Therapy</td>
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Bazedoxifene plus Conjugated Estrogen Effect on Daily Number of Hot Flashes

FIG. 2. Mean daily number of hot flashes with up to 12 weeks of treatment with BZA/CE or placebo for the MITT population using LOCF. At week 2, the mean daily number of hot flashes with BZA 20 mg/CE 0.625 mg was statistically significant ($P < 0.01$) from placebo. Statistical significance ($P < 0.01$) was achieved for both doses of BZA/CE during weeks 3 through 12 compared with placebo. BZA, bazedoxifene; CE, conjugated estrogens; LOCF, last observation carried forward; MITT, modified intent-to-treat.

Pinkerton, J V Menopause 2009;17:1116
Bazedoxifene plus Conjugated Estrogen Effect on Daily Severity Score of Hot Flashes

FIG. 3. Mean daily severity score of hot flushes with up to 12 weeks of treatment with BZA/CE or placebo for the MITT population using LOCF. The mean daily severity score of hot flushes was statistically significant ($p < 0.001$) for both BZA/CE doses during weeks 3 through 12 compared with placebo. The mean daily severity score was calculated by summing the number of mild, moderate, and severe hot flushes multiplied by 1, 2, and 3, respectively, divided by the total number of hot flushes. BZA, bazedoxifene; CE, conjugated estrogens; LOCF, last observation carried forward; MITT, modified intent-to-treat.

Pinkerton, J V Menopause 2009;17:1116
**TSEC: Tissue Selective Estrogen Complex**

Bazedoxifene (20 mg) with CE (0.625 or 0.45 mg)

- Relieves vasomotor symptoms
- Improves vaginal symptoms
- Improves sleep and quality of life
- Decreases bone turnover and bone loss
- Effects breast tenderness, vaginal bleeding, and rates of endometrial hyperplasia similar to placebo therapy
- No changes in mammographic breast density

TSEC: Additional Safety Data

For bazedoxifene 20 mg with CE 0.625 mg or 0.45 mg:

- VTE rates not additive
- Rates for MI and CVA were not increased compared to placebo
- Longer follow-up and larger study populations are needed to clarify risks

Taylor HS and Ohleth K. Menopause 2012
Conjugated Estrogen and Bazedoxifene (Duavee)

- Conjugated estrogen 0.45 mg and bazedoxifene 20 mg tablets (Duavee)
- FDA approved 10/3/13 for treatment of moderate to severe vasomotor symptoms in women with a uterus and prevention of postmenopausal osteoporosis
- First therapy to pair conjugated estrogen with an estrogen agonist/antagonist (TSEC)- uses bazedoxifene instead of progestin to prevent endometrial hyperplasia
- Phase III clinical trials in Selective Estrogens, Menopause, And Response to Therapy program (SMART):
  - 74% reduction in frequency of hot flashes at 12 wks vs 47% with placebo
  - 39% reduction in VMS severity vs 13% with placebo
  - Increases in BMD at years one and two at total hip and lumbar spine
- Side effects: muscle spasms, nausea, diarrhea, upset stomach, abd pain, throat pain, dizziness, neck pain
Case 2

• 52 yr old woman with recent diagnosis of breast cancer. S/p surgery, chemoRx, RT. Now on tamoxifen
• Since starting tamoxifen, she has severe hot flashes, day and night but more bothersome at night.
• Difficulty functioning well at work.
Case 2

What is best option for management of her hot flashes?

• Black cohosh
• Soy supplements
• Paroxetine
• Gabapentin
<table>
<thead>
<tr>
<th>Pharmacologic Treatment of Hot Flashes</th>
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<tbody>
<tr>
<td><strong>Hormone Therapy</strong></td>
</tr>
<tr>
<td>– Estrogen Therapy and EPT</td>
</tr>
<tr>
<td>– TSEC-conjugated estrogen and bazedoxifene (Duavee)</td>
</tr>
<tr>
<td>– Progestogen (oral MPA, depot MPA, Megace, norethindrone)</td>
</tr>
<tr>
<td><strong>Non hormonal prescription therapies</strong></td>
</tr>
<tr>
<td>– Gabapentin (and pregabalin)</td>
</tr>
<tr>
<td>– SSRIs/SNRIs</td>
</tr>
<tr>
<td>– clonidine</td>
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</tbody>
</table>
Importance of Placebo Effect

• Efficacy of various agents studies in reducing VMS in clinical trials is confounded by placebo effect

• Placebo effect can reduce VMS by 20-50%
  

• Women with higher anxiety scores may be more likely to respond to placebo
  
  van Die Menopause 2009
Selective Serotonin Reuptake Inhibitors and Selective Serotonin Norepinephrine Reuptake Inhibitors (SSRIs & SNRIs)

- Randomized, placebo controlled trials show significant reduction in hot flashes with
  - venlafaxine
  - desvenlaxafine
  - paroxetine
  - citalopram
  - escitalopram
- Less support with sertraline, fluoxetine, citalopram
Low Dose Paroxetine (Brisdelle)

- Paroxetine (Paxil) first and only non hormone therapy for VMS approved by FDA 7/2013
- Simon et al Menopause 2013;20:1027 --two randomized controlled trials of paroxetine vs placebo
- Marketed as “Brisdelle” 7.5 mg qhs
- Side effects: headache, fatigue, N/V
- Avoid paroxetine in women taking tamoxifen
  Cytochrome P-450 2D6 involved in metabolism of tamoxifen and SSRIs. Tamoxifen metabolites decreased by 24-64% at 4 wks with paroxetine Rx. Breast Ca recurrence 2 x higher in one study with 2 yrs tamoxifen plus CYP2D6 Rx
  Paroxetine > fluoxetine>>>>venlafaxine
Gabapentin (Neurontin)

- Reduces frequency of hot flashes in randomized, placebo controlled trials
- Side effects: headache, dizziness, drowsiness disorientation—improves within 2-4 wks.
- Gabapentin 300-900 mg at bedtime may be helpful relieving night sweats and minimizes side effects if given daytime
  - May be associated with weight gain
  - Combination with SSRI (venlafaxine) is no more effective than gabapentin alone
- Rejected by FDA May 2013 for vasomotor symptom indication
Pooled Analysis of Hot Flash Therapies

• Additional reduction in hot flash score vs. placebo (24% decrease in hot flashes): *Loprinzi et al J Clin Oncol 2009*
  - Paroxetine 41%
  - Venlafaxine 33%
  - Fluoxetine 13%
  - Sertraline 3-18%
  - Gabapentin 38%

• Escitalopram similar efficacy (Freeman, JAMA 2011)
Clonidine

- Shown to relieve hot flashes in some clinical trials—inconsistent efficacy
- Consider in a woman with hypertension
- 0.1 mg/d –transdermal patch or oral option dosed two-three times daily.
- Side effects: dry mouth, dizziness, constipation, sedation.
Complementary Therapies

- Lack of consistent evidence for benefit for botanicals, black cohosh, red clover, Vitamin E, mind/body alternatives including anxiety control, acupuncture, paced breathing, hypnosis
  - No evidence better than placebo, but considerable heterogeneity (red clover, soy supplements)
- Black Cohosh (Cimicifuga):
  - Cochrane 2012- no evidence that better than placebo but heterogeneity
Treatment of Genitourinary Syndrome of Menopause
Low Dose Vaginal Estrogen Therapy

• Effectively treats vaginal dryness and dyspareunia
• Estradiol tablet (Vagifem) 10 mcg daily x 1 week, then twice weekly
• Estrogen ring (Estring) q 3 months
• Estrogen cream 0.50 gm vaginally 2 times weekly
• Progestin not required
• Vaginal estrogen
  – Increases blood flow to vagina
  – Increases elasticity of vulvovaginal tissue
  – Decreases vaginal pH
Treatment of *Genitourinary Syndrome of Menopause*

**OSPEMIFENE**

- Ospemifene (Osphena) 60 mg po daily
- First SERM FDA approved (2/26/13) for moderate-severe dyspareunia
- 1889 women age 40 to 80 randomized to ospemifene 60 mg vs placebo
- Two 12 wk trials showing efficacy (vaginal maturation index, vaginal pH, symptoms – dryness/dyspareunia
- One long-term (1 year) safety study
- No studies in women with breast cancer
- Similar contraindications to estrogen

*Bachmann Menopause 2010, Portman Menopause 2013, Simon Menopause 2013*
Patient Resources

• Menopause Map (www.hormone.org)
• North American Menopause Society (www.menopause.org)
• Free app: MenoPro
Summary

• HT is safe for young, healthy postmenopausal women (<5 -10 yrs postmenopause)
• Indicated for women with moderate to severe symptoms
• In women with no prior use, 5 yrs of E+P is considered safe
• Start with low dose E and titrate up, unless severe sx
• Consider transdermal vs oral route
Summary

• Dose/duration of progestin for low dose E not established
• Taper and stop after 4 to 5 years (breast cancer risk)
• After stopping, try SSRIs/SNRIs or gabapentin if recurrent flashes
• Vaginal estrogen should be discussed with all women, particularly when systemic estrogen is stopped