Approach to the patient with menopausal symptoms

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Learning Objectives

Identify the common symptoms (including their natural history) of perimenopausal and menopausal women

Identify appropriate candidates for menopausal hormone therapy (and choose the optimal hormone therapy for an individual based upon her medical history)

Utilize nonhormonal strategies and medications to treat hot flashes in women who are not candidates for hormone therapy
Overview: Menopausal hormone therapy (MHT)

- 2017 Update
  - Trends in MHT use
  - WHI in 2017
  - Estimate of risk/benefits for women ages 50-59
    - Endo Society Guidelines

Management

- Perimenopausal/menopausal symptoms
- Regimens: dose, route, choice of estrogen and progestin
- Duration of therapy
- Nonhormonal alternatives
Menopausal hormone therapy (MHT) is

- Safe
- Appropriate for women with moderate to severe VMS without contraindications (20% of early PMW fit criteria)
- Underprescribed (>12.5 million PMW untreated)

Duration of therapy

- “Shortest duration possible”, BUT hot flashes persist for many years. New ACOG and NAMS statements about longer use. Breast Ca determines duration
Trends in oral MHT use

Sprague et al
Obstet Gynecol 2012
Challenges for women seeking treatment

- Percentage of women prescribed MHT pre- and post-WHI: 25-40% → 3%
- Why?
  - Lack of awareness of most current MHT evidence
  - Reason women and MD’s avoid MHT – fear of breast cancer
  - Current generation of new trainees have no experience (Manson NEJM 2016)
Consequences of not treating PMW

Untreated hot flashes:

• Quality of life
• Sleep disturbances
• Economic impact (Sarrel Menopause 2015)
  – Lost productivity
  – Increased healthcare costs
Consequences of not treating PMW

- Increase in use of compounded “bioidentical hormones” (as many women on BHT as MHT)
  - Perceived to be safer
  - A high percentage of women believe they are FDA-approved products (Pinkerton and Santoro, Menopause 2015)
  - Expensive (includes extensive salivary testing); concerns re: standardization and purity
Women’s Health Initiative
Program Design

Hysterectomy

YES
N=10,739

CEE 0.625 mg/d

Placebo

NO
N=16,608

CEE 0.625 mg/d + MPA 2.5 mg/d

Placebo

Trial stopped in 2004:
No CHD or breast ca;
stroke concern

Trial stopped in 2002:
breast cancer risk and apparent
CV risks.
Why different from epidemiologic studies?

Timing of exposure (timing hypothesis)

- WHI patient population: mean age 63 years
  - Probable underlying atherosclerosis and vulnerable plaque. E effects

- Evidence for timing hypothesis:
  - WHI subgroup analyses ages 50-59, <10 yrs postmenopause
  - Coronary calcification study
  - New RCTs: KEEPS, ELITE
  - Cochrane 2016: CHD and mortality
ELITE Trial

- Early Versus Late Intervention Trial With Estradiol
  - 643 postmenopausal women
  - < 6 yrs or ≥ 10 yrs from menopause (mean age 55 or 65)
  - Oral E2 1 mg vs placebo for 6 years (vaginal P 12 days if uterus)
  - Carotid IMT: (data support timing hypothesis)
    - ≥10 yrs from menopause no diff from placebo
    - < 6 yrs slower progression of atherosclerosis

KEEPS: KRONOS Early Estrogen Prevention Study

- 726 women within 36 months of LMP
- Ages 42-58 (menopause ≥ age 40)
- Oral CE 0.45 mg, transdermal E2 50 mcg, placebo; Micronized P 200 mg x 12 (4 yrs)
- Endpoints: carotid IMT, coronary artery calcium scores
- E improved markers of CVD risk
- Carotid IMT and CAC no different MHT vs placebo

Harman Ann Intern Med 2014
Cochrane review 2015: MHT for prevention of CHD

- 19 trials - 40,410 postmenopausal women (6 new trials)
- Menopausal hormone therapy:
  - Primary or secondary prevention - no protective effect for MI, CV death, mortality (all ages combined)
  - Subgroup analysis - < 10 yrs postmenopo - decreased mortality and CHD (RR 0.70 and 0.52). No increased stroke, but increased VTE

Cochrane Database Syst Rev 2015, Issue 2
Breast Cancer: WHI

- CEE + MPA 5.6 years treatment, total follow-up 13 years; HR 1.28 (during intervention phase, risk was only in prior users). **Important role of MPA in risk**
- CEE alone 7.2 years treatment, total follow up 13 years; HR 0.79

Endocrine Society Guidelines 2015 (Stuenkel JCEM 2015)
- Calculated 5 year risk for women 50-59 taking E+MPA = 4-5/1000
- Calculated 5 year risk for women 50-59 taking E alone = -3.5 cases/1000
- *The risk attributable to MHT is small and the risk decreases after stopping*  
  Manson JAMA 2013
MHT and breast cancer

Regimens that may be associated with lower risk:

- **Micronized progesterone** vs MPA (Fournier 2008)
- Low dose versus standard dose estrogen
- Cyclic vs continuous administration of progestin
- Transdermal vs oral estrogen
  - No increase breast cell proliferation (biopsy) or mammographic density (Gynecol Endocrinol 2012;28 suppl2:12)
## Overall risk vs benefit: WHI data

Number of events per 1000 women per 5 years use

<table>
<thead>
<tr>
<th></th>
<th>Risks E+P-only</th>
<th>Benefits E+P-only</th>
<th>Risks E-only</th>
<th>Benefits E-only</th>
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<tbody>
<tr>
<td>CHD</td>
<td>2.5</td>
<td></td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3</td>
<td></td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.5</td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>PE</td>
<td>3</td>
<td></td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>All fractures</td>
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<tr>
<td>Hip fracture</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>5</td>
<td></td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
<td></td>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td>Total R +B (no DM, fx)</td>
<td>11</td>
<td>24</td>
<td>3.0</td>
<td>34</td>
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<tr>
<td></td>
<td>11</td>
<td>6.5</td>
<td>3.0</td>
<td>21.5</td>
</tr>
</tbody>
</table>
Vasomotor symptoms: SWAN

Prevalence:
• Peaks in late menopausal transition/ early postmenopause (SWAN study 85%)
• African-American > Caucasian > Hispanic, Japanese, Chinese
• Obese women at higher risk
• Women with PMS at higher risk

Women with variations in tachykinin receptor 3 (TACR3) more likely to have hot flashes (WHI)
Vasomotor symptoms: Duration

• 50% > 7 years (SWAN JAMA Int Med 2015)
• Dependent upon when they begin: pre-, peri, or postmenopausal: median duration 11.8, 9.4, and 3.4 years
• 9% with hot flashes after age 70 (Grady)
• Long duration of symptoms has important implications for duration of therapy
Mood disorders – how common?

• Depression/mood disorders (35-40% in menopausal transition)
  • More common in women with hot flashes
    • Nighttime but not daytime HF associated with mood symptoms (not just sleep deprivation)
• History of mood disorders
• Known PMS
• Family history
Depression: Treatment considerations

- Choose initial therapy based upon predominant symptom (depression vs VMS)
- Often need both estrogen and SSRI citalopram, escitalopram, duloxetine
- Often progestin intolerant
  - Continuous vs cyclic regimen
  - Can use continuous OCs
  - Consider Lnorg-IUD
- Other options: CBT not well studied
Other menopausal symptoms

- Sleep disturbances
  - 40% in absence of VMS
- Arthralgias (? related to variant SNP associated with MS symptoms in women taking AIs)
- Vulvovaginal atrophy (Genitourinary syndrome of menopause (GSM))—urogenital symptoms tend to develop progressively in the years or decades after menopause
- Cognitive issues?
• Individualize therapy based upon clinical factors and patient preference
• Before initiating MHT, estimate patient’s:
  • 10-year cardiovascular risk
  • 5-year breast cancer risk

Stuenkel et al JCEM 2015
## Choosing Candidates: Evaluate CVD risk

<table>
<thead>
<tr>
<th>10-year CVD risk</th>
<th>MHT recommendation if &lt;10 years since menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;5%)</td>
<td>MHT ok</td>
</tr>
<tr>
<td>Moderate (5-10%)</td>
<td>MHT ok, but use transdermal</td>
</tr>
<tr>
<td>High (&gt;10%)</td>
<td>Avoid MHT</td>
</tr>
</tbody>
</table>

*Calculated using ACC/AHA risk calculator*  
*Stuenkel et al, JCEM 2015; Adapted from Manson, Fertil Steril 2014*
<table>
<thead>
<tr>
<th>Risk category</th>
<th>5-y NCI or IBIS Breast cancer risk assessment, %</th>
<th>Suggested approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;1.67</td>
<td>MHT ok</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.67-5</td>
<td>Caution</td>
</tr>
<tr>
<td>High</td>
<td>&gt;5</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

Stuenkel et al, JCEM 2015
MHT for vasomotor symptoms

- Low-dose estrogen: effective for hot flashes, fewer side effects, better risk profile
- Route: transdermal versus oral
- 17-B estradiol versus CEE or EE
- Progestin: micronized progesterone versus MPA
- **Choice:** Transdermal 17-B-E2 + micronized progesterone
Estrogen dose and Hot Flashes
HOPE Trial

Week
Percentage Hot Flash Frequency (Mean)

Placebo
CEE 0.45 mg/d
CEE 0.3 mg/d
CEE 0.625 mg/d

Utian, Fertil Steril 2001;75:1065
Transdermals avoid first pass hepatic metabolism; less effect on:

- Clotting factors
- Triglycerides
- C-reactive protein
- SHBG

Lower risk of:

- **VTE** (Canonico Circ 07, BMJ 08)
- **Stroke** (if dose < 50 mcg) Renoux BMJ 2010)
- Increase in **mammographic density**

Less favorable effect on LDL, HDL
Advantages of micronized progesterone

• Neutral metabolic effect. (eg does not negate benefits of oral E)

• Vascular –Unlike MPA, P does not negate vasodilatory effect of E (primate data). Differential effects on endothelial function

• Ischemic stroke risk (Canonico Stroke 2016) MP better than MPA

• Breast cancer - ? lowest risk with micronized P ; (European observational studies; Endo Society metaanalysis JCEM 2015)
My approach: Late transition/early postmenopause

**Moderate** symptoms

- Transdermal E2 (0.025 mg=25 mcg) + *cyclic* MP 200 mg days 1-12
  - Start with 0.05 mg (50 mcg) if more *severe* symptoms
  - Cyclic P regimens helps minimize bleeding with cyclic P. Eventually transition to *continuous*.

- Consider **low dose OC** in some women in 40s with heavy bleeding who desire contraception

- Oral E2 ok for healthy women without DVT risks who prefer oral preps (0.5-1 mg)
My approach: Postmenopausal women

- Transdermal E2 (0.025 mg) + continuous MP 100 mg (less BTB if 1 year since FMP or already on MHT 1 year).
  - Higher starting E2 dose for severe sx

- Oral E2 ok for healthy women who prefer oral

Primary ovarian insufficiency (menopause < age 40):
- treat until age 50-51, average age of menopause!
Women who cannot tolerate progestins

- 20% significant side effects, 10% need alternative
- BTB and mood issues
- Off-label options
  - Progestin IUD (levonorgestrel) - contraceptive doses (LNG-20 and LNG-14) (Somboonporn Menopause 2011)
    » Breast cancer concerns in premenopausal women (Ob Gyn 2014 124:292)
  - Quarterly progestin regimens, vaginal progestins: safety not established
- Tissue selective estrogen complex (SERM+CEE)
Duration of therapy and stopping

- Current practice 2-5 years
- Extended use: ACOG, NAMS statements
  - Extended use (beyond age 60) may be appropriate for women with severe vasomotor symptoms and low risk cardiovascular complications
  - The clinician and patient must agree that the benefits of further treatment outweigh the risks
  - Periodic weaning to assess need (use nonhormonal agents while weaning – herbal therapies ineffective)
Nonhormonal therapies: Antidepressants

SSRIs

- **Citalopram** 20 mg
- **Escitalopram** 10 to 20 mg
- Paroxetine 7.5 mg (Brisdelle- low dose mesylate salt; FDA approved) or paroxetine HCl 20 mg, CR 12.5-25 mg
- Avoid paroxetine in women on tamoxifen (CYP2D6 inhibitor)
- Sertraline and fluoxetine are ineffective

SNRIs

- Venlafaxine 75 mg; Desvenlafaxine 50 mg
Nonhormonal therapies: Other

- **Gabapentin 300-900 mg** (split dose or single bedtime dose) *(good choice for night time symptoms)*
- Clonidine – use limited by side effects
  - Dose: transdermal 0.1mg/week

Range of effect: only a 40 to 55% reduction vs placebo 25-30% reduction *Loprinzi et al J Clin Oncol 2009*
- Response not explained by mood effect
Genitourinary syndrome of menopause

- Water-based gels and lubricants
- Low-dose vaginal estrogen
  - E2 or CEE creams: difficult to administer low doses
  - Estradiol tablets: 10 µg twice weekly (serum E2<10pg/ml; 37 pmol/L)
  - Vaginal ring 8 ug/day (serum E2 = 7 pg/mL; 26 pmol/L)
  - No significant endometrial thickening
  - Improved sexual QOL (Setty, Menopause August 2015)
  - Avoid in patients on aromatase inhibitors!
Key points

- For many/most symptomatic women < age 60 or < 10 years postmenopause, the benefits of MHT outweigh the risks.
- Women with moderate to severe menopausal symptoms are currently undertreated.
- Reluctance to prescribe coincides with an increase in use of bioidentical hormone therapy.
- Individualized approach: assess baseline CVD and breast cancer risks.
- Start with low dose E and titrate up, unless severe symptoms.
- Preferred regimen: transdermal E2 and MP.
Key points

• Tapering and stopping after 5 years (breast cancer risk) is the current standard – this does not address the needs of women with long-duration severe VMS

• Extended use (beyond age 60) may be appropriate for women with severe vasomotor symptoms and low risk cardiovascular complications

• After stopping, recurrent VMS, try SSRIs/SNRIs or gabapentin

• Vaginal estrogen should be discussed with ALL women, particularly when systemic estrogen is stopped
Other risks

- **Ovarian cancer**
  - WHI: 50-59 group - HR with EPT/E 0.30 (2 cases vs 6 in placebo group; -1.5 per 1000/5 years of use) JAMA 2003;290(13):1739
  - All ages, nonsignificant increase (HR 1.41) (similar to meta-analysis)
  - **Meta-analysis 52 studies**: increase of 0.5 cases/1000 women/5 years of use Lancet 2015;385:1835

- Gallbladder disease – not with transdermals

- Lung cancer – unlikely (Schwartz, J Thorac Oncol 2015)