Modern Management of Menopause

Michael Policar, MD, MPH
Clinical Professor of Ob, Gyn, and Repro Sciences
UCSF School of Medicine
policarm@obgyn.ucsf.edu

No commercial disclosures for this lecture

Topics To Be Discussed

- New information from the WHI
- The expanding range of treatments for managing menopausal symptoms
  - Which treatments are available to your patient?
- Practice Recommendations
  - How can your patient use these treatments safely, effectively, and conveniently?

Key Points:


Available at: menopause.org

NAMS Definitions

- ET  Estrogen (E) therapy
- EPT  Combined E+P therapy
- HT  Hormone therapy (ET, EPT)
- MHT  Menopausal hormone therapy (ET, EPT)
- Progestogen  Progesterone or progestin (P)
- CC-EPT  Continuous-combined E+P therapy
  - E+P given every day
- CS-EPT  Continuous-sequential E+P therapy
  - E daily with sequenced P

Case Study

- Ms S is a 52 year old woman with moderate-severe hot flashes and difficulty getting to sleep
- Her menses were regular until one year ago, became irregular, and then stopped 6 months ago
- She has tried a number of herbal remedies, each of which helped for only a few months
- Her medical history, BP, physical exam are normal
- The hot flashes affect her work productivity and she wants to try something else

Would you recommend that she…..

1. Try a different over-the-counter supplement
2. Prescribe a SSRI or SNRI anti-depressant medication
3. Prescribe the lowest dose estrogen and progestin
4. Prescribe a “mid-range” dose of estrogen and progestin
5. Receive a consultation with an ObGyn to discuss this subject and have a treatment plan developed

Explaining HT Risk and Benefit

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age</td>
<td>Safer if younger</td>
</tr>
<tr>
<td>Time since menopause</td>
<td>Safer if shorter time since LMP</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>Worse symptoms if early menopause</td>
</tr>
<tr>
<td>Cause of menopause</td>
<td>Worse symptoms if surgical menopause</td>
</tr>
<tr>
<td>HT types, route, doses used</td>
<td>Choice of product or delivery system</td>
</tr>
<tr>
<td>Prior use of any hormone</td>
<td>Hormone vs non-hormonal treatment</td>
</tr>
<tr>
<td>Baseline disease risks</td>
<td>Hormone vs non-hormonal treatment</td>
</tr>
<tr>
<td>Emerging conditions during treatment</td>
<td>Hormone vs non-hormonal treatment</td>
</tr>
</tbody>
</table>


SWAN Study

Study of Women Across the Nation

- Longitudinal community sample >16,000 women
  - Non-Hispanic white, African American, Hispanic, Japanese American, and Chinese American
- Reported racial and cultural differences in risk factors, symptoms, physiology, and attitudes re: menopause
- Reference
Observations from the SWAN Study

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Af-Am</th>
<th>Hispanic</th>
<th>Chinese</th>
<th>Japanese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor symptoms, %</td>
<td>31</td>
<td>46</td>
<td>35</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Attitude toward menopause</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>Comp/altern med use, %</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>46</td>
<td>60</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8</td>
<td>31.5</td>
<td>29.2</td>
<td>23.3</td>
<td>22.9</td>
</tr>
<tr>
<td>Genistein intake daily, µg</td>
<td>834</td>
<td>271</td>
<td>310</td>
<td>6398</td>
<td>11,165</td>
</tr>
<tr>
<td>Depressive symptoms, %</td>
<td>22.7</td>
<td>27.2</td>
<td>43.3</td>
<td>14</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Act 1
Let’s Get This Out of the Way….

The WHI Re-analyzed

Clinical Implications: Unified Hypothesis
- **Mild cardioprotection**
  - Women in their early-mid 50s, who
  - Initiate HT soon after menopause, with
  - Few or no heart disease or stroke risk factors
  - And who use estrogen-only regimens
- **Increased heart disease risk**
  - Women in their mid-60s or later, who
  - Initiate HT long after menopause, who have
  - Heart disease or stroke risk factors
  - And who use estrogen and progestin regimens

HT and CVD: The Unified Hypothesis

Phillips LS, Langer RD, Postmenopausal hormone therapy: critical reappraisal and a unified hypothesis. Fertility and Sterility 2005; 83:558-66
**HT & Coronary Heart Disease (CHD)**

- HT may reduce CHD risk when initiated in younger and more recently postmenopausal women
- Longer HT duration associated with reduced CHD risk and mortality
  - Long-term HT associated with less accumulation of coronary artery calcium
  - Some evidence of lower CHD risk in women who used HT ≥ 5 years


**HT & Coronary Heart Disease (cont’d)**

- Short-term HT may increase CHD risk in women farther from menopause at time of initiation
- **HT currently not recommended as sole or primary indication for coronary protection in women of any age**


**HT & Venous Thromboembolism**

- Oral HT increases VTE risk in menopausal women
- VTE risk emerges early (1-2 y); decreases over time
- Lower VTE risk with EPT or ET in women <60 y.o.
- Lower HT doses may be safer than higher doses
- Likely lower risk with transdermal vs. oral ET
- VTE risk fall into the “rare” category


**HT and Stroke**

- In the WHI EPT + ET trials
  - Increased ischemic stroke risk
  - No effect on hemorrhagic stroke risk
  - In women 50-59 at study entry, HT had no effect on risk of stroke (RR 1.13; 95% [CI], 0.73-1.76)
- Transdermal estrogen not associated with increased stroke risk (Renoux C. *BMJ* 2010; 340: c2519)
**HT & Breast Cancer**

- EPT use >3-5 years increased breast cancer risk
  - Increased absolute risk of EPT in WHI: “rare”
  - 4-6 additional cases/10,000/yr of EPT for ≥ 5 yrs

- Estrogen only regimens
  - WHI ET trial showed no increased risk after 7.1 yrs
  - 6 fewer cases/10,000 women/yr of ET use (not SS)
  - Other studies showed that ET for < 5 yrs has little or no impact on breast cancer risk


**HT & Total Mortality**

- HT may reduce total mortality when initiated soon after menopause
  - Both ET and EPT reduce total mortality by 30% when initiated in women <60 years old
  - HT not associated with mortality reduction among women who initiate HT at ≥60 years old


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**Therapeutic Interventions**

- Lifestyle changes
- Botanicals and PhytoSERMs
- Non-hormonal Rx medications
- Hormone Therapy (MHT)

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**Hot Flashes: Lifestyle Changes**

- Exercise routinely, at least 3-4 days/week
- Cool room temperature, especially at night
- Dress in layers (remove outer layers if warm)
- Avoid hot and spicy foods
- Relaxing activities
- Avoid cigarettes
- Minimize alcohol
Botanicals and PhytoSERMs

**Probably better than placebo**
- Black cohosh

**No evidence of efficacy**
- Soy isoflavones
- Red clover isoflavones
- Evening primrose oil
- Dong quai
- Ginseng
- Vitamin E
- Chasteberry (Vitex)

**Botanicals: Black Cohosh**
- Total of 14 trials reported, including 4 randomized trials using placebo and/or estrogen treatment arm
  - 3 of 4 RCTs found black cohosh to be beneficial
  - 12 of 14 trials reported *some* benefit
  - Currently, longest trial is 6 months
- NIH-funded, large, randomized, prospective, 2-year trial ongoing
  - Preliminary data fail to show binding to E receptors
  - Binding to serotonin receptor noted

Botanicals and PhytoSERMs

- Evidence supports positive effect of black cohosh vs placebo
  - Improvement is less than with HT
- Some of the impact is due to placebo effect, which is none-the-less therapeutic
- Relatively little risk of adverse effects
- **Reasonable first-line choice for women**
  - With mild menopausal symptoms
  - Who feel strongly about avoiding hormones
  - Who are willing to use medications that are not “proven” effective by EBM or regulated by FDA

Non-Hormonal Hot Flash Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>% of women with &gt;50% HF Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>62-65%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>38-60%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20%</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>45%</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td></td>
</tr>
<tr>
<td>Methylpapine</td>
<td>65%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>38%</td>
</tr>
</tbody>
</table>

Recent study supports hot flash reduction with escitalopram (Lexapro)
- % women with >50% ↓ HF
  - Escitalopram: 55%
  - Placebo: 36%

Menopause 2004; 11(1): 11-33
ACOG Task Force on HT.
Freeman EW, JAMA 2011
### Gabapentin (GBP) and Hot Flashes (HF)

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose</th>
<th>% HF ↓ GBP</th>
<th>% HF ↓ Placebo</th>
<th>% HF ↓ Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butt DA 2008</td>
<td>300 mg TID</td>
<td>51%</td>
<td>26%</td>
<td>NA</td>
</tr>
<tr>
<td>Guttuso TJ 2003</td>
<td>900 → 2700 mg</td>
<td>54%</td>
<td>31%</td>
<td>NA</td>
</tr>
<tr>
<td>Pandya KG 2005</td>
<td>300 mg TID</td>
<td>46%</td>
<td>18%</td>
<td>NA</td>
</tr>
<tr>
<td>Reddy SY 2006</td>
<td>Up to 2400 mg</td>
<td>71%</td>
<td>54%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Conclusion: gabapentin equal to, or more effective, than SSRIs

### Prescription HT Options: ET and EPT

<table>
<thead>
<tr>
<th>Oral</th>
<th>Transdermal</th>
<th>Intravaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Micronized estradiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Conjugated equine estrogens (CEE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Synthetic conjugated estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Esterified estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Estropipate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Estradiol acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Emulsion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Spray</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EPT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• CC-EPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CS-EPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• E+P (combination) patches</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Hormone Therapy Regimens

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Therapy (ET)</td>
<td>Estrogen Therapy (ET)</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Continuous combined (CC) EPT</td>
<td>Continuous combined (CC) EPT</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Progestin</td>
<td>Progestin 14d</td>
</tr>
<tr>
<td>Continuous-sequential (CS) EPT</td>
<td>Continuous-sequential (CS) EPT</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Progestin 14d</td>
<td>Off for 14 d</td>
</tr>
<tr>
<td>Continuous-pulsed (CP) EPT</td>
<td>Continuous-pulsed (CP) EPT</td>
</tr>
<tr>
<td>3d</td>
<td>3d</td>
</tr>
</tbody>
</table>

### Choice of HT Regimen

- If no uterus: **estrogen only**
- If uterus present
  - Goal is to avoid vaginal bleeding entirely, or, at least, to make it predictable
  - Endometrial activity predicts bleeding pattern
  - **Recent spontaneous or induced bleeding**
    - Use continuous sequential
  - **No bleeding for >2-3 cycles**
    - Use continuous combined
HT Dosages

- Therapeutic goal is lowest effective estrogen dose (plus low progestogen dose for women with a uterus) consistent with individual treatment goals, benefits, and risks
- **Lower doses better tolerated, may have more favorable benefit-risk ratio than standard doses**
- Additional local ET may be needed for persistent vaginal symptoms


HT Starting Dosages

- Lower daily doses typically used with systemic ET
  - 0.3 mg oral CE
  - 0.5 mg oral micronized 17ß-estradiol
  - 0.014-0.025 mg transdermal 17ß-estradiol patch
- Typical lowest doses of progestogen
  - 1.5 mg oral MPA
  - 0.1 mg oral norethindrone acetate
  - 0.5 mg oral drospirenone
  - 50-100 mg oral micronized progesterone


Choice of Estrogens

- Start *low dose* transdermal or oral estrogen
- If suboptimal response, modify by
  - Change the estrogen dose (upward)
  - Change the estrogen preparation
  - Change delivery systems (oral → transdermal)
  - Consider an estrogen-androgen combination
- Injectable estrogen not recommended
  - Dosage equivalencies are not known
  - Estrogen cannot be discontinued easily


HT Routes of Administration

- No clear benefit of one route of administration for systemic ET
- Non-oral routes may offer both advantages and disadvantages compared with oral route
- Transdermal ET may be associated with lower DVT risk than oral (observational data, not RCTs)
- Local ET preferred when solely vaginal symptoms

Oral vs. TD-E: The Risk of VTE
The ESTHER Study

Adjusted Odds Ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonusers</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Oral estrogen</td>
<td>3.5</td>
<td>(1.8-6.8)</td>
</tr>
<tr>
<td>Transdermal</td>
<td>6.6</td>
<td>(3.5-16.1)</td>
</tr>
</tbody>
</table>


“First Line” Use: Transdermal Estrogen

- Underlying medical conditions
  - History of DVT or PTE
  - High triglyceride levels
  - Gall bladder disease
- Need for “steady state” drug release
  - Daily mood swings (especially while on oral HT)
  - Migraine headaches
- Inability to use oral tablets
  - Stomach upset due to oral estrogen intake
  - Problems with taking a daily pill

Compounded Bioidentical Hormones

“Then, suddenly, the Seven Dwarfs of Menopause arrived at my door without warning: Bitchy, Sweaty, Sleepy, Bloated, Forgetful, and All-Dried-Up….What was it that sent those wretched dwarfs packing? Natural bioidentical hormones.”


Compounded Hormone Therapy

- The marketing of compounded hormonal therapy
  - Only bioidentical hormones are used
  - Combination of 2 or 3 estrogens is more “natural”
  - Dosage is tailored to the individual
  - More “pure” than commercial products
  - Safer delivery systems (no dyes, etc)
- The reality
  - The same hormones are used in commercial and compounded 17b-E₂ and progesterone
Compounded Hormone Therapy

Compounded hormones will probably work about as well as commercial HT products, but...
- Value of adding $E_1 + E_3$ has not been evaluated
- Progesterone skin cream is not absorbed
- Compounded hormone doses are not standardized
- Salivary hormone levels are not useful
- FDA-approved HT products will offer
  - Bioidentical hormones
  - Choice of delivery systems
  - Formulary coverage/ lower out-of-pocket costs

Treatment of Hot Flashes

- If mild symptoms, try lifestyle, CAM therapy
- Indications for hormone therapy
  - Moderate or severe symptoms
  - Non-hormonal treatments have failed
  - No interest in non-hormonal therapy
- Titrate estrogen dosage upward if needed
- When estrogen can’t be used, offer
  - SSRI or SNRI
  - Gabapentin, clonidine, a-methyldopa
  - Progestins alone
- Attempt discontinuation after 2 years

Sources of Exogenous Hormones

Practice Guidelines

*How can your patient use these treatments safely, effectively, and conveniently?*
**Treatment of Sleep/ Irritability Sxs**

- If mild symptoms
  - Lifestyle change, CAM therapy
- If severe symptoms or no response to above
  - Low dose HT, then titrate upward
  - If mood swings, transdermal E preferred
- Depression component, or no response to HT
  - SNRI or SSRI

**HT and Vaginal Atrophy**

- When HT is considered solely for this indication, local (not systemic) vaginal ET is recommended
- Progestogen generally *not indicated* with low-dose, local vaginal ET
- Vaginal lubricants often improve vaginal dryness and painful intercourse

**Vaginal Estrogen Therapies**

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand</th>
<th>Dosage</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated estrogen cream</td>
<td>Premarin cream</td>
<td>0.625 mg/ gram</td>
<td>Daily, then 1-3 time/wk</td>
</tr>
<tr>
<td>Estradiol cream</td>
<td>Estrace</td>
<td>0.01% (0.1 mg/ gm)</td>
<td>Daily, then 1-3 time/wk</td>
</tr>
<tr>
<td>Estradiol vaginal tablet</td>
<td>Vagifem</td>
<td>25 micrograms</td>
<td>Daily for 2 wks, BIW</td>
</tr>
<tr>
<td>Estradiol ring</td>
<td>Estring</td>
<td>7.5 mcg/ 24 hrs</td>
<td>Every 90 days</td>
</tr>
<tr>
<td>Estradiol ring*</td>
<td>Femring</td>
<td>0.05 mg/d 0.1 mg/d</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>

*Intended for use as systemic HT

**HT & Urinary Health**

- Local ET may benefit some women with urge incontinence who have vaginal atrophy
- Unclear if ET by any route is effective for overactive bladder
- Controversial if local ET can improve stress incontinence (systemic ET may worsen or provoke it)
- Local vaginal ET may reduce risk of recurrent UTI
- No HT product approved for urinary health in US/Canada

**HT & Sexual Function**
- Treatment of moderate to severe vaginal atrophy with systemic ET/EPT or local ET can relieve dyspareunia
- One oral systemic ET product FDA is approved for dyspareunia
- HT is not recommended as sole treatment of other sexual function problems (e.g., diminished libido)


**HT & Cognitive Aging/Decline, Dementia**
- HT not recommended at any age for the sole or primary indication of preventing cognitive aging or dementia
- HT seems to increase dementia incidence when initiated at ≥ 65 years old
- Inadequate data if HT started soon after menopause increases or decreases later dementia risk
- Limited data do not support HT for Alzheimer’s disease


**HT and Fracture Prevention**

**Pros**
- Good data on fracture prevention (mainly 2° prevention)
- Relatively lower cost than bisphosphonates
- Less concern of adverse effects with ET alone (vs EPT)

**Cons**
- Requires long term use and surveillance, but
- Increased risk of breast cancer after 3-5 years of use
- Post-menopausal bleeding can be troublesome

**Utility**
- Fracture prophylaxis *if using HT for another indication*
- Otherwise, consider bisphosphonates as first line

**HT and “Quality of Life”**
- RCTs and retrospective studies show that HT has no effect on “quality of life” measures
- Many woman who wean from HT state that they “feel worse”...even after 20 years after menopause!
- **Conventional wisdom**
  - In women who “feel better on/ worse off” of HT, continue low dose HT if few or no risk factors
  - When (& how often) to re-attempt wean uncertain
  - Don’t start HT for solely for improving QOL
After 2 years of use, recommend drug vacation to determine whether HT is still needed
- Vasomotor symptom recurrence similar whether tapered or abrupt discontinuance
  - 25-50% chance of symptoms recurring when HT discontinued
- Decision to resume HT must be individualized


HT Discontinuance

- Extending HT use is acceptable
  - For women well aware of risks and benefits
  - With lowest effective dose
  - For prevention of further osteoporosis-related fracture when alternate therapies not appropriate
  - With clinical supervision