Hormone Therapy: No Sweat for Menopausal Symptoms

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University of Colorado School of Medicine

Disclosures

- Stock Options: Menogenix, Inc
- Clinical Advisory Board: Astellas Pharma, Inc

Learning Objectives:

At the end of this lecture the learner is expected to:

- Enumerate the symptoms that are most likely to be relieved by hormone therapy
- Engage in shared decision making with patients regarding personal preferences and route of administration
- Manage patient expectations of therapy
- Initiate appropriate treatment

Precision Medicine: NIH Definition

"an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"
Isn't This What We've Been Doing All Along?

Balancing Benefits and Risks

The WHI was not designed to address the benefits of hormones for symptomatic women. We need to apply the appropriate tools for the outcomes of interest.

We Need to Apply the Appropriate Tools for the Outcomes of Interest

FDA Approved HT

**Estrogens**
- Transdermal estradiol*
- Oral estradiol*
- Oral conjugated equine estrogens
- Oral estrone
- Vaginal estradiol*
- Estradiol sprays and gels*

**Progestins**
- Oral micronized progesterone*
- Vaginal progesterone*
- Oral medroxyprogesterone acetate
- Oralnorethindrone
- Intrauterine levonorgestrel

*refers to compounds that are ‘bioidentical’
FDA Approved HT

<table>
<thead>
<tr>
<th>SERMS</th>
<th>Other</th>
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<tbody>
<tr>
<td>Ospemifene</td>
<td></td>
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<tr>
<td>Raloxifene</td>
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<tr>
<td>CEE/bazedoxifene</td>
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The Seven Dwarves of Menopause: Which Are Caused by Menopause? Which Can Be Relieved by Hormones?

- Sweaty
- Sleepless
- Bone-dry
- Grumpy
- Anxious
- Dopey
- Sexless

Benefits of Hormone Therapy

- **Unequivocal**
  - Hot flashes and night sweats
  - Vaginal dryness
  - Poor sleep
  - Adverse mood

- **Conflicting/Inadequate Data**
  - Sexual function
  - Urinary incontinence
  - Joint pain
  - ‘Brain fog’
  - Changes in body composition
  - Skin dryness/wrinkling

The Road to Menopause

- Median Age 47
- Median Age 49
Hot Flashes/Night Sweats

- Affect up to 85% of all women transitioning into menopause
- Worse/prolonged symptoms
- If menopause is surgical
- If transition is early/premature
- Interaction with sleep: night sweats

Natural History of Hot Flashes

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>% affected*</th>
<th>Author</th>
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<tbody>
<tr>
<td>Premenopause</td>
<td>20-45%</td>
<td>Gold, 2006</td>
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<tr>
<td>Pre- to-Early Perimenopause</td>
<td>25-55%</td>
<td>Gold, 2006</td>
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<tr>
<td>Early- to-Late Perimenopause</td>
<td>50-80%</td>
<td>Gold/Politi, 2008</td>
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<tr>
<td>Late Peri-to-Postmenopause</td>
<td>35-75%</td>
<td>Gold/Politi</td>
</tr>
<tr>
<td>Late Postmenopause (&gt;5yr)</td>
<td>16-44%</td>
<td>Barnabei, Politi</td>
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References:
Hot Flashes (and Vaginal Symptoms) in Hispanic Women By Country of Origin

<table>
<thead>
<tr>
<th>Symptom</th>
<th>PR (56)</th>
<th>Cuban (44)</th>
<th>DR (42)</th>
<th>CA (29)</th>
<th>SA (106)</th>
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<tr>
<td>Vaginal dryness</td>
<td>17.9</td>
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<td>58.6</td>
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<td>Hot flashes</td>
<td>35.7</td>
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<td>24.7</td>
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<td>uncomfortable</td>
<td>89.5</td>
<td>77.8</td>
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<td>100</td>
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<tr>
<td>Trouble sleeping</td>
<td>66.1</td>
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<td>64.3</td>
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<td>85.3</td>
<td>50.7</td>
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All Hot Flash Outcomes Improve with HT

- Hot flash diaries: frequency and severity
- Objectively recorded hot flashes
- Night sweats
- Wakening after sleep onset (WASO)
- Hot Flash Interference

Vaginal Dryness/GSM

- Reported by 25-57% of menopausal women
- Likely under-treated
- Moisturizers and lubricants: little to no medical evidence
- FDA approved therapies:
  - Estradiol (cream, pill, ring)
  - Estradiol softgel (pending FDA approval)
  - Ospemifene: ER beta agonist
  - DHEA

(Hot Flashes and) Vaginal Symptoms in Hispanic Women By Country of Origin

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Scary FDA Labeling Persists for Vaginal Estrogen Products

**WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA**

- Increased risk of:
  - Endometrial cancer (in a woman with a uterus who uses unopposed estrogens)
  - Stroke, deep vein thrombosis (DVT), pulmonary embolism, myocardial infarction...invasive breast cancer...and increased risk of probable dementia in postmenopausal women 65 years of age and older

Ospemifene and DHEA

- ER beta agonist SERM
- FDA approved for vaginal dryness/dyspareunia
- No endometrial stimulation
- May be effective against breast proliferation
- May be effective as bone antiresorptive
- 6.5 mg nightly vaginal insert
- Indication: dyspareunia
- Minimal increase in serum E2 after 7 days (<2 pg/ml higher than PBO)
- Significant primary endpoint in 2 pivotal trials (most bothersome symptom related to dyspareunia) (H-140)
- No apparent endometrial stimulation

Mood, Sleep, Cognition

- May improve with HT
- Specific treatments are appropriate for
  - Adverse mood (15-20%)
  - Moderate to severe depression: antidepressants
  - Persistent poor sleep (30-60%): hypnotics, CBT
  - Cognitive issues: may respond to low dose CNS stimulants

And the Punch Line...

Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications.
Absolute Risks and Benefits of MHT
WHI Cases /10,000 Women-Years

<table>
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<tr>
<th>EVENT</th>
<th>E+P</th>
<th>E-Alone</th>
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<tbody>
<tr>
<td>CHD</td>
<td>+6</td>
<td>-3</td>
</tr>
<tr>
<td>Stroke</td>
<td>+7</td>
<td>+12</td>
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<tr>
<td>VTE</td>
<td>+18</td>
<td>+8</td>
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<tr>
<td>Breast Ca</td>
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<td>-6</td>
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<tr>
<td>Hip Fracture</td>
<td>-5</td>
<td>-6</td>
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<tr>
<td>Colon Ca</td>
<td>-6</td>
<td>+1</td>
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<tr>
<td>Ovarian Ca</td>
<td>+1.5</td>
<td>--</td>
</tr>
<tr>
<td>Lung Ca</td>
<td>+2.5</td>
<td>+2.0</td>
</tr>
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</table>

Statistically significant

WHI Publications, various.

But Doctor, What About My...
- ‘Brain fog’; some evidence for adult ADD meds (atomoxetine)
- Sex drive: clinical trials currently favor CBT over CNS active agents
- Joint aches and pains: association clearest with use of Ais
- Migraines: improve after menopause, may respond to E2
- Dry eyes: worse with hormones!
- Dry skin: common complaint, causation not established
- Wrinkles: mixed data for improvement with HT
- Contours: mixed data for HT; the real culprit may be high FSH

Oral vs. Transdermal Estrogen and Thromboembolic Complications
(OR and 95% CI)

<table>
<thead>
<tr>
<th>Study Publication</th>
<th>Oral Estrogen</th>
<th>Transdermal Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarabin, et al</td>
<td>3.5 (1.8-6.8)</td>
<td>0.9 (0.5-1.6)</td>
</tr>
<tr>
<td>Canonico, et al</td>
<td>4.2 (1.5-11.6)</td>
<td>0.9 (0.4-2.1)</td>
</tr>
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Can We Be More Precise?
African-American women (N=1616):
- less risk for breast cancer on E Alone HT, dependent on degree of African ancestry: HR 0.32 [0.12-0.86]
- Global index favors hormones in 50-59 age group: HR 0.65 [0.43, 0.98]
- Null effect of hormone use on CHD, VTE

Chlebowski R, Menopause 2017; 24:133-141
Clinical Guidelines

The Endocrine Society (Stuenkel, 2015) and the North American Menopause Society (2012) recommendations favor:

- Use of ‘natural’ E and P
- Use of non-oral E
- Consideration for extended use in women without a uterus (E alone) who remain symptomatic
- Periodic re-evaluation of risks, benefits and alternatives

The Bottom Line

- HT is still the most effective first line treatment available for the common symptoms of menopause
- HT has the potential to address multiple symptoms at the same time at low risk for women when given over the short term
- If a symptom is atypical with an unknown likelihood of response: give HT a try for 3 months; if no benefit is observed, discontinue therapy