Menopause Management: Hormone Therapy

LEIGH MORRISON, MD
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FALL UPDATE IN FAMILY MEDICINE
Disclosures

- None
Objectives

- Review the risks and benefits of systemic hormone therapy for vasomotor symptoms
- Review the recommendations regarding dosing, duration, and discontinuation of hormone therapy
- Review the evidence for treatment of vasomotor symptoms in menopause
Goals

- Encourage informed discussion of risks and benefits of hormone therapy in the office
- Help providers identify appropriate candidates for hormone therapy
- Provide a reference for risk-benefit discussion and prescribing hormone therapy as supported by ACOG and NAMS guidelines
Abbreviations

- HT = hormone therapy
- ET = estrogen therapy
- EPT = combined estrogen-progestin therapy
- MPA = Medroxyprogesterone acetate
- WHI = Women’s Health Initiative
- NAMS = North American Menopause Society
- ACOG = American College of Obstetrics and Gynecologists
## Vasomotor Symptoms

- **Hot flash**
  - Sudden sensation of extreme heat in the upper body
  - Lasting 1-5 minutes
  - Mean overall duration of symptoms is **7.4 years**

- Perspiration
- Flushing
- Chills
- Clamminess
- Anxiety
- Heart Palpitations
- Sleep disruption
Treating Vasomotor Symptoms

- **Gold standard:**
  - Hormone therapy

- **2004: Cochrane Systematic Review**
  - ET or EPT reduced weekly symptom frequency by 75% compared to placebo
  - Also reduction in symptom severity (OR 0.13)

*Why aren’t we prescribing more hormone therapy?*
Women’s Health Initiative (WHI)

- 1991 – National Institutes of Health
- Multicenter, double-blind, placebo-controlled trial
- Women age 50-79 at enrollment
- Assess the impact of HT on the development of cardiovascular disease in postmenopausal women
WHI – 2002

- CEE + MPA vs. Placebo
  - n = ~17,000
  - Mean follow up 5.2 years
- Women with a uterus
- CEE-alone vs. Placebo
  - n = ~11,000
  - Mean follow up 6.8 years
- Women without a uterus
## Estrogen + Progesterone (All Ages)

<table>
<thead>
<tr>
<th>Absolute Risk</th>
<th>Absolute Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease = 6</td>
<td>Colorectal cancer = 7</td>
</tr>
<tr>
<td>Breast cancer = 9</td>
<td>Total fractures = 47</td>
</tr>
<tr>
<td>Stroke = 7</td>
<td>New onset diabetes = 16</td>
</tr>
<tr>
<td>VTE = 18</td>
<td></td>
</tr>
</tbody>
</table>

Absolute risks and benefits per 10,000 women/year
Absolute Risk by Age: EPT

- **CHD**: 5, 1
- **Breast Cancer**: 5, 8, 23
- **Stroke**: 4, 9, 13
- **VTE**: 11, 16, 13

Number of Events vs Placebo (per 10,000 women/year)

- **50–59 yrs**: CHD 5, Breast Cancer 5, Stroke 4, VTE 11
- **60–69 yrs**: CHD 1, Breast Cancer 8, Stroke 9, VTE 16
- **70–79 yrs**: CHD 23, Breast Cancer 13, Stroke 13, VTE 25
Estrogen Alone (All Ages)

Absolute Risk

- Stroke = 12
- VTE = 7
- PE = 3

Absolute Benefit

- Breast cancer = 7
- Coronary heart disease = 5
- Total fractures = 56
- New onset diabetes = 21

Absolute risks and benefits per 10,000 women/year
Absolute Risk by Age: ET

Number of Events vs Placebo (per 10,000 women/year)

- 50–59 yrs
- 60–69 yrs
- 70–79 yrs

Age Group

- CHD
- Breast Cancer
- Stroke
- VTE
Cardiovascular Risk & All-Cause Mortality

- HT initiated in women younger than 60 years or within 10 years of menopause onset
  - Lowered CVD in postmenopausal women (RR 0.52)
  - Reduced all cause mortality (RR 0.70)
  - No increased risk of stroke
  - Increased risk of VTE (RR 1.74)

A Eisinga, et al. 2015
Breast Cancer

- **EPT:**
  - Increase in breast cancer risk
  - Hazard ratio: 1.24, 95% CI, 1.01-1.53
  - 9 additional cases per 10,000 person-years

  - Observational studies suggest that micronized progesterone may have less impact on breast cancer risk

JE Manson, et al. JAMA 2013
Breast Cancer

- **Comparisons:**
  - Slightly greater risk than observed with one daily glass of wine
  - Less risk than two daily glasses of wine
  - Similar risk reported with obesity, low physical activity, and other medications

- Breast cancer is common with or without HT
- Only 1 in 5 breast cancers occurring in women using EPT can be attributed to HT

WY Chen, et al. 2011
Limitations of WHI

- Only one route of administration for HT
- Only one formulation of estrogen studied
- Only one progesterone studied

- Limited enrollment of women with bothersome vasomotor symptoms <60 years or who were fewer than 10 years from menopause onset
Indications for HT

- Moderate-to-severe vasomotor symptoms
  - Women <60 years old or within 10 years of menopause onset
  - Without contraindications

- Prevention of osteoporosis among women at high risk of osteoporotic fracture who are unable to tolerate standard preventive therapy
Contraindications for HT

- **Absolute:**
  - Unexplained vaginal bleeding
  - Liver disease
  - History of DVT/PE
  - Known clotting disorder or thrombophilia
  - Untreated hypertension
  - History of breast, endometrial, or other estrogen-dependent neoplasia
  - Hypersensitivity to hormone therapy
  - History of coronary vascular disease, stroke, or TIA

- **Relative:**
  - Triglycerides >400
  - Gallbladder disease
  - Elevated risk of breast cancer
Does the patient have moderate-to-severe hot flashes and/or night sweats, defined as bothersome symptoms that interfere with daily activities, impair quality of life, and/or interrupt sleep?

Yes  No

Is the patient interested in considering menopausal hormone therapy (HT) AND free of traditional contraindications to HT?

See Contraindications and Cautions

Yes  No

Patient's CVD Risk Score is 1.9% (low risk) over 10 years.

Patient appears to be a candidate for either oral or transdermal estrogen therapy. Women with hysterectomy are candidates for estrogen-alone therapy.

Estrogen Therapy options and dosages

Duration of treatment

Recommendation if patient has metabolic syndrome

Handout on risks/benefits of HT

Email summary and handout to patient and/or yourself
### Table 1. Estrogen Medications for the Treatment of Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Medication</th>
<th>Available dosages (mg)</th>
<th>Bioidentical?</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enjuvia (conjugated estrogen)</td>
<td>0.3, 0.45, 0.625, 0.9, 1.25 (per day)</td>
<td>No</td>
<td>$87</td>
</tr>
<tr>
<td>Estrace (estradiol)</td>
<td>0.5, 1.0, 2.0 (per day)</td>
<td>Yes</td>
<td>$131</td>
</tr>
<tr>
<td>Menest (esterified estrogen)</td>
<td>0.3, 0.625, 1.25, 2.5 (per day)</td>
<td>No</td>
<td>$48</td>
</tr>
<tr>
<td>Premarin (conjugated estrogen)</td>
<td>0.3, 0.45, 0.625, 0.9, 1.25 (per day)</td>
<td>No</td>
<td>$143</td>
</tr>
<tr>
<td><strong>Transdermal patch (estradiol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alora</td>
<td>0.025, 0.05, 0.075, 0.1 (twice per week)</td>
<td>Yes</td>
<td>$90</td>
</tr>
<tr>
<td>Climara</td>
<td>0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 (once per week)</td>
<td>Yes</td>
<td>$50</td>
</tr>
<tr>
<td>Minivelie</td>
<td>0.025, 0.0375, 0.05, 0.075, 0.1 (twice per week)</td>
<td>Yes</td>
<td>$137</td>
</tr>
<tr>
<td>Vivelle Dot</td>
<td>0.025, 0.0375, 0.05, 0.075, 0.1 (twice per week)</td>
<td>Yes</td>
<td>$84</td>
</tr>
<tr>
<td><strong>Transdermal gel (estradiol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divigel</td>
<td>0.25, 0.5, 1.0 (per day)</td>
<td>Yes</td>
<td>$118</td>
</tr>
<tr>
<td>Elestrin</td>
<td>0.52 (per day; adjust dosage based on response)</td>
<td>Yes</td>
<td>$109</td>
</tr>
<tr>
<td>Estrogel</td>
<td>0.75 (per day)</td>
<td>Yes</td>
<td>$126</td>
</tr>
<tr>
<td><strong>Transdermal spray (estradiol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evamist</td>
<td>1.53 per spray (start with 1 spray per day, adjust up to 3 sprays per day based on response)</td>
<td>Yes</td>
<td>$118</td>
</tr>
<tr>
<td><strong>Vaginal (estradiol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femring</td>
<td>0.05, 0.10 (for 90 days)</td>
<td>Yes</td>
<td>$355</td>
</tr>
</tbody>
</table>

# Route & Dosing - EPT

Table 2. Combination Estrogen/Progestogen Medications for the Treatment of Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Medication</th>
<th>Available dosages (mg of estrogen/progestogen unless otherwise indicated)</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activella (estradiol/norethindrone acetate)</td>
<td>0.5/0.1, 1.0/0.5 (per day)</td>
<td>$215</td>
</tr>
<tr>
<td>Angeliq (estradiol/drospirenone)</td>
<td>0.5/0.25, 1.0/0.5 (per day)</td>
<td>$133</td>
</tr>
<tr>
<td>Duavee (conjugated equine estrogen/bazedoxifene)</td>
<td>0.45/20.0 (per day)</td>
<td>$153</td>
</tr>
<tr>
<td><strong>Femhrt (estradiol/norethindrone acetate)</strong></td>
<td>2.5 mcg/0.5 mg (per day)</td>
<td>$150</td>
</tr>
<tr>
<td>Prefest (estradiol/norgestimate)</td>
<td>1.0/0.09 (per day; estrogen alone for 3 days followed by estrogen/progestogen for three days, then repeat)</td>
<td>$120</td>
</tr>
<tr>
<td>Premphase (conjugated estrogen/medroxyprogesterone)</td>
<td>0.625/5.0 (per day; estrogen alone for days 1 to 14 then add progestogen for days 15 to 28)</td>
<td>$161</td>
</tr>
<tr>
<td>Prempro (conjugated estrogen/medroxyprogesterone)</td>
<td>0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5.0 (per day)</td>
<td>$161</td>
</tr>
<tr>
<td><strong>Transdermal patch</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climara Pro (estradiol/levonorgestrel)</td>
<td>0.45/0.015 (once per week)</td>
<td>$149</td>
</tr>
<tr>
<td>CombiPatch (estradiol/norethindrone acetate)</td>
<td>0.05/0.14, 0.05/0.25 (twice per week)</td>
<td>$158</td>
</tr>
</tbody>
</table>

*NOTE: None of these therapies are bioidentical.

Oral vs. Transdermal ET

- No RCT data comparing risks and benefits
- Case-control and cohort studies suggest no increased risk of VTE or stroke from transdermal ET
- Biologically plausible as transdermal ET avoids the first pass hepatic effect
ACOG 2014:

“Given the variable response to HT and the associated risks, it is recommended that health care providers individualize care and treat women with the lowest effective dose for the shortest duration that is needed to relieve vasomotor symptoms”

NAMS 2017:

“A more fitting concept is ‘appropriate dose, duration, regimen, and route of administration’”

“Individualization with shared decision making remains key, with periodic reevaluation to determine an individual women’s benefit-risk profile”
<table>
<thead>
<tr>
<th><strong>Discontinuation</strong></th>
</tr>
</thead>
</table>

- **ACOG 2014:**
  - “...recommends against routine discontinuation of systemic estrogen at age 65 years.”

- **NAMS 2017:**
  - “The recommendation to use the Beers criteria to routinely discontinue hormone therapy after age 65 is **not supported by data.**”
Treating Vasomotor Symptoms

- **Gold Standard:**
  - Hormone therapy

- **Less effective:**
  - SSRIIs
  - SSNRIIs
  - Clonidine
  - Gabapentin
SSRIs & SSNRI s

- Effective treatment of hot flashes
  - Healthy, non-depressed women

- Desvenlafaxine 100 mg daily
  - 2013 RCT, n=365
  - 62% of participants had reduction of 5.35 moderate-to-severe hot flashes per day
  - Compared to 41% of participants with placebo

JV Pinkerton, et al. Menopause 2013
SSRIs & SSNRIss

- Reported adverse effects
  - Nausea
  - Dizziness
  - Dry mouth
  - Nervousness
  - Constipation
  - Somnolence
  - Sweating
  - Sexual dysfunction

- Adverse affects typically resolved with time and dose adjustment
Clonidine

- Clonidine 0.1 mg daily
  - Systematic review and meta-analysis, 2006
  - Small benefit compared to placebo

- Adverse effects
  - Dry mouth
  - Insomnia
  - Drowsiness
  - Blood pressure was not adversely affected
Gabapentin

- Gabapentin 900 mg daily
  - 2003 RCT, n=59
  - 45% reduction in hot flash frequency (29% with placebo)
  - 54% reduction in composite score (31% with placebo)
  - Greater reduction with higher, open-label dosing

- Gabapentin 600 mg daily vs. low-dose transdermal estradiol (25 mcg)
  - 2010 RCT, n=45
  - Symptom relief more effective in the estrogen group

Gabapentin

- **Adverse effects**
  - Dizziness
  - Somnolence
  - Peripheral edema

- **Venlafaxine 75 mg daily vs. gabapentin 300 mg TID**
  - 2010 Cross-over RCT, n=56, breast cancer survivors
  - 68% preferred venlafaxine
  - 32% preferred gabapentin
  - Both agents reduced hot flash scores by 66%
Conclusions

- Healthy symptomatic women younger than 60 years or who are within 10 years of menopause onset:
  - More favorable effects of HT on CHD and all-cause mortality
  - Potential rare increase in risks of breast cancer, VTE, stroke

- Consider transdermal route for estrogen as studies suggest no increased risk of VTE or stroke

- Individualization of hormone therapy with shared decision making remains key
References

Hormone Therapy

- JAMA, December 12, 2017

Clinical Considerations

Patient Population Under Consideration
This recommendation statement applies to asymptomatic, postmenopausal women who are considering hormone therapy for the primary prevention of chronic medical conditions (Figure 2). It does not apply to women who are considering hormone therapy for the management of menopausal symptoms, such as hot flashes or vaginal dryness. It also does not apply to women who have had premature menopause (primary ovarian insufficiency) or surgical menopause.