New Guidelines for Menopause Management

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I have no commercial disclosures for this lecture
Key Points:
Position Statement
on Hormone Therapy

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Available at: menopause.org

### NAMS Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full name</th>
</tr>
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<tbody>
<tr>
<td>ET</td>
<td>Estrogen (E) therapy</td>
</tr>
<tr>
<td>EPT</td>
<td>Combined E+P therapy</td>
</tr>
<tr>
<td>HT</td>
<td>Hormone therapy (ET, EPT)</td>
</tr>
<tr>
<td>MHT</td>
<td>Menopausal hormone therapy</td>
</tr>
<tr>
<td>Progestogen</td>
<td>Progesterone or progestin (P)</td>
</tr>
<tr>
<td>CC-EPT</td>
<td>Continuous-combined E+P therapy</td>
</tr>
<tr>
<td>CS-EPT</td>
<td>Continuous-sequential E+P therapy</td>
</tr>
</tbody>
</table>

Act 1

*Let’s Get This Out of the Way….*

The WHI Re-analyzed

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**Background: Late 1980s**

- In 40 retrospective observational studies, both EPT and ET reduced the risk of heart attack by 50%
  - Most studies included women in their 50s
  - Women were self-selected for hormone use (or not); studies were subject to selection bias
- **Conventional wisdom**
  - All women should use HT for heart protection, unless there was a reason not to do so
  - Women with CVD risk factors, *especially* previous MI, stroke, HTN or diabetes, should use HT
Background: 1990s

- 1990: Wyeth requested that FDA add labeling to HT products that included cardioprotection
- FDA insisted that RCTs be performed to prove that HT improved *CVD outcomes* vs. placebo
- Two RCTs initiated to evaluate cardioprotection
  - HERS: secondary prevention trial
  - WHI: primary prevention trial
- Average age in both studies was 64 years old...necessary to measure differences in MI rates
- Women with menopausal symptoms *excluded*

Women’s Health Initiative (WHI)

- 1993-2005: RCT with 17,000 women
- Postmenopausal women 50-79 years old
  - 33%: 50-59 yrs old; 45%: 60-69 yo; 22% 70-79 yo
  - *Average age: 64 years old*
- End points
  - Primary prevention of MI and stroke
  - Hip fracture, various cancers
- Treatment arms
  - If uterus: CC-EPT (CEE+MPA) vs. placebo
  - If no uterus: ET (CEE) vs. placebo
### WHI: EPT Arm Study Results
Released July 2002: Findings after 5.2 years

<table>
<thead>
<tr>
<th>Event</th>
<th>RR</th>
<th>Attributable Risk/10K/yr</th>
<th>Attributable Benefit/10K/yr</th>
<th>Number needed to harm or benefit/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attack</td>
<td>1.29</td>
<td>7</td>
<td></td>
<td>1,100</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41</td>
<td>8</td>
<td></td>
<td>1,200</td>
</tr>
<tr>
<td>Breast CA</td>
<td>1.26</td>
<td>8</td>
<td></td>
<td>1,300</td>
</tr>
<tr>
<td>TE event</td>
<td>2.11</td>
<td>18</td>
<td></td>
<td>600</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63</td>
<td>6</td>
<td></td>
<td>1,700</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.66</td>
<td>5</td>
<td></td>
<td>2,000</td>
</tr>
</tbody>
</table>

Discontinued early, as “risks greater than benefits”

### WHI: ET-Only Study Arm
Released 2004: Findings after 7 years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>No difference in risk</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>No difference in risk</td>
</tr>
<tr>
<td>Stroke</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Dementia, cognitive change (&gt; 65 years old)</td>
<td>Trend toward increased</td>
</tr>
</tbody>
</table>
The Women’s Health Initiative
– *Was* a drug study of the effect of hormones on CVD, cancer, fractures, and memory in older women (mainly in 60s, long post-menopausal)
– *Was not* a menopause study...
  • Only 3.5% subjects were “early menopause”
  • Excluded symptomatic menopausal women

Should the WHI be used to evaluate the safety and efficacy of EPT in treating women with menopausal symptoms?

**WHI: HT and Risk of CV Disease by Age and Years Since Menopause**

Roussow JE. *JAMA*. 2007: Combined secondary analysis

<table>
<thead>
<tr>
<th>Age at HT initiation</th>
<th>Heart attack</th>
<th>Stroke</th>
<th>Death from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59 years</td>
<td>↓ 7%</td>
<td>↑ 13%</td>
<td>↓ 30%</td>
</tr>
<tr>
<td>60–69 years</td>
<td>↓ 2%</td>
<td>↑ 50%</td>
<td>↑ 5%</td>
</tr>
<tr>
<td>70–79 years</td>
<td>↑ 26%</td>
<td>↑ 21%</td>
<td>↑ 14%</td>
</tr>
</tbody>
</table>

*Women who initiated HT closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion* for statistical significance.”

*Statistically significant defined as p<0.01.*
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

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 & Venous Thromboembolism

- Oral HT increases VTE risk in menopausal women
- VTE risk emerges soon after HT initiation (1-2 y) and decreases over time
- Lower VTE risk with EPT or ET in women <60 y.o.
- Lower HT doses may be safer than higher doses, but no RCT evidence
- Possible lower VTE risk with transdermal than with oral ET, but no RCT evidence
- Risks fall into the “rare” category


HT & Breast Cancer

- EPT use >4-5 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
  - Other studies showed that ET for < 5 yrs has little or no impact on breast cancer risk

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions
USPSTF 2012

• The USPSTF recommends against the use of
  – EPT for prevention of *chronic conditions* in postmenopausal women
    • Grade: D Recommendation
  – ET for the prevention of *chronic conditions* in postmenopausal women who have had a hysterectomy
    • Grade: D Recommendation

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

Therapeutic Interventions

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

Not better than pbo
Not better than pbo
Not better than pbo
Not better (as monotx)
Not better than pbo
Not better than pbo
No studies
**Botanicals: Black Cohosh**

- 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, large, randomized, prospective, 2-year trial
  - Preliminary data fail to show binding to E receptors
  - Binding to serotonin receptor noted

**Botanicals and PhytoSERMs**

- Positive effect of black cohosh vs placebo
  - Improvement is less than with estrogen
- 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>% treated patients with &gt;50% ↓HF</th>
<th>% placebo patients with &gt;50% ↓HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>54-70%</td>
<td>30%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>50-76%</td>
<td>35-57%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>40-56%</td>
<td>21-41%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>46-84%</td>
<td>27-47%</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>55%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*J Clinical Oncology 2009 (June)*

### 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>
### 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>• Micronized estradiol</td>
<td>• Patches</td>
</tr>
<tr>
<td></td>
<td>• Conjugated equine estrogens (CEE)</td>
<td>• Gels</td>
</tr>
<tr>
<td></td>
<td>• Synthetic conjugated estrogens</td>
<td>• Emulsion</td>
</tr>
<tr>
<td></td>
<td>• Esterified estrogens</td>
<td>• Spray</td>
</tr>
<tr>
<td></td>
<td>• Estropipate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Estradiol acetate</td>
<td></td>
</tr>
<tr>
<td>EPT</td>
<td>• CC-EPT</td>
<td>• E+P combination patches</td>
</tr>
<tr>
<td></td>
<td>• CS-EPT</td>
<td></td>
</tr>
</tbody>
</table>

### Hormone Therapy Regimens

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

OCs in Perimenopause

• Low-dose OCs (\(< 30\) mcg estrogen) are commonly prescribed for perimenopausal women because they relieve menopausal symptoms *and* prevent pregnancy
  • Other benefits: cycle control, fewer ovarian cancers
• Other CHC (patch, ring) also may be helpful
• Progestin IUD and Depo Provera will not address vasomotor symptoms

Hormone Therapy Dosages

• Therapeutic goal is lowest effective estrogen dose (plus corresponding 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


Hormone Therapy Starting Dosages

• Lower daily doses typically used with systemic ET
  • 0.3 mg oral CE
  • 0.5 mg oral micronized 17β-estradiol
  • 0.014-0.025 mg transdermal 17β-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 vs. 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

“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

Off-Label EPT Uses

- Insufficient endometrial safety evidence to recommend off-label use of
  - Long-cycle progestogen (ie, P every 3-6 months for 12-14 days)
  - Vaginal administration of progesterone
  - Levonorgestrel intrauterine system (Mirena)
  - Low-dose estrogen without progestogen
- Close endometrial surveillance recommended with these approaches

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

Sources of Exogenous Hormones
Compounded Hormone Therapy

Compounded hormones will work about as well as commercial HT products, but...

- Value of adding E₁ + E₃ 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

Act 3

Practice Guidelines

*How can your patient use these treatments safely, effectively, and conveniently?*
Individualization of Therapy

- An individual risk profile is essential
- Each woman must be informed of her known risks
- Acceptance of HT risks varies with primary indication (e.g., relieve existing symptom or prevent disease)
- Benefit-risk ratio more acceptable for short-term symptom relief in a younger population
- Long-term HT or use in older women less acceptable
- Women with premature menopause have increased symptoms and risks if not treated


Explaining HT Risk

HT risk is related to

- A woman’s baseline disease risks
- Her age
- Age at menopause
- Cause of menopause
- Time since menopause
- Prior use of any hormone
- HT types, route of administration, doses used
- Emerging medical conditions during treatment

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

Treatment of Sleep/ Irritability Symptoms

- 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


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**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</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 or 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


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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
The Finale

HT Discontinuance and Symptom Recurrence

- 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

Fertility and Sterility Aug 2012; 98 (2):313-14

Endorsed by 15 medical associations

A decade after the Women's Health Initiative—the experts do agree


• Systemic HT is an acceptable option for healthy women up to age 59 or <10 years of menopause and who are bothered by moderate to severe menopausal symptoms.
• Individualization is key in the decision to use HT
• Consider quality-of-life priorities as well as her personal risk factors such as age, time since menopause, and her risk of blood clots, heart disease, stroke, and breast cancer.