Management of Menopause: Should New Data Change Our Practice?

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Case 1: 43 y/o LMP 6 months ago
- ↑ warmth & insomnia for months
- Progesterone cream x 4 months → no Δ
- PREGNANCY TEST (FSH, TSH)
- “Early Menopause” = natural or induced, occurs before average age (51), ≤ 45
- Menopause symptoms: hot flashes, night sweats, problems sleeping, vaginal dryness
- Reluctant to start “hormones”

Nelson, Evidence Report #120, 2005

Case 2: 51 y/o, 10 yrs after ER+ breast ca treated with lumpectomy, XRT, tamoxifen; LMP 5 mos ago, 12 hot flashes/day x 3 mos

Case 3: 65 y/o, on estrogen for 15 years after hysterectomy, hot flashes when she misses a few days...should she stop?

Menopause Management

Case 1: 43 y/o, amenorrhea for 6 months, ↑ warmth & insomnia, on progesterone cream
Case 2: 51 y/o, 10 yrs after ER+ breast ca treated with lumpectomy, XRT, tamoxifen; LMP 5 mos ago, 12 hot flashes/day x 3 mos
Case 3: 65 y/o, on estrogen for 15 years after hysterectomy, hot flashes when she misses a few days...should she stop?

Consistent Terms
E = Estrogen
P = Progesterone
HT = Hormone Therapy
CEE = Premarin
MPA = Provera
WHI = Women’s Health Initiative
Conjugated Equine Estrogen: Brief 60+ Year History

- 1941: FDA approves DES for menopause symptoms
- 1942: FDA approves CEE for menopause symptoms
- 1960-70s: 2-3 fold increase in CEE rx’s until….
- 1975: Unopposed E and endometrial cancer
- 1980’s: Added progestins “protect” uterus
- 1982-84: Osteoporosis prevention
- 1992: ACP statement: beneficial for CHD risk
- 1998: HERS trial published
- By 2001: 15 Million women using HRT
- 2002: WHI estrogen/progestin results
- 2004: WHI estrogen alone results

Women’s Health Initiative

- 2 NIH-funded concurrent randomized trials in postmenopausal women
  - uterus - CEE+MPA vs. placebo (16,606)
  - no uterus - CE vs. placebo (10,739)
- Multiple outcomes
- Planned follow-up 9 years
- Both trials stopped early (after 5 and 7 years) due to harm or lack of benefit

In 2002, why was the WHI Estrogen + Progestin trial stopped early?
1. ↑ Breast Cancer
2. ↑ Pulmonary Embolus
3. ↑ Coronary Heart Disease
4. ↑ Stroke
5. All of the Above

In 2004, why was the WHI Estrogen Alone trial stopped early?
1. ↑ Breast Cancer
2. ↑ Pulmonary Embolus
3. ↑ Coronary Heart Disease
4. ↑ Stroke
5. All of the Above
WHI Participants

<table>
<thead>
<tr>
<th>E + P (n=16,606)</th>
<th>Estrogen (n=10,739)</th>
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<tbody>
<tr>
<td>Age 63.2</td>
<td>63.6</td>
</tr>
<tr>
<td>BMI 28.5</td>
<td>30.1</td>
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<tr>
<td>% nonwhite 16.1%</td>
<td>24.5%</td>
</tr>
<tr>
<td>% past HT 26.1%</td>
<td>47.8%</td>
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<tr>
<td>% oophorectomy ?</td>
<td>40.7%</td>
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<tr>
<td>Placebo rate/1000 CHD 3.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Stroke 2.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Breast cancer 3.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Hip Fracture 1.5</td>
<td>1.1</td>
</tr>
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</table>

Observational vs. Clinical Trial

<table>
<thead>
<tr>
<th>Relative Risks</th>
<th>Observational</th>
<th>WHI E+P</th>
<th>WHI E only</th>
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</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>0.7*</td>
<td>1.3*</td>
<td>0.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.1*</td>
<td>1.4*</td>
<td>1.4*</td>
</tr>
<tr>
<td>Pulmonary emb</td>
<td>2.1*†</td>
<td>2.1*</td>
<td>1.3</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.3‡</td>
<td>1.3*</td>
<td>0.8</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>0.8*</td>
<td>0.6*</td>
<td>1.0</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>0.7*</td>
<td>0.7*</td>
<td>0.6*</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.7*</td>
<td>2.0*</td>
<td>1.5</td>
</tr>
<tr>
<td>Death</td>
<td>0.8*</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

† Venous thromboembolism ✱ 5 years of use *p-value < .05

What about younger women?

Meta-analysis, Salpeter, JGIM 2004

- 30 RCTs, n = 26,708, age range 36-87
- Mean age < 60, 17 trials, n = 4141
  - Deaths: HT = 53/2576, control = 68/1565
  - Odds Ratio = 0.61 (0.39 - 0.95)
  - NNT = 61 (39 - 481)
- Mean age > 60, 13 trials, n = 22,567
  - Deaths: HT = 465/11571, control = 433/10966
  - Odds Ratio = 1.03 (0.9 – 1.18)
  - NNH = Not Significant

WHI - Individual Risk and Benefit

<table>
<thead>
<tr>
<th>Risk per 1000/year</th>
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<tr>
<td></td>
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<tr>
<td>Harm</td>
</tr>
<tr>
<td>CHD</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Breast cancer</td>
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<tr>
<td>Pulm. embolus</td>
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<tr>
<td>Benefit</td>
</tr>
<tr>
<td>Hip fracture</td>
</tr>
<tr>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Net bad events</td>
</tr>
</tbody>
</table>
**Weighing Risks/Benefits**

- To what extent are symptoms interfering with your life?
- What non-pharmacologic options have you tried?
- If you’ve exhausted all other options and your symptoms are interfering, consider HT
- Estrogens: oral, transdermal, vaginal rings
- Progesterones: oral, transdermal, IUD
  Cyclic (1-2 wks/month or q 3 mos) vs. daily

**Case 1: Individual Account of Risk/Benefit**

- Symptoms are interfering with work and home
  - 3 school aged children
  - Work as a bank manager
- Insomnia, hot sensations and vaginal dryness very uncomfortable
- Progesterone cream tried in effort to avoid estrogen and prescription hormones
- Will HT help her symptoms/quality of life?

**Estrogen, E+P, and affect**

- RCT (PEPI, Greendale 98) showed no difference in anxiety, cognitive, and affective symptoms
- Observational study (SOF, Whooley, JGIM 00):
  - Current E (n = 869), OR of 0.6* for depression, with at least 6 symptoms
  - Current E + P (n = 281), OR of 0.8 (NS)
- Confounders: indication, treatment bias, and placebo effects

**Quality of Life (Hayes NEJM 03)**

- General health, Vitality, Mental health, Depressive symptoms, Sexual satisfaction no different in WHI E + P substudy
- 50-54 y/o women with moderate-to-severe vasomotor symptoms
  - Improved vasomotor symptoms
  - Small benefit in sleep disturbance
- Conclusion: E+P had no clinically meaningful effect on QoL for women without significant symptoms
E + P and Quality of Life: HERS and WHI

- HERS and WHI (E+P) data both showed that QoL changes depend on baseline menopausal symptoms.
- No change in physical function, general health, energy, sexual satisfaction, even with symptoms.
- But, women with vasomotor symptoms reported improved mental health/mood symptoms (HERS) and sleep (WHI).

WISDOM
Welton, BMJ, 2008

- 3712 women, 50 – 69 y/o, with uteri randomized to E + P vs. placebo.
- 30% with hot flashes at baseline.
- After 1 year, 9% in E + P group had hot flashes, 25% in placebo group had them.
- “Small but significant improvements” in 3/9 QoL domains: vasomotor symptoms, sleep, sexual function.

Vaginal Dryness

- Vaginal Moisturizer Replens: safe for q day use.
- May improve vaginal itching, irritation and dyspareunia - equivalent to vaginal estrogen creams.
- Benefit can be seen in first 2 weeks.
- Water-based lubricants (Astroglide, Probe, Silk): PRN.
- Vaginal estrogens: creams, gels.
  - Estrin stays in for 3 months.
  - Vagifem- vaginal tablet inserted 2x per week.

Low Doses of E for Hot Flashes

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Daily Dose</th>
<th>% in HF E†</th>
<th>% in HF Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>†Oral CEE (premarin)</td>
<td>0.625</td>
<td>94</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>0.45</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>†Oral E2 (estradiol)</td>
<td>2.0</td>
<td>96</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>NIS</td>
<td></td>
</tr>
<tr>
<td>†Transdermal E2 (estradiol patch)</td>
<td>0.1</td>
<td>96</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

Scarabin, Lancet 2003
**Progestins to Protect Uterus**
- Routes of administration:
  - Oral: Medroxyprogesterone acetate (MPA), Norethindrone, Micronized Progesterone
  - Transdermal: Norethindrone (combipatch)
  - Vaginal/Endometrial: Prochieve, Mirena
- Alone or combined with estrogen
- Cyclic versus continuous:
  - Cyclic: 10-14 d/month or q 3-4 months
  - Daily: ½ dose every day

**E + P and Mammograms**
- WHI analysis during the 5.6 years of the trial
  - 35% abnl mammos in E+P (23% in placebo)*
  - 10% biopsies in E+P (6% in placebo)*
- After stopping HT, its adverse effect on mammograms modulated, but remained significantly different from placebo for at least 12 months*

* = P<0.001

**Case 1: Conclusion**
- The patient tried OTC vaginal lubricants, which were only a minor help with dryness
- Behavioral techniques didn’t help insomnia and hot flashes
- Transdermal estradiol was begun and symptoms improved within 2 weeks.
- After second month of unopposed E, cyclic micronized progesterone begun (progesterone cream alone not proven to protect uterus)

**Case 2: 51 y/o with severe hot flashes**
- Interfere with work, sleep, ADL
- Stage 1 ER+ breast cancer at 41
- Tamoxifen for 5 years

**Next step…..**
1. Check FSH
2. Estrogen alone
3. Estrogen plus progestin
4. Venlefaxine (Effexxor)
5. SSRI (like paxil, prozac, zoloft)
6. Other
Hot Flashes: Natural History and Risk Factors

Natural History*
- Over 50% of US women report menopausal HF
- Most resolve in 2-5 yrs
- 30-50% improve in months
- 10-15% persist
- Variable, unpredictable

Risk Factors†
- Surgical menopause
- African-American, Latina
- Higher BMI
- Cigarette smoking

†Randolph, J Clin Endocrinol Metab, 2004

Causes of Hot Flashes

- Not simply estrogen deficiency
  - Estrogen levels similar in women with and w/o HF
  - Other women with low, high or variable estrogen levels do not flush
- Central Nervous System thermoregulatory center in hypothalamus in women with HF is “narrow”
  - Differences in CNS neurotransmitters: adrenaline, serotonin, opiates
  - Differences in peripheral blood vessels


Estrogen Relieves Hot Flashes

Conjugated estrogens (0.625 mg) plus a progestin (MPA) reduced hot flushes compared to placebo.

Estrogen Relieves Hot Flashes

Observational studies prone to bias

- One RCT of 442 mostly Scandinavian women stopped early after 2 years
  - Half received ERT or EPRT (depending on uterus)
  - 26 in hormone group recurred vs. 7 in other group
  - HR = 3.5 (1.5 – 8.1)
- One RCT showed no ↑ recurrence after 4.1 yrs
  - Progestins limited and given intermittently
  - HR = 0.82 (0.35 – 1.9)

HT in Breast Cancer Survivors

Greendale (PEPI), Obst Gynecol 1998

Bordeleau, Clin Ther 07
Non-Hormonal Options

Meta Analysis; Nelson et al. JAMA 06

- 43 RCTs; Δ hot flashes = outcome
  - 10 antidepressants, 10 clonidine,
    - 6 other meds, 17 isoflavones
- Evidence for efficacy, but less than estrogen
  - SSRI/SNRI, gabapentin, clonidine
  - 1-2 less hot flashes/day compared to placebo
- Heterogeneity in populations, methodology
- Adverse events and cost may restrict use

Non-HT Rx’s for Hot Flashes

<table>
<thead>
<tr>
<th>% Reduction</th>
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<tbody>
<tr>
<td>SSRIs/SSNRI</td>
</tr>
<tr>
<td>citalopram 30mg*</td>
</tr>
<tr>
<td>fluoxetine 20-30mg*</td>
</tr>
<tr>
<td>paroxetine 12.5-25mgCR/20 mg*</td>
</tr>
<tr>
<td>venlafaxine 37.5-75 mg</td>
</tr>
<tr>
<td>Gabapentin 300 mg TID: 2 + trials</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>
* = inhibits CYP2D6 enzyme (tam metabolism)

Venlafaxine and Hot Flashes

- 221 breast cancer survivors, randomized to:
  - Placebo; 37.5 mg; 75 mg; 150 mg
  - HF ↓ 27%; 37%; 61%; 61% after 4 weeks
  - All 3 venlafaxine doses significantly ↓ HF compared with placebo
- Side effects: dry mouth, ↓ appetite, nausea, constipation
- Benefits occur within 7 days
- Start with 37.5 and double if needed at 1 week

Herbs and Supplements

- Effective
  - Vitamin E 800 IU QD (↓ 1 HF/day)
- Mixed/poor evidence
  - Black cohosh
  - Phytoestrogens

- No benefit
  - Chinese herbs
  - Dong quai
  - Evening primrose
  - Ginseng
  - Red Clover

- No data
  - Chasteberry
  - Licorice
  - Wild yam
Non-Pharmacologic Therapies

- Lifestyle changes
  - keep room cool, wear light clothing\(^1\)
- Diaphragmatic breathing
  - Deep, slow breathing
  - > 50% reduction in hot flash frequency\(^2\)
- Acupuncture - negative trials
- Yoga - several lay books, no trials

\(^1\) Kronenberg, J Therm Biol, 1992
\(^2\) Freedman Am J Obstet Gynecol, 1992

Soy and Menopausal Symptoms

- Soy Phytoestrogens – mixed results for hot flash
- Possible weak estrogenic effects in the breast
  - stimulation of nipple aspirate fluid
  - soy and red clover caused proliferation of estrogen-sensitive breast cancer cells (MCF-7)
- Caution for women with a history of estrogen-sensitive breast cancer


Case 2: Conclusion

- Venlafaxine 37.5 mg once a day is begun and the patient keeps a hot flash diary
- A week later, hot flashes ↓ from 12 to 8 a day
- The patient doubles the venlafaxine to 75 mg/d
- Hot flash diary shows in week 2 ↓ from 8 to 3 a day and no longer interfering with daily life
- Venlafaxine is recommended for at least 6 months
**Case 3: 65 y/o on ERT 15 years**

- TAH/BSO at 50, started CEE 0.625 after
- Hot flashes when she misses CEE dose
- Sister died of breast cancer at 55, recent DXA → osteopenia, no CHD risk factors, father recently died of Alzheimer’s at 88

Should she stop CEE?
1. Yes
2. No
3. Unsure

**WHI Estrogen - Breast Cancer Risk**

HR 0.77 (95% CI 0.59, 1.01)

**Bone Loss Resumes When Estrogen is Stopped**

Christiansen, Osteo Intl, 1996
Women with Mod-Severe Symptoms

<table>
<thead>
<tr>
<th>Years since menopause</th>
<th>RR of CHD on HT</th>
<th>95% CI</th>
<th>P for trend</th>
<th>P for interaction with vasomotor symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0.84</td>
<td>0.40–1.77</td>
<td>&lt;0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>10-19</td>
<td>1.38</td>
<td>0.63–3.0</td>
<td></td>
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<tr>
<td>20+</td>
<td>2.76</td>
<td>1.53–4.97</td>
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</table>

↑ stroke risk at all times since menopause

Rossouw JAMA 07

“Long-Term” WHI Follow-Up

- 3 year follow-up of WHI E + P arm only
- ↑ CV events in trial not observed in follow-up
- ↑ fatal and non-fatal cancer
  HR = 1.24 (1.04 – 1.48) for all malignancies
- Breast cancer risk still ↑, but trending to decreasing risk in follow-up after stopping E+P
  HR = 1.24 (0.91 – 1.78) for breast cancer in F/U

Heiss JAMA 08

Hormones and Dementia: WHI

<table>
<thead>
<tr>
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<th>HRT (N=2229)</th>
<th>Pbo (N=2303)</th>
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<td>1</td>
<td></td>
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<tr>
<td>Alzheimers</td>
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<td>12</td>
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<tr>
<td>other</td>
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<td>8</td>
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<table>
<thead>
<tr>
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<th>Pbo (N=1483)</th>
<th>RH</th>
<th>p-value</th>
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<tbody>
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<td>Dementia</td>
<td>28</td>
<td>19</td>
<td>1.5</td>
<td>.11</td>
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</table>
**Stopping Hormones: Cold Turkey or Taper?**

- 50-75% of women successful with cold turkey
- No evidence to support type, duration of taper
  - 30 vs. 24% in one study*
  - Dose taper - slowly reduce dose
  - Day taper - slowly reduce days/week
  - Can take months (Estrogen is highly protein-bound)
- Hints for either method
  - Motivation is key
  - Close follow-up, frequent check-ins
  - Could substitute behavioral intervention or new drug

*Grady, Obstet Gynecol, 2003

**Conclusions**

- Menopause symptoms can differ significantly from woman to woman…hard to predict who will have most symptoms and how long they will last
- Low dose and short duration HT recommended for symptoms of menopause only
- Women with ER+ breast cancer should avoid HT—consider alternatives if symptoms severe
- Estrogen withdraw is common—the “cold turkey” and taper options are available
- HT not recommended for prevention

**Menopause Management**

- Fan operates automatically!
- Ventilated top and sides!
- Cheaper than estrogen
- No side effects!
- Both fashionable and functional

Thanks for your Attention!