Modern Management of Menopause

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Thanks to Judy Walsh, MD for several slides

Consistent Terms
- E = Estrogen
- P = Progesterone
- HT = Hormone Therapy
- CEE = Premarin
- MPA = Provera
- WHI = Women’s Health Initiative

Outline
- Case 1—Hot flashes, poor sleep, irritability
  - Hot flash etiology, risk factors, and duration
  - Menopausal symptoms and quality of life
- Case 2—Vaginal symptoms and decreased libido
  - Vaginal creams and testosterone
  - “Bioidentical” hormones and other alternatives
- Case 3—Breast cancer survivor
  - Hormones, alternatives, breast health, cancer risk
  - Breast density and abnormal mammograms
- Case 4—Long-term HT use and stopping HT
Case 1: Minnie Pause

- Minnie Pause is a 53 year old woman who had her last menstrual period 18 months ago. She has 4-6 hot flashes/day, poor sleep, and irritability.
- “How much longer will this last?”
- “Which symptoms are from menopause?”
- “Will hormones help my symptoms?”

“Hot Flashes”

Causes*
- Not simply ↓ Estrogen
- Narrow thermoregulatory zone in hypothalamus

Natural History†
- Over 50% of US women report menopausal HF
- Variable, unpredictable

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

“How much longer will this last?”

1. Average duration of hot flashes is about 2 yrs, so they should be gone in about 6 months.
2. Average duration is about 4 years
3. They will never go away

Meta-analysis of 10 studies, over 35K women
- Clear definition of vasomotor symptoms
- Prevalence of symptoms and “bothersome sx”
- The bad news: symptoms↑ 2 yrs before FMP, peaked one year after FMP, and returned to premenopausal levels 8 years after FMP
- 50% had symptoms 4 yrs after FMP and 10% had symptoms up to 12 years after FMP

Politi MC, JGIM 08
**Implications for Minnie and for Practice**

- Minnie may not yet be “over the hump”
- Risks and benefits of hormone therapy must be considered within a longer period of use
- What symptoms are clearly linked to menopause?

**Hormones, Affect, QoL**

- Randomized Placebo-Controlled Trial Data
- PEPI (1998) – no difference in anxiety, cognitive, and affective symptoms
- HERS (1999) – women with symptoms reported improved mental health/mood
- WHI (2002) – women with symptoms reported improved sleep
- WISDOM (2008) – small but significant improvements in symptoms, sex, sleep
What would you recommend as a first step for Minnie?

1. Oral estrogen
2. Oral estrogen and progesterone
3. Estrogen patch
4. Estrogen patch and progesterone
5. Behavioral changes
6. Alternative prescription treatment
7. None of the above

Estrogen Relieves Hot Flashes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0%</td>
</tr>
<tr>
<td>Conjugated Estrogens</td>
<td>15%</td>
</tr>
<tr>
<td>Estrogen Patch and Prog</td>
<td>21%</td>
</tr>
<tr>
<td>Oral Estrogen and Prog</td>
<td>24%</td>
</tr>
</tbody>
</table>

Low Doses of E for Hot Flashes

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Daily Dose</th>
<th>% Improvement in HF Estrogen</th>
<th>% Improvement 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>78%</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>Oral E2 (estradiol)</td>
<td>2.0</td>
<td>96%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>89%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>79%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>57%</td>
<td>NS</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>45%</td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>86%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Minnie Pause: Conclusion

- Minnie's vasomotor symptoms were interfering with her life...after discussing her values and options...
- Transdermal estradiol was begun and hot flashes and sleep improved within 2 weeks.
- After second month of unopposed E, cyclic micronized progesterone begun
- After one year of treatment, discuss stopping HT, understanding that symptoms may continue for 2 or more years

References:
1. Utian, Fertil Steril, 2001;
2. Notelovitz, Obstet Gynecol, 2000;
Scarabin, Lancet 2003
Case 2: Desiree Low

- 50 years old, hysterectomy (no oophrectomy) 6 months ago for dysfunctional uterine bleeding
- Main complaints are decreased libido and vaginal dryness, no hot flashes
- She wants to avoid prescription hormones and creams
- But, she’s open to trying “natural” hormones and testosterone

What would you recommend as a first treatment for Desiree?

1. Over the counter vaginal creams and lubricants
2. Sex therapist
3. Estrogen (orally or transdermally)
4. Estrogen plus testosterone
5. Bioidentical hormones
6. None of the above

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
  - Estring stays in for 3 months
  - Vagifem- vaginal tablet inserted 2x per week

Background: Self-reported Sexual Desire in US Women

Adapted from Shifren JL et al, Obstet & Gynecol, 2008.
Testosterone: 2 recent RCT’s

- Background:
  - Hypoactive Sexual Desire Disorder
  - Satisfactory sexual events
  - Not FDA approved
- Transdermal spray in 261 premenopausal women, 16 weeks*
- Patch in 814 postmenopausal women not on estrogen, 52 weeks**

*Davis S, Annals 08 **Davis S, NEJM 08

Testosterone Spray: Results

Testosterone Patch: Results

Testosterone Trials: Impact

- Adverse events in pre-menopause included hypertrichosis, headache, nausea, acne, dysmenorrhea
- Adverse events in post-menopause included excess hair growth
- 4 women on active patch dx with breast cancer (vs. 0 in placebo)
- Long-term safety follow-up is key
“Bioidentical” Hormones

- Identical in molecular structure to human estrogens, progesterone, and testosterone
- No FDA oversight
- Dosage may be inaccurate or inconsistent
- Purity not monitored
- Safety unknown
- Efficacy unproven

Desiree’s conclusion

- Over the counter creams and lubricants helped vaginal dryness, which helped dyspareunia
- Her libido seemed to increase for a month
- Then, it seemed to return to its baseline
- However, this did not affect her relationship
- She avoided testosterone and bioidentical hormones after you reviewed pros and cons

Case 3: Maggie Graham

- 50 year old breast cancer survivor
  - 9 months since LMP
  - 6-8 hot flashes/day, interfere with work, sleep, ADL
- Stage 1 ER+ breast cancer at 41
  - Lumpectomy, XRT, Tamoxifen for 5 years
- “How would hormones affect my breast health?”
- “What are non-hormone options?”

How would you treat Maggie?

1. Estrogen alone
2. Estrogen plus progestin
3. Venlefaxine (Effexor)
4. SSRI
5. Gabapentin
6. Other
“How would hormones affect my breast health?”

- Most studies of HT in breast cancer survivors are observational and 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).

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.

Nelson, Lancet 08

Invasive Breast Cancer in WHI—11 yrs follow-up

HR for death 1.96 p = 0.049
HR node + 1.78 p = 0.03

WHI Estrogen - Breast Cancer Risk

![Graph showing WHI Estrogen Breast Cancer Risk](image)

**HR 0.77 (95% CI 0.59, 1.01)**

WHI Investigators, JAMA, 2004

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**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  
Chlebowski, Archives 08

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**Back to Maggie…**

- You recommend Maggie keep a symptom diary
- She tried lifestyle changes (cool room, light clothing¹ and diaphragmatic breathing²)
  - Hot flash diary average ↓ from about 7 to about 6
- She then began Vitamin E, hypnosis³ and acupuncture⁴
  - Hot flash diary average ↓ from about 6 to 5/day

¹Kronenberg, J Therm Biol, 1992  
²Freedman Am J Obstet Gynecol, 1992  
³Stearns, JCO 2008  
⁴Walker, JCO 2009
Maggie Graham: Conclusion

- You prescribe venlafaxine 37.5 mg once a day
- A week later, hot flashes ↓ from 5 to 4 a day
- The patient doubles the venlafaxine to 75 mg/d
- Hot flash diary shows in week 2 ↓ from 4 to 2 a day and no longer interfering with daily life
- Venlafaxine is recommended for at least 6 months

Case 4: Alana Hormone

- 65 year old healthy woman
- TAH/BSO at 50 for menorrhagia, started CEE 0.625 mg afterwards
- Remains on CEE 0.625 mg 15 years later
- Hot flashes when she misses CEE dose
- Recent DXA → osteopenia
- No CHD risk factors
- Father recently died of Alzheimer's at 88

Should Alana stop CEE?

1. Yes
2. No
3. Unsure

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. ↑ Coronary Heart Disease
2. ↑ Stroke
3. ↑ Pulmonary Embolus
4. ↑ Breast Cancer
5. All of the Above

“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

Heiss JAMA 08

In 2004, why was the WHI Estrogen Alone trial stopped early?

1. ↑ Coronary Heart Disease
2. ↑ Stroke
3. ↑ Pulmonary Embolus
4. ↑ Breast Cancer
5. All of the Above

Increased stroke risk at all times since menopause

### TABLE 1. RR (CI) for CHD events by age and time since menopause in the WHI studies (5)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>CEE</th>
<th>CEE/MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.63 (CI0.36–1.09)</td>
<td>1.29 (CI0.79–2.12)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.94 (CI0.71–1.24)</td>
<td>1.03 (CI0.74–1.43)</td>
</tr>
<tr>
<td>70-79</td>
<td>1.13 (CI0.82–1.54)</td>
<td>1.48 (CI0.94–2.11)</td>
</tr>
</tbody>
</table>

Time since menopause

- <10  0.48 (CI0.20–1.17)  0.88 (CI0.54–1.43)
- 10–19 0.96 (CI0.64–1.44)  1.23 (CI0.85–1.77)
- ≥20  1.12 (CI0.86–1.46)  1.66 (CI1.14–2.41)

P value for trend

<table>
<thead>
<tr>
<th>HR</th>
<th>CEE</th>
<th>CEE/MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td></td>
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</tr>
</tbody>
</table>
Bone Loss Resumes When Estrogen is Stopped

![Graph showing bone loss resumes when estrogen is stopped](Christiansen, Osteo Intl, 1996)

Hormones and Dementia: WHI

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>Pbo</th>
<th>RH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=2229)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>40</td>
<td>21</td>
<td>2.0</td>
<td>.01</td>
</tr>
<tr>
<td>vascular</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimers</td>
<td>20</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>15</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=1464)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>28</td>
<td>19</td>
<td>1.5</td>
<td>.11</td>
</tr>
</tbody>
</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% success stopping in one observational study*
  - RCT—about 50% success with either type (taper was qod)**
  - Dose or day taper - ↓ dose or ↓ 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  **Lindh-Astrand, Menopause 2010

Alana Hormone Conclusion

- Alana decided she wanted to stop ET because of the stroke and dementia risk
- She stopped cold turkey
- She had “estrogen withdrawl” hot flashes for 5 months, but is now symptom-free without estrogen
Overall 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

Additional References

  - Risk defined as “possibility or chance of harm”
  - Put level of risk in perspective
  - HT should not be used as an anti-depressant
  - No data to support any particular regimen
  - Use greater caution in women over 60
- Gast 2009
  - Menopausal complaints associated with a less favorable cardiovascular risk profile
- Jacobsen 2008
  - HT associated with increased GERD

Additional References

- Grodstein 2008
  - HT associated with increased stroke risk regardless of time of initiation
- Canonico 2010 and Cushman 2010
  - Observational study suggests that transdermal (compared to oral) estrogens do not raise risk of venous thromboembolism
- Elkins 2008
  - Hypnosis and exercise may improve vasomotor symptoms
**WHI Participants**

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

**Observational vs. Clinical Trial**

<table>
<thead>
<tr>
<th>Disease Event</th>
<th>Observational</th>
<th>WHI E+P</th>
<th>WHI E only</th>
</tr>
</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
### WHI - Individual Risk and Benefit

<table>
<thead>
<tr>
<th>Risk per 1000/year</th>
<th>Harm</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>E+P + Estrogen</td>
<td>CHD + 0.7</td>
<td>Hip fracture - 0.5</td>
</tr>
<tr>
<td></td>
<td>Stroke + 0.8 + 1.2</td>
<td>Colorectal cancer - 0.6</td>
</tr>
<tr>
<td></td>
<td>Pulm. embolus + 0.8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Breast cancer + 0.8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>E+P + Estrogen</td>
<td>Net bad events +2.0* +0.6</td>
</tr>
</tbody>
</table>

### 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

### Annual US Breast Cancer Incidence

![Graph showing annual US breast cancer incidence](image)

### Herbs and Supplements

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

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

- **Mixed/poor evidence**
  - Black cohosh
  - Phytoestrogens

- **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

What about younger women?

Meta-analyses, Salpeter

- Both meta-analyses used RCT data and defined “younger post-menopause” as <60
- 2009 methods were Bayesian
  - preferred for combining heterogenous discrepant studies
- 2004 used 30 RCT’s, main outcome was mortality
  - Odds Ratio in younger women was 0.61 (0.39 – 0.95)
  - Odds Ratio in older women was 1.03 (0.9 – 1.18)
- 2009 used RCT and observational data
  - Odds Ratio in younger women was 0.72 (0.62 – 0.82)

Hormones 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 quality of life domains: vasomotor symptoms, sleep, sexual function
- No significant differences in depression and overall quality of life
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

Women with Mod-Severe Symptoms

<table>
<thead>
<tr>
<th>Years since menopause</th>
<th>&lt;10</th>
<th>10-19</th>
<th>20+</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR of CHD on HT</td>
<td>0.84</td>
<td>1.38</td>
<td>2.76</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.40-1.77</td>
<td>0.63-3.0</td>
<td>1.53-4.97</td>
</tr>
</tbody>
</table>

P for trend < 0.01, P for interaction with vasomotor symptoms = 0.06

↑ stroke risk at all times since menopause

References:
Loprizini Lancet 2000
Rossouw JAMA 07