Management of Menopause: Should New Data Change Our Practice?

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UCSF Women’s Health, Primary Care
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
Case 1: Minnie Pause

Minnie Pause is a 53 year old woman who had her last menstrual period 18 months ago. She is still having hot flashes and awakens at least twice a night with them. Over the counter remedies have not helped much.

“How much longer will this last?”
“Will hormones help all of my symptoms?”
“What are pros and cons of using hormones?”

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

+Randolph 2000; Loprinzi 2000; Joerres 2003
‡Randolph, J Clin Endocrinol Metab, 2004
“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
- “Will hormones help all of my symptoms?”
- What symptoms are clearly linked to menopause?

Hormones 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
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

Estrogen Relieves Hot Flashes

![Graph showing the effectiveness of estrogen in reducing hot flashes](graph.png)
Back to Minnie….

- "Will hormones help all my symptoms?"
- Hormones will likely help hot flashes and sleep disturbances from hot flashes
- Unclear whether they will help other symptoms, including mood and overall quality of life
- "What are the pros and cons of using hormones?"

Weighing Risks/Benefits: Individuals and Public Health

- Individually, risks and benefits could be interpreted as having low absolute numbers.
- From a public health standpoint, though, could widespread HT use cause significant harm?

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
Menopause and Hormones: WHI

- What is the Women’s Health Initiative (WHI)?
- What has it revealed about menopause and post-menopausal hormone therapy (HT)?
- What lessons have we learned from WHI?
  - public health and clinical trial design
- Have any broad public health implications resulted from WHI?

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
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

WHI Participants

<table>
<thead>
<tr>
<th></th>
<th>E + P (n=16,606)</th>
<th>Estrogen (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></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  †8 years of use  *p-value < .05
**WHI - Individual Risk and Benefit**

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

**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)
- Mean age > 60, 13 trials, n = 22,567
  - Deaths: HT = 465/11571, control = 433/10966
  - Odds Ratio = 1.03 (0.9 – 1.18)

**Low Doses of E for Hot Flashes**

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Daily Dose</th>
<th>% ↓ in HF</th>
<th>% ↓ in HF</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>N/A</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>

Minnie Pause: Conclusion

- Minnie tried over-the-counter creams and pills, as well as behavioral techniques, but none really helped her symptoms.
- 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, discussing stopping HT, understanding that symptoms may continue for 2 or more years

Case 2: 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 progesterin
3. Venlefaxine (Effexxor)
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

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**WHI E+P - Breast Cancer Risk**

![Graph showing WHI E+P - Breast Cancer Risk]

**WHI Estrogen - Breast Cancer Risk**

![Graph showing WHI Estrogen - Breast Cancer Risk]
**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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**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>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>50-60%</td>
<td>SSRIs/SSNERIs</td>
</tr>
<tr>
<td>50%</td>
<td>Gabapentin 300 mg TID: 2 + trials</td>
</tr>
<tr>
<td>40%</td>
<td>Clonidine</td>
</tr>
<tr>
<td>20-50%</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

* inhibits CYP2D6 enzyme (tam metabolism)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs/SSNERIs</td>
<td>50-60%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+/⁻</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+/+?</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>++</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>++</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>50%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>40%</td>
</tr>
<tr>
<td>Placebo</td>
<td>20-50%</td>
</tr>
</tbody>
</table>

Caution in women with ER+ breast cancer—stimulate nipple aspirate
Causes proliferation of estrogen-sensitive breast cancer cells

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“We’re having soy patties, soy soup, soy salad, soy fries, soy shakes and soy pie…and the same thing for lunch and dinner. Welcome to menopause!”

- Caution in women with ER+ breast cancer—stimulate nipple aspirate
- Causes proliferation of estrogen-sensitive breast cancer cells

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

Loprizini Lancet 2000

Back to Maggie…

- You recommend Maggie keep a symptom diary
- She tried lifestyle changes (cool room, light clothing$^1$ and diaphragmatic breathing$^2$)
  - Hot flash diary average ↓ from about 7 to about 6
- She then began Vitamin E, hypnosis$^3$ and acupuncture$^4$
  - Hot flash diary average ↓ from about 6 to 5/day

$^1$Kronenberg, J Therm Biol, 1992
$^2$Freedman Am J Obstet Gynecol, 1992
$^3$Stearns, JCO 2008
$^4$Walker, 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 3: 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

Bone Loss Resumes When Estrogen is Stopped

[Graph showing % Forearm BMC vs Months for Re-randomized E2 and Placebo groups]

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

<table>
<thead>
<tr>
<th>Years since menopause</th>
<th>&lt;10</th>
<th>10-19</th>
<th>20+</th>
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<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

Rossouw JAMA 07

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“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>
<th></th>
<th>HRT (N=2229)</th>
<th>Pbo (N=2303)</th>
<th>RH</th>
<th>p-value</th>
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</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ERT (N=1464)</th>
<th>Pbo (N=1483)</th>
<th>RH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<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
**Effects of Estrogen-Alone and Placebo on Disease Rates**

<table>
<thead>
<tr>
<th>Disease</th>
<th>CEE</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Heart Attack</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**↓ HT → ↓ Breast Cancer?**

- Cause and effect? ↓ mammography? Rapid drop?
- Time trend mammo analysis in WHI E+P
- Breast cancer diagnoses increased over the 5 study years and decreased markedly after HT stopped
- Mammo rates were similar in HT and placebo
- Women continuing E+P after 5 years double rates of breast cancer
- Marked drop in breast cancer incidence appears to be causally related to decreases in HT use

Chlebowski, NEJM 09

**Lessons for Public Health**

- Individually, there are differences between relative risks and absolute risks
- Small relative risks for common diseases can largely impact public health
- Accurate communication with public is key
Lessons for Clinical Trial Design

- Basic Science + Observational Data ≠ RCT Results
- Bias in observational studies- hard to measure and control
- Subgroup analysis – starting points

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

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?

References:
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

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

Key articles

- New evidence based guidelines for the use of hormone therapy
  - 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 route of administration or dosing regimen
  - Use greater caution in women over 60

NAMS, Menopause, 2008
Key Articles

- Menopausal complaints are associated with a less favorable cardiovascular risk profile
  - Gast, 2009
- Hormone therapy associated with an increased risk of GERD
  - Jacobson, 2008
- Hormone therapy associated with an increased risk of stroke regardless of time of initiation
  - Grodstein, 2008

Key Articles

- Hormone therapy is associated with improvement in some quality of life measures in women with vasomotor symptoms and may improve sexual function and vitality
  - Hess, 2008; Welton, 2008
- Hypnosis and exercise may improve vasomotor symptoms
  - Elkins, 2008

![Graph showing cumulative abnormal mammograms and biopsies over years]