Post-menopausal Hormone Tx
Is the pendulum swinging again?

- Pre-2002 Nurses Health Study (observational)
  - Hormones widely recommended for post-menopausal (PM) women; lots of potential benefit including ↓ heart disease
- 2002 WHI (large, blinded, placebo controlled 5yr RCT)
  - PM hormones appear to do more harm than good, unless you find too many limitations & flaws with the evidence
- 2012 DOPS (open label, smoker, alcohol RCT, KEEPS (RCT - underpowered, underpowered))
  - PM hormones aren’t so bad after all, if used soon after menopausal onset, in younger women, for short time. In fact, one underpowered study says they may even be good. Another, underpowered study suggests safety may be related to formulation used. Some masked; others point out flaws.
- 20?? - ??

DOPS
Bias & Validity Concerns

- Changed 1st endpoint
  - Designed for fracture & BMD
- Very underpowered for other endpoints
  - Acknowledged at outset with planned 20yrs
- Open label & no placebo
  - Performance bias, detection bias, selection bias
- Results conflict WHI subgroup age 50-59
  - Larger, blinded RCT; although onset of MP longer
  - WHI ~ 28,000 pt yrs vs DOPS ~10,000 pt yrs
  - Stroke, MI, death, VTE, BMD, x mortality
- Combining results for E+P vs E only arms inappropriate
  - E.g. opposite effects on breast ca in seen in WHI arms
  - Conflicts of interest (several potential)

KEEPS Aging & Cognition preliminary - awaiting publication

- RCT, 727 women, age 42-58, <3yr MP
  - Transdermal E2 50ug/d + norethisterone + annual visit vs Oral CEE 0.45mg/d + Prometrium vs Placebo
- X4yrs
  - Note: with short term, & small numbers of women at low risk, one would expect non-significant results on major endpoints.
- Results
  - CV outcomes & AE’s neutral

Post-menopausal Hormone Tx
Big picture Synthesis – Oct 2012

- For long-term use in older women, potential harms outweigh benefits.
- For short-term use in younger women at lower risk, there is less harm. Use for symptomatic management reasonable.
- There is potential for more benefit than harm
  - if starting early post-menopause or
  - with certain formulations/routes (e.g. Transdermal)
  - however, this is still theoretical & not supported by the more rigorous RCTs.
- Recent trials limited by
  - short term, KEEPS, small numbers & strong potential for bias & DOPS

Hormone - Post-menopausal
RxFiles Drug Comparison Chart – 9th Ed – Pg 90

11Yr Follow-up publication to WHI
- Criticisms and limitations
- Benefits & harms (per patient-yr)
  - more stroke 9-11/10,000
  - DVT 7-12/10,000
  - gallbladder dx 33/10,000...
- less fracture 46-56/10,000
- Options for vasomotor symptoms
## Estrogen-Oral

<table>
<thead>
<tr>
<th>Source</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Strength</th>
<th>Equivalent / Usual Dose</th>
<th>Price/Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equine</td>
<td>Conjugated equine est. (CEE)</td>
<td>PREMARIN</td>
<td>0.3, 0.625 mg est. only, 1.25 mg tab</td>
<td>0.625 mg po OD</td>
<td>153</td>
</tr>
<tr>
<td>plant</td>
<td>Conjugated estrogen sulfate</td>
<td>CESTR</td>
<td>0.3, 0.625, 0.9 mg tab</td>
<td>1mg po OD</td>
<td>81</td>
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<tr>
<td>plant</td>
<td>Micronized estradiol-17β</td>
<td>ESTRACE</td>
<td>0.1 mg</td>
<td>1mg po OD</td>
<td>138</td>
</tr>
<tr>
<td>plant</td>
<td>Estradiol (estrone sulfate)</td>
<td>OGEN</td>
<td>0.625, 1.25, 2.5 mg tab</td>
<td>0.625 mg po OD</td>
<td>109</td>
</tr>
<tr>
<td>synth</td>
<td>CEE + MPA (Blister-card)</td>
<td>PREMLEGS</td>
<td>0.625 mg tab + 2.5 mg tab (or 5mg tab)</td>
<td>1 tab of each OD</td>
<td>175</td>
</tr>
<tr>
<td>synth</td>
<td>Ethinyl estradiol /norethindrone</td>
<td>FemHRT</td>
<td>5µg/kg + NE 1mg tab</td>
<td>5µg/kg daily</td>
<td>315</td>
</tr>
</tbody>
</table>

**Combination HE; harm > benefit over > 5 yrs**

**Postmenopausal Transdermal/Topical**

- avoids 1st pass effect; maybe preferred if liver dysf, HTN, smoker or hypertriglyceridemia (Ldl↓, T↑, T↓); but evidence limited for relative benefits / harms vs oral.
- patch: rotate sites (abdominal/thighs/buttocks)
- gel: do not rotate sites (arm, abdomen or thigh)
- TR-E, BL-EST Cr.: controversial: promoted as “bio-identical”; SOGC: no advantages & expensive

**Estrogen-Vaginal**

- with txs transmucosal absorption
- for urogenital Sxs: Codys'/90 atrophy/dryness/stress incontinence
- less systemic effect (but creams require regular application)

**Progestagens - Oral**

- for endometrial ca protection in with an intact uterus on estrogen (dose required depends on estrogen dose/route.)
- if continuous regimen, will prevent bleeding ⊗ concern

**Androgens**

- for symptoms of androgen deficiency post bilateral oophorectomy & post-menopause; ↓ adipose, fat & TBW
- studies re. optimal prep, dose & long-term safety are lacking

### Osteoporosis Therapy

- **Risk factors**:
  - older age
  - female gender
  - multiple risk factors: sedentary lifestyle, low calcium intake, smoking, alcohol use, family history of osteoporosis

- **Prevention strategies**:
  - Calcium + vitamin D supplementation
  - Regular weight-bearing exercise
  - Estrogen replacement therapy (if appropriate)

- **Treatment options**:
  - Bisphosphonates (ibandronate, alendronate)
  - Estrogen plus progestin
  - Calcitonin
  - Raloxifene

### Vasomotor Medications

<table>
<thead>
<tr>
<th>Vasomotor Medications</th>
<th>Relevance to Vaginal Estrogen</th>
<th>Orals (low-dose) - perimenopause option for symptomatic, healthy non-smokers</th>
<th>Evidence of effectiveness for cycle control/collection</th>
</tr>
</thead>
</table>

### Weighing Benefits & Harms of Post-Menopausal Hormone Therapy on Chronic Conditions

**Type**

- Estrogen + Progestin
- Estrogen only

**Considerations & Controversies Regarding Individualization of Therapy**

- **Breast Cancer**: Data from WHI trials suggest that breast cancer risk is increased with hormone therapy, particularly when combined with tamoxifen. However, the benefit-to-risk ratio remains unclear.
- **Cardiovascular Disease**: While hormone therapy may reduce cardiovascular disease risk, data from the WHI trials are conflicting.
- **Other Considerations**: Women should discuss the potential benefits and risks of hormone therapy with their healthcare provider, considering their individual health status and preferences.
References: The Rx Files Postmenopausal and Herbal Pharmacotherapy

4 Therapeutic Research Faculty. Natural Database Monographs. Natural Database . 2002. Ref Type: Electronic Citation.
17 Clifton-Bligh PB, Barber RJ, Fulcher GR, Nery ML, Moreton T. The effects of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. Menopause 2001;8:259-65.
30 Franks E. Micromedex. 2010.
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Additional references:
Agaa H-Amir, Drost J, Ashani L, Aiyenr A, et al. Cresc tus Latino (Saffron) in the treatment of postmenopausal osteomuscular syndrome: a double-blind, randomised, placebo-controlled trial. Maturitas 2008 Mar;55(4):515-9. Saffron was an effective treatment for premenstrual syndrome (PMS) in this well-designed but small and short-term study. Consider recommending saffron, if cost is not an obstacle. Larger and longer studies are needed to confirm this result. (LOE = 1b)
Berry DA, et al.; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005 Oct 27;353(17):1784-92. [InfPoEMs: Almost half of the reduction in breast cancer mortality over the past decade can be attributed to the increased use of screening mammography. The remainder appears to be due to improvements in therapy. (LOE = 1b)]
Caninoico M, Oger E, Plu-Bureau G, et al; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study.Circulation. 2007 Feb 20;115(7):840-5. Oral but not transdermal estrogen is associated with an increased VTE risk. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. If confirmed, these findings could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogen.
Caninoico M, Plu-Bureau, G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008 May 20. [Epub ahead of print] Oral estrogen increases the risk of venous thromboembolism, especially during the first year of treatment. Transdermal oestrogen may be safer with respect to risk. In addition, there was no indication that estrogen preparations containing oral estrogen could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogen.
Caninoico M, Plu-Bureau, G Luxembourg GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women, but did not improve scores on cognitive measures. The overall risks and benefits of long-term treatment remain uncertain. (LOE = 1b)
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This drug should be considered for treatment of hot flashes in women with breast cancer. (InfoPOEMs: Women's Health Initiative) This meta-analysis of 13 large observational studies found that combined estrogen and progestin hormone replacement therapy (CHT) for postmenopausal women is more likely than estrogen-only hormone therapy (ET) to be associated with breast cancer among women taking raloxifene. All-cause mortality and overall quality-of-life were similar in both treatment groups. (LOE = 2a)  

Shah NR, Borenstein J, Dubois RW. Postmenopausal hormone therapy and breast cancer among older women: a nested case-control study. BMJ 2010;340:c2519, doi: 10.1136/bmj.c2519 (Published 3 June 2010)  


Vaidya D, Becker DM, Bittner V, et al.  


(InfoPOEMs: Estrogen/progestin therapy does not routinely be used to prevent chronic disease in postmenopausal women. The Task Force making this recommendation did not address short-term (1-2 years) treatment of symptoms of menopause. The risks with chronic therapy are minimal, but so are the benefits.)  


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Vaidya D, Becker DM, Bittner V, et al.  


SHEP: Study Of Heart And Estrogen/Progestin Replacement Therapy (SHEP): US Preventive Services Task Force Recommendation Statement. Ann Intern Med 2002. The SHEP trial found that estrogen/progestin therapy did not reduce in postmenopausal women's risk of heart disease or stroke. These results were consistent with the findings of other studies. All-cause mortality and overall quality-of-life were similar in both treatment groups. (L)
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Canalis E, Raisz LG, Melmed R. Mechanisms of anabolic therapies for osteoporosis. J Clin Endocrinol Metab. 2006 Feb;91(2):225-31. Low-BMI prevalent vertebral fractures are independently related to new vertebral fractures over 15 years of follow-up. Women with a prevalent vertebral fracture have a substantially increased absolute risk of a new fracture, especially if they have osteoporosis diagnosed by BMD.


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Dormuth CR, Carney G, Carleton B, et al. Vitamin K and the Prevention of Fractures: A Systematic Review and Meta-analysis. A systematic review of randomized controlled trials of vitamin K supplements for the prevention of fractures. Ann Intern Med. 2009 Jul 7. [Epub ahead of print]. We found no evidence of a beneficial or harmful effect of raloxifene on the incidence of cardiovascular events overall or on coronary events in postmenopausal women. However, our results do not exclude the possibility that vitamin K may have a role in the prevention of osteoporosis-related fractures.

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The antiresorptive effects of a single 5-mg dose of zoledronate are sustained at 2 years: a randomized, placebo-controlled trial in osteoporotic postmenopausal women. J Clin Endocrinol Metab. 2009 Feb;94(2):538-44. Epub 2008 Dec 2.

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Biodiethormone:

Progesterone cream no more effective than placebo for relief of menopausal symptoms: The conclusion in a double-blind placebo-controlled study to evaluate the effect of progesterone cream on postmenopausal women (Menopause International, Volume 15, Issue 2, June 2009, Pages 63-69


Links:


The North American Menopause Society www.menopause.org