HRT Alternatives in Light of the WHI

Current Q&As

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Recent trials have resulted in much discussion regarding the benefits and risks of hormone replacement therapy (**HRT**).

The **Womens Health Initiative (WHI)** [1] is the first randomized controlled trial to evaluate the long-term benefits and risks of HRT in 16,608 healthy postmenopausal women. It found that the risks outweigh the benefits of combination HRT, specifically conjugated equine estrogen (**CEE**; e.g. ***PREMARIN***) 0.625mg daily + medroxyprogesterone (**MPA**; e.g. ***PROVERA***) 2.5mg daily over a mean of 5.2 years. **See Table 1**.

The **Heart and Estrogen/progestin Replacement Study** (**HERS**) found that combination HRT did not reduce coronary heart disease (**CHD**) events or cardiovascular (**CV**) outcomes in 2,763 postmenopausal women with CHD over 4.1 years.[2,3,4] **HERS II** provided a subsequent unblinded 2.7 year follow-up to this study and CV results were consistent with the original trial.[5] Other outcomes (thromboembolism, biliary tract surgery and cancer rates) were also unfavorable.[6]

Thus, evidence shows that the risks of long-term combination HRT (CEE+MPA) exceed the benefits. Various groups caution against overreaction noting study limitations, the small absolute risk and the safety of short-term HRT for symptom control.[7,8,9] Others state a need to be more vigilant in demanding well-designed, randomized trial evidence before widely prescribing long-term preventative treatments.[10,11]

Table 1: Summary of results from WHI over ~5.2yr study period

Outcomes positive ; negative	CEE+ MPA %	Placebo %	RR %	AR %	NNT; NNH
***CHD** early ↑ in risk	1.93	1.50	↑ 29	↑ 0.43	232
Stroke ↑ after >1yr	1.49	1.05	↑ 42	↑ 0.44	227
DVT	1.35	0.64	↑111	↑ 0.71	140
PE early ↑ in risk	0.82	0.38	↑116	↑ 0.44	227
Total CVD	8.16	6.74	↑ 21	↑ 1.42	70
***Breast Ca**invasive -↑ risk after ~4yrs	1.95	1.53	↑ 27	↑ 0.42	238
Colorectal Ca - benefit after ~3yrs	0.53	0.83	↓ 36	↓ 0.3	333
Hip Fracture	0.52	0.77	↓ 33	↓ 0.25	400
All Fracture	7.64	9.73	↓ 22	↓ 2.09	48
Global Index ♣	8.82	7.69	↑ 14	↑ 1.13	**88**

Ca=cancer **CHD**=coronary heart disease **CVD**=cardiovascular disease **DVT**=deep vein thrombosis **PE**=pulmonary embolism **AR**=absolute risk **RR**=relative risk **NNT**=number needed to treat to benefit 1 patient **NNH**=number needed to harm one
***** primary outcomes of study **♣**Global Index summarized balance of risks & benefits
Note: Only statistically significant outcomes included in table. For breast cancer the confidence interval (Nominal 95% CI = 1.00-1.59) had just reached significance.

What we still don't know.

- Whether estrogen-only HRT shares safety concerns. Interim results from the ongoing WHI estrogen-only arm, in women with previous hysterectomy, were inconclusive.
- Whether the results would be different with lower doses, other oral/transdermal regimens, or a younger population (average age of recruitment in WHI was 63 years, >10 years after the average age of menopause onset; newly menopausal women can have significant symptoms and evidence still supports the effectiveness and safety of short-term HRT).
- The HRT impact on quality of life, not measured in WHI.

Are there advantages to other oral or transdermal estrogens compared to CEE (e.g. Premarin)?

- Non-CEE alternatives such as oral estradiol-17β ***ESTRACE***, estropipate ***OGEN*** and transdermal estradiol-17β are available. Potential advantages and disadvantages are summarized in **Table 2**. Unfortunately, long-term clinical outcome studies are lacking.

Is Prometrium likely to be better than Provera?

- Oral micronized progesterone (***PROMETRIUM***) has some theoretical advantages. It is an endogenous "natural" hormone and preserves the beneficial effect of estrogen on HDL.[12] Some believe that the negative outcomes seen in HERS and the WHI may be due to the choice of MPA as the progestagen. Unfortunately, outcome studies are lacking.

What do we know about compounded HRT creams?

- Bioidentical Hormone Replacement Therapy (BHRT) attempts to restore hormonal balance by replacing according to the body's "natural" hormonal pattern. Hormones used are compounded from a synthetic source. **See Table 2**.
- **Estrogen creams** (e.g. ***Triest***) are likely to be well absorbed and well tolerated. Proponents emphasize the role of estriol (E3) in protecting breast tissue and the endometrium from the stimulatory effects of estradiol and estrone.[13] Long term clinical outcome studies are lacking.
- **Progesterone creams** are effective for some patients as monotherapy for the control of vasomotor symptoms.[14,15] Absorption is variable causing concern that they may not protect against endometrial cancer in combination regimens.

Herbal Options: see Table 3

Related RxFiles Links:

- *HRT: Age & the WHI http://www.rxfiles.ca/acrobat/HRT-Age-and-the-WHI.pdf*
- *HRT: Data in Perspective: http://www.rxfiles.ca/acrobat/HRT-WHI-Extras-Perspectives.pdf*
- *Postmenopausal Drug/Herbal Treatment Charts: www.rxfiles.ca (ongoing updates members)*
  {Charts also available in the RxFiles Drug Comparison Charts book 6th Edition 2007-2008}

Table 2: Comparison of Postmenopausal - Hormonal Treatment Options [16,17] (see also Table 4 comparison chart)

		Advantages	Disadvantages	Long-term Outcome Trials
ESTROGEN	**Conjugated equine estrogen (CEE) PREMARIN +Medroxyprogesterone (MPA) PROVERA**	↓ hip fractures & all-fractures, ↓colorectal cancer (still some controversy: meta-analyses of observational trials found ↓ heart disease)[18]	◆long term risks outweigh benefits: ↑breast ca., ↑coronary heart disease, ↑clots (DVT/PE), ↑biliary tract surgery	**WHI** 5.2yrs **HERS** 4.1yrs **HERS II** 6.8yrs
	CEE alone {estrogen-only therapy}	This arm of WHI trial not stopped early indicating that risk versus benefit at 5 years is inconclusive	◆not suitable for ♀ with a uterus who require progestagen for endometrial protection; {↑ovarian ca.? [19]}	**WHI** 5yrs ongoing **ERA** 3.2yrs [20] (no CV benefit in ♀ with CAD)
	Alternate Oral estrogens Conjugated Estrogens C.E.S.	◆plant source, non-equine estrogens	◆estrogen mixture; not endogenous	lacking
	Estradiol 17β ESTRACE	◆estradiol an endogenous hormone	◆potential advantages of endogenous estrogens based on possibility that negative outcomes in trials could be related to non-human/equine estrogens	lacking
	Estropipate OGEN	◆converts to estrone (endogenous)		lacking
	Transdermal estradiol various patches/gels e.g. ESTRADERM, ESTRADOT, VIVELLE, OESCLIM, ESTROGEL	◆endogenous ◆avoids first-pass liver metabolism ∴no ↑ in triglycerides & less stimulation of clotting factors (proposed advantage in ♀ smokers)	◆less reduction in LDL levels; does not raise HDL	lacking
	Transdermal estrogens Triest Cream (compounded) estriol$^{80\%}$+estradiol$^{10\%}$+ estrone$^{10\%}$	◆replace endogenous estrogens in "bio-identical" proportions to how they occur in pre-MP ♀s [21]	◆comparative dose not well studied ◆studies on estriol & risk of CVD/ osteoporosis are equivocal[22,23,24,25]	lacking
	Vaginal estrogens ESTRING, VAGIFEM, creams	◆effective for **urogenital** symptoms ◆low-dose; predominant local effects	◆creams may cause endometrial proliferation (more than tab or ring)[26]	lacking; but less systemic effect
PROGESTAGEN	**Medroxyprogesterone (MPA) PROVERA**	**Norethindrone acetate** (**NETA**) also available. Used as the progestagen in ESTRACOMB & ESTALIS patches.	◆may be factor in negative outcomes seen in combination HRT trials ◆negates the estrogenic ↑HDL PEPI	**WHI** 5.2yrs
	Micronized progesterone PROMETRIUM (in peanut oil)	◆endogenous "natural" progestagen ◆less adverse HDL effect compared to MPA (PEPI)[27]; may improve sleep[28]	Note: the term "natural" somewhat misleading as products synthetically processed	lacking
	Transdermal progesterone cream (compounded)	◆endogenous "natural" progestagen ◆may relieve vasomotor symptoms[14,15]	◆absorption highly variable; concern re. lack of endometrial protection ◆conflicting data on bone density [14]	lacking
	Vaginal progesterone	◆absorbed (available as compounded suppositories or use Prometrium tab)		lacking
SERM	**Raloxifene EVISTA**	◆↓ risk of vertebral fracture 1°&2° [29,30] ◆may protect against breast cancer[31] ◆no adverse effects on lipids ◆↓CV events in ♀ at high CV risk[32] ?	◆worsens menopausal symptoms (vasomotor, vaginal dryness) ◆no benefit on non-vertebral fracture ◆↑ risk of DVT similar to estrogen	1°:fracture vertebreal 3yr; 2° analysis: CV 4yr & Breast Ca 3yr risk. **MORE**

♀=women **ca.**=cancer **CVD**=cardiovascular disease **DVT**=deep venous thrombosis **HRT**=hormone replacement therapy **MP**=menopausal **PE**=pulmonary embolism

Options to reduce CARDIOVASCULAR risk

There is good outcome evidence for:

- **lifestyle interventions** (diet, exercise, stop smoking)
- **statins**
- **antihypertensives**
- **low-dose ASA**

} in high-risk patients

Options to reduce the risk of OSTEOPOROSIS

- **lifestyle interventions** (weight bearing exercise, diet)
- **calcium** 1000-1500mg/day + **vitamin D** 400-800 IU/day (Multivitamin preps often good economical option)
- **bisphosphonates** (etidronate, alendronate, risedronate, pamidronate)
- **raloxifene** EVISTA
- **calcitonin** MIACALCIN nasal spray

Options for GENITOURINARY symptoms

- **non-hormonal vaginal moisturizers** e.g. REPLENS offer an excellent option for symptomatic relief
- **vaginal hormonal options** (e.g. ESTRING, VAGIFEM, estrogen creams) low doses offer local relief for urogenital symptoms with less risk of systemic hormonal effects. A progestagen may be required for women using vaginal cream.

Options for VASOMOTOR symptoms [16,33]

- **lifestyle -** exercise & periodic deep breathing (≤50% effective)
- **estrogen, short-term (oral or transdermal)** ~70-90% effective for severe symptoms & quality of life issues; safety concerns primarily with long-term use >5yrs
- **progestagen, short-term** (e.g. MPA IM; megestrol 10-80mg/d [34])
- **SSRIs -** standard doses[35] or **venlafaxine** 37.5-75mg/day[36,37]; 40-60% effective in breast cancer survivor trials (many on tamoxifen)
- **phytoestrogens** (e.g. soy, isoflavones) – mild-mixed results
- **black cohosh** – a herbal product with some limited evidence of efficacy and safety in short-term use (<6months)
- **clonidine** 0.05-0.1mg po bid (no effect to modest effect)

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References available on website or on request

References: *RxFiles* – HRT Alternatives in light of WHI - September 2002

[1] Writing Group for the Women's Health Initiative (**WHI**) Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women - Principal Results From the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288: 21-333. (Available from: http://jama.ama-assn.org/issues/v288n3/ffull/joc21036.html)

[2] Hulley S, Grady D, Bush T, et al (**HERS**). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-13.

[3] Simon JA, Hsia J, Cauley JA, et al (**HERS**). Postmenopausal hormone therapy and risk of stroke. Circulation 2001;103:638-642.

[4] Hsia J, Simon JA, Lin F, et al (**HERS**). Peripheral arterial disease in a randomized trial of estrogen with progestin in women with coronary heart disease. Circulation 2001;102:2228-32.

[5] Grady D, Herrington D, Bittner V, et al. Cardiovascular Disease Outcomes During 6.8 Years of Hormone Therapy - Heart and Estrogen/Progestin Replacement Study Follow-up (**HERS II**). JAMA 2002;288:49-57. (http://jama.ama-assn.org/issues/v288n1/ffull/joc20521.html, accessed Sept 6, 2002).

[6] Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular Disease Outcomes During 6.8 Years of Hormone Therapy - Heart and Estrogen/Progestin Replacement Study Follow-up (**HERS II**). JAMA 2002;288:58-66. (http://jama.ama-assn.org/issues/v288n1/ffull/joc20522.html, accessed Sept 6, 2002).

[7] Press Release, Society of Obstetricians and Gynaecologists of Canada (SOGC). SOGC Cautions Women not to Overreact to US Study. July 10, 2002 (http://sogc.medical.org/SOGCnet/sogc_docs/press/releases2002/hrt_e.htm, accessed Aug 19, 2002).

[8] Press Release, ACOG. Statement on the estrogen plus progestin trial of the Women's Health Initiative by the American College of Obstetricians and Gynecocogists (ACOG). July 9, 2002. (http://www.acog.org/from_home/publications/press_releases/nr07-09-02.cfm, accessed Aug 19, 2002).

[9] Whitehead, M. Hormone replacement therapy: findings of women's health initiative trial need not alarm users. BMJ 2002;325:113-4.

[10] Yusuf S, Anand S. Hormone replacement therapy: a time for pause. CMAJ 2002;167:357-9.

[11] Day A. Lessons from the Women's Health Initiative; primary prevention and gender health. CMAJ 2002;167:361-2.

[12] The Postmenopausal Estrogen/Progestin Interventions (**PEPI**) Trial Investigators. Effect of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1995;273:199-208.

[13] Wepfer S. A review of bioidentical hormone replacement therapy (Part 2). Int J Pharm Compound 2001;5:462-4.

[14] Wepfer S. A review of bioidentical hormone replacement therapy (Part 1). Int J Pharm Compound 2002;6:50-4.

[15] Leonetti H, Longo S, Anasti J. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. Obstet Gynecol 1999;94:225-8.

[16] SOGC. The Canadian Consensus Conference on Menopause and Osteoporosis 2000/2001. JOGC 2001; (http://sogc.medical.org/SOGCnet/sogc_docs/common/guide/pdfs/osteoMeno.pdf)

[17] Micromedex 2002: DrugDex Drug Evaluations.

[18] Nelson H, Humphrey L, Nygren P, Teutsch S, Allan J. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002;288:872-81.

[19] Lacey JV Jr, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA. 2002 Jul 17;288(3):334-41.

[20] Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med. 2000 Aug 24;343(8):522-9.

[21] Regier L. "Natural" Hormone Replacement Therapy (NHRT):What We Know & Don't Know. RxFiles Q&A Summary September 1999 (http://www.sdh.sk.ca/rxfiles/acrobat/nhrt%2Dq%26a.pdf)

[22] Michaelsson K, BaronJ, Farahmand B, Ljunghall S. Use of low potency estrogens does not reduce the risk of hip fracture. Bone 2002;30:613-8.

[23] Itoi H, Minakami H, Sato I. Comparison of the long-term effects of oral estriol with the effects of conjugated estrogen, 1-alpha-hydroxyvitamin D3 and calcium lactate on vertebral bone loss in early menopausal women. Maturitas 1997;28:11-17.

[24] Itoi H, Minakami H, Iwasaki R, Sato I. Comparison of the long-term effects of oral estriol with the effects of conjugated estrogen on serum lipid profile in early menopausal women. Maturitas 2000;36:217-22.

[25] Schairer C, Adami H, Hoover R, Persson. Cause-specific mortality in women receiving hormone replacement therapy. Epidemiology 1997;8:59-65.

[26] Willhite L, O'Connell M. Urogenital Atrophy: Prevention and Treatment. Pharmacotherapy 2001;21:464-80. (http://www.medscape.com/viewarticle/409697)

[27] The Postmenopausal Estrogen/Progestin Interventions (**PEPI**) Trial Investigators. Effect of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1995;273:199-208.

[28] Montplaisir J, Loorain J, Denesle R et al. Sleep in menopause: differential effects of two forms of hormone replacement therapy. Menopause 2001;8:10-16.

[29] Ettinger B, Black DM, Mitlak BH. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (**MORE**) Investigators. JAMA. 1999 Aug 18;282(7):637-45.

[30] Maricic M, Adachi JD, Sarkar S, Wu W, Wong M, Harper KD. Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. Arch Intern Med. 2002 May 27;162(10):1140-3.

[31] Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the **MORE** randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA. 1999 Jun 16;281(23):2189-97.

[32] Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the **MORE** (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA. 2002 Feb 20;287(7):847-57.

[33] Barton D, Loprinzi C, Wahner-Roedler D. Hot flashes: aetiology and management. Drugs Aging. 2001;18(8):597-606.

[34] Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE, et al. Megestrol acetate for the prevention of hot flashes. N Engl J Med. 1994 Aug 11;331(6):347-52.

[35] Stearns V, Hayes D. Approach to menopausal symptoms in women with breast cancer. Current Treatment Options Oncology 2002;3:179-90.

[36] Barton D, La VB, Loprinzi C, et al. Venlafaxine for the control of hot flashes: results of a longitudinal continuation study. Oncol Nurs Forum. 2002 Jan-Feb;29(1):33-40.

[37] Loprinzi C, Kugler J, Sloan J et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-63.