

Post-menopausal Hormonal 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, smaller, shorter RCT). KEEPS (RCT - await publication)
 - 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 reassured; others point out flaws.
- ◆ 20??
- ??

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DOPS

Danish Osteoporosis Prevention Study

- ◆ n=1006, age 45-58, healthy women
- ◆ RCT, open label, 10 yr + 6 yr follow-up triphasic E2 + norethisterone ± annual visit
norethisterone = norethindrone
- ◆ Results: ↓ primary
 - composite of death, hosp for HF, MI
 - 16/502 vs 33/504; HR=0.48; p=0.015; NNT=30/10yr
 - Results remained through follow-up at 16yrs
- ◆ BIAS & Validity Concerns: Yes
 - Significant!

<http://www.bmi.com/content/345/bmi.e6409>



DOPS

Bias & Validity Concerns

- ◆ Changed 1^o 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-years vs DOPS ~10,000 pt-years
 - trend: ↑ stroke, breast ca, VTE; but ~/ ↓ 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)

<http://www.bmi.com/content/345/bmi.e6409?tab=responses>



KEEPS Aging & Cognition

preliminary - awaiting publication

- ◆ RCT, 727 women, age 42-58, <3yr MP
 - Transdermal E2 50ug/d + Prometrium 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

www.KEEPStudy.org



Post-menopausal Hormone Tx

Big picture Synthesis – Oct 2012

- ◆ For long-term use in older women, potential harms outweigh benefits.
- ◆ For short-term early 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 **KEEPS & DOPS** & strong potential for bias **DOPS**



Hormone - Post-menopausal

RxFiles Drug Comparison Chart – 9th Ed– Pg 90

<http://www.rxfiles.ca/files/uploads/documents/members/GHT-Postmenopausal-RxandHerbal.pdf>

POST-MENOPAUSAL HORMONAL THERAPY

Drug	Formulation	Indication	Contraindications	Warnings	Adverse Effects	Interactions	Monitoring
Estrogen	Oral, Transdermal	Menopausal symptoms, Osteoporosis prevention	History of VTE, Breast cancer, Liver disease	Stroke, VTE, Breast cancer, Endometrial cancer	Hot flashes, Headaches, Nausea	Warfarin, Tamoxifen	Regular monitoring for VTE, Breast cancer
Progestin	Oral, Intrauterine	Menopausal symptoms, Endometrial protection	History of VTE, Breast cancer, Liver disease	Stroke, VTE, Breast cancer, Endometrial cancer	Hot flashes, Headaches, Nausea	Warfarin, Tamoxifen	Regular monitoring for VTE, Breast cancer

- 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

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See also: RxFiles Comparison Charts

Non-Hormonal Therapy for Menopause

Hormone Therapy (HT) for Menopause (MP)

<https://www.rxfiles.ca/RxFiles/uploads/documents/members/CHT-Postmenopausal-RxandHerbal.pdf>