Bioidentical Hormones: What Are the Issues?
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What IS “Bioidentical” (or “Human identical”) Hormone Therapy?

Why is Bioidentical Hormone Therapy Controversial?

Why Consider BioHT vs. “Traditional” HT?

How May BioHT Be Prescribed consistent with high standard of evidence-based care?

Absolute Excess Risks (cases per 10,000 person/years) by Age and Years Since Menopause in Combined WHI Trials (E+P and E-Alone)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age (years)</th>
<th>Years Since Menopause</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>50-59</td>
<td>60-69</td>
</tr>
<tr>
<td>CHD</td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>Total mortality</td>
<td>-10</td>
<td>-4</td>
</tr>
<tr>
<td>Global index†</td>
<td>-4</td>
<td>+15</td>
</tr>
</tbody>
</table>

* P=0.22 compared with age 50-59 years or <10 years since menopause
† Global index is a composite outcome of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture and mortality

Assessing Hormone Levels to Adjust “BioHT” Dosing Provides False Sense of Efficacy & Safety

HT should be prescribed at “lowest effective dose”, guided by symptoms

Serum hormone levels in reproductive aged women vary throughout day and menstrual cycle, so impossible to “match” an individual woman’s “ideal” hormone levels

Checking serum levels with compounded HT products likely necessary for safety, not efficacy, due to risk of excessive dosing

Salivary hormone levels not reproducible, poorly reflect serum levels, affected by diet and other variables

Transdermal Progesterone Cream: Insufficient to Induce a Detectable Effect on Endometrium!!

Luteal phase levels: ~ 5-16 ng/ml

Patch size required: ~ 30 times E2 patch

Study of 64 mg P-cream: slight increase circulating P levels, insufficient to achieve any biological response in endometrium

DBRCT P-cream (32 mg QD) vs. Placebo x 12 weeks

No change in VMS, mood, sexuality, serum lipids, bone markers

Progestosterone levels increased from 0.1 to 0.3 ng/ml

Oral vs. Transdermal Estrogen Delivery

Transdermal E2 does not undergo first-pass hepatic metabolism

Cells of target tissues

HDL, LDL, Triglycerides

Renin substrate

Antithrombin III

C-reactive protein (CRP)

Activated protein C resistance (APCr)
Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women

Current Estrogen Therapy (DVT & PE) (n = 259) Controls (n = 603) Risk VTE compared to non-users (Odds Ratio with 95% CI)

<table>
<thead>
<tr>
<th>Estrogen Therpay</th>
<th>VTE Cases</th>
<th>Controls</th>
<th>Risk VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Estrogen</td>
<td>45</td>
<td>39</td>
<td>4.2 (1.5-11.6)</td>
</tr>
<tr>
<td>Transdermal Estrogen</td>
<td>67</td>
<td>180</td>
<td>0.9 (0.4-2.1)</td>
</tr>
</tbody>
</table>


Risk of Stroke: Transdermal vs. Oral Hormone Therapy

- Population based nested case-control study
- United Kingdom’s General Practice Research Database
- Women aged 50-79 years
- 15,710 cases stroke matched to 59,958 controls

Compared with HT Non-Use:

- Transdermal HT: RR 0.95 (0.75-1.2)
- Low dose E2 patches: RR 0.81 (0.62-1.05)
- High dose E2 patches: RR 1.89 (1.15-3.11)*
- Oral HT (low & high dose): RR 1.69 (1.15-1.42) *

Renou C et al. BMJ 2010; 340:c2519

RR: rate ratio
Low dose E2 patches: <50 mcg
Low dose oral E: CE <0.625 or E2 <2 mg

Transdermal vs. Oral Hormone Therapy

Benefits
- Choice of formulation (patch, gel, spray)
- Convenience (1-2 patches weekly)
- Consistent blood levels
- Multiple & low doses
- “Bioidentical estradiol”
- No ‘first pass hepatic effect’ (limited effect on lipids, clotting factors, free testosterone, thyroid)
- Possible lower risk VTEs & CVA

Drawbacks
- Cost
- Limited E + P combination products
- Topical gels less convenient (daily dosing)
- Patch irritation

Effects of Estrogen or Estrogen/Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Women: PEPI Trial

<table>
<thead>
<tr>
<th>Lipid Parameter (mg/dl)</th>
<th>Placebo</th>
<th>Estrogen (CE) Alone</th>
<th>Estrogen (CE) + MPA (cyclic)</th>
<th>Estrogen (CE) + Progestosterone (cyclic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL</td>
<td>- 1.2</td>
<td>+ 5.6*</td>
<td>+ 1.6*</td>
<td>+ 4.1*</td>
</tr>
<tr>
<td>LDL</td>
<td>- 4.1</td>
<td>- 14.5*</td>
<td>- 17.7*</td>
<td>- 14.8*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>- 3.2</td>
<td>+ 13.7*</td>
<td>+ 12.7*</td>
<td>+ 13.4*</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>- 4.2</td>
<td>- 7.6</td>
<td>- 14.1*</td>
<td>- 7.8</td>
</tr>
</tbody>
</table>

* p<0.001 vs. placebo
** p=0.004 vs. regimens w/ MPA

Writing Group PEPI Trial. JAMA 1995; 273:199

FDA Approved Formulations of “Bio-HT”

**ESTRADIOL**
Systemic doses of estradiol for treatment of hot flashes
- Oral tablet: Estrace, generics
- Skin patch: Alora, Clima, Esclim, Menostar, Vivelle Dot
- Estraderm, generics
- Skin gel/cream: EstroGel, Elestrin, Divigel, Estrasorb
- Skin spray: Evamist
- Vaginal ring: Femring

**PROGESTERONE**
Systemic doses of progesterone to protect endometrium
- Oral tablet: Prometrium

*E3N French epidemiologic cohort study*
*Self-administered questionnaires 1990-2002*
*50,377 postmenopausal women w/ up to 12 years F/U*

Compared with HT Never-Use:

- Estrogen alone: RR 1.29 (1.02-1.65)*
- Estrogen + progesterone: RR 1 (0.83-1.22)
- Estrogen + dydrogesterone: RR 1.16 (0.94-1.43)
- Estrogen + other progestagens: RR 1.69 (1.50-1.91)*

No association with risk according to route of estrogen administration (oral or transdermal)

Low doses of estradiol for treatment of vaginal dryness and dyspareunia

- Vaginal cream: Estrace vaginal cream
- Vaginal ring: Estring
- Vaginal tablet: Vagifem

FDA Approved Low Dose Vaginal Formulations of “Bio-HT”


Conclusions: Bioidentical Hormone Therapy

- HT is most effective treatment for bothersome VMS & benefits generally outweigh risks for healthy, symptomatic women at menopause transition
- “Bioidentical HT” (estradiol & progesterone) available with FDA approved products
- Consider transdermal estradiol option
- Low dose topical FDA approved “bioidentical” estradiol products available for vaginal dryness & dyspareunia
- NO benefit & significant potential risk with use of compounded HT

Serum Estradiol Levels with Vaginal Estradiol (10 mcg) Tablet Use

The Naked Truth About Bioidentical Hormones

Bioidentical Hormone Therapy: Custom-Compounded vs. Government-Approved

OR

Menopause Society