Menopause: Hormones, Hot Flashes, Dryness, Oh My!

G. Wright Bates, M.D.
Professor and Director
Division of Reproductive Endocrinology and Infertility
University of Alabama at Birmingham

Objectives
- Review the pros and cons of hormone replacement therapy.
- Recommend properly administered hormone replacement therapy as a treatment therapy.
- Highlight use of technology for optimizing patient care

The speaker has no conflict of interest or relevant financial disclosures
By the year 2025, the number of postmenopausal women is expected to rise to 1.1 billion worldwide.

**Menopause**

- “Permanent cessation of menstruation following decline in ovarian function”
- Mean age: 51.4 years
- Range: 35 - 57 years
- Perimenopause
  - Highly variable
  - Can last 2 - 8 years

**Possible Results of Menopause**

- Early:
  - Hot flashes
  - Sweating
  - Insomnia
  - Psychological symptoms

- Intermediate:
  - Vaginal atrophy
  - Dyspareunia
  - Urge/stress incontinence
  - Skin atrophy

- Late:
  - Osteoporosis
  - Coronary heart disease
  - Dementia
Hot Flushes

- Hot flushes are the most common symptom of perimenopause: 68% to 93% of women.
- 84% moderate to severe.
- Hot flushes may be characterized by visibly reddened skin, excessive perspiration, dizziness, headaches, palpitations, and may be associated with chills.
- 31% experience hot flush prior to menstrual changes.
- These symptoms usually last 6 months to 5 years.
- Up to 1 in 5 women experience flushing for decades (9% at 72 year old women in Sweden).


Kronenberg F. Ann NY Acad Sci. 1990;592:52-86.

Ethnic Predisposition

- Prevalence: African-American > Hispanic > Caucasian > Chinese > Japanese
- U.S. > Australia > Sweden > China > Mexico
- Symptoms decreased in all postmenopausal women with time

Physiology of Vasomotor Symptoms

- Decreased Estrogen and Inhibin
- Dysfunction of Thermoregulation: increased core temp narrowed thermoregulatory zone
- Correlated poorly with Estrogen levels or LH pulses
- Disruption of noradrenergic system
- Increased opiate release (PLACEBO 51%)
- Etc. (substance P, POMC, somatostatin)
Proposed Therapies for Menopausal Symptoms Relief

- Accupuncture
- Muscle Relaxation exercises
- Alpha wave EEG biofeedback
- Magnetic Therapy
- Dietary Modification
- Mind Control

Accupuncture

- Randomized placebo (sham surgery) controlled trial
- Acupuncture was performed on 163 women, and the sham procedure on 164
- 10 treatments for 8 weeks
- Mean HF scores after acupuncture were 15.36 and after sham treatment 15.04
- Mean difference 0.33 (95% confidence interval [CI], −1.87 to 2.52; P = .77)

No difference in vasomotor symptoms

*Ann Int Med.* Published online January 18, 2016

Menopausal Symptoms: Lifestyle Modifications

- Keep Cool
- Lose Weight
- Continue Exercise
- Stop Smoking (especially THC)
- Relaxation Techniques
  - Paced Respirations
    - Meditation
    - Massage
  - Yoga
  - Leisure Baths
Substances Lacking Evidence for Menopausal Symptoms Relief

- Agrimony
- Catnip
- Chamomile
- Damiana
- Dandelion
- Vitamin E
- Fenugreek
- St John’s Wort
- Gotu kola
- Hops
- Licorice root
- Passion flower
- Sage
- Sarsaparilla
- Witch Hazel
- Chasteberry
- Ginkgo Bilbo
- Valerian

Antidepressants

- Paroxetine (Paxil) 7.5* – 20 mg qD
  - 67% reported decreased number of events (37%)
  - 75% reported decreased severity
  - 7.5 mg dose FDA approved for vasomotor Sx

- Fluoxetine (Prozac) 20 mg qD
  - Decreased incidence and severity of Hot Flashes (50 vs. 36%) in patients over 4 weeks with h/o breast CA

- Venlafaxine (Effexor XR)
  - Combined serotonin AND norepinephrine reuptake inhibitor
  - Effective for Depression and Anxiety (Insomnia, PMDD)
  - Rapid onset of action
  - Good side-effect profile
Antidepressants

- Venlafaxine (Effexor XR)
  - 3 trials demonstrate efficacy
  - RCT (n=155) Patients on 75mg a day experienced over a 60% reduction in hot flashes by 4 weeks (placebo 27%, 37.5mg 37%)
  - Overall improvements in Quality of Life

Non-hormonal Drugs

Lacking proven efficacy
- Methyldopa
- Clonidine
- Bellergal (combination ergotamine, belladonna alkaloids, phenobarbitol)

Demonstrated Efficacy in some cases
- Gabapentin

WHI Results

Overall Relative and Attributable Risk for Women 50 to 80 Years of Age

<table>
<thead>
<tr>
<th>Health Event</th>
<th>Overall Hazard Ratio</th>
<th>Confidence Interval</th>
<th>Attributable Risk per 10,000 Women/Year</th>
<th>Attributable Risk per 10,000 Women/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.29</td>
<td>1.02-1.63</td>
<td>0.65-1.97</td>
<td>7</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.26</td>
<td>1.00-1.59</td>
<td>0.22-1.52</td>
<td>5</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41</td>
<td>1.07-1.85</td>
<td>0.46-2.31</td>
<td>5</td>
</tr>
<tr>
<td>VTE</td>
<td>2.11</td>
<td>1.81-2.52</td>
<td>0.53-2.55</td>
<td>13</td>
</tr>
<tr>
<td>DIx</td>
<td>2.07</td>
<td>1.67-2.57</td>
<td>0.51-3.75</td>
<td>13</td>
</tr>
<tr>
<td>PE</td>
<td>2.13</td>
<td>1.90-4.56</td>
<td>0.59-4.56</td>
<td>8</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63</td>
<td>0.43-0.92</td>
<td>0.22-1.24</td>
<td>6</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.66</td>
<td>0.46-0.98</td>
<td>0.03-1.33</td>
<td>5</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76</td>
<td>0.69-0.86</td>
<td>0.02-0.89</td>
<td>44</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; PE = pulmonary embolism

MenoPro / NAMS

- Health Care Provider or Patient
- Age
- Moderate – Severe Hot flashes
- Tried behavior modification for 3 months
- Patient interested in HT
- free of contra-indications
HT Contraindications

- Unexplained vaginal bleeding
- Liver disease
- Clotting disorder
- Untreated hypertension
- History of estrogen dependent cancer
- History of CHD, stroke or TIA
- $\geq 1$ 1st degree relatives with breast cancer (Increased risk of breast cancer)

HT Considerations

- Less than 10 years passed menopause
- Hysterectomy
- Race
- Smoker
- HTN: Systolic BP
- Diabetes
- Cholesterol medication: Total and HDL

CVD Risk Score over 10 years

Recommendations

NAMS 2015: WHI 50 – 59 yoa

<table>
<thead>
<tr>
<th>CEE-MPA Trial</th>
<th>CEE-Alone Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>23</td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td>33</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>11</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>4</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>3</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>21</td>
</tr>
</tbody>
</table>
NAMS 2015

Systemic Hormone Therapy after 65:

- Lowest effective dose
- If woman who has persistent bothersome menopausal symptoms
- Benefits of menopause symptom relief outweigh the risks

“Use of HT should be individualized and not discontinued solely based on a woman’s age”


Patients with a low CVD Risk Score appear to be candidates for either oral or transdermal estrogen therapy. Women with hysterectomy are candidates for estrogens-alone therapy.

Estrogen Therapy options and dosages

Duration of treatment
Recommendation if patient has metabolic syndrome

Handout on risks/benefits of HT

Email summary and handout to patient and/or yourself

Oral estrogen products

<table>
<thead>
<tr>
<th>Active ingredient(s)</th>
<th>Product Name(s)</th>
<th>Dosages (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β-estradiol*</td>
<td>Estrace</td>
<td>0.5, 1.0, 2.0</td>
</tr>
<tr>
<td>Conjugated estrogens</td>
<td>Premarin</td>
<td>0.3, 0.45, 0.625, 0.9, 1.25</td>
</tr>
<tr>
<td>Synthetic conjugated estrogens, a</td>
<td>Cenestin</td>
<td>0.3, 0.45, 0.625, 0.9, 1.25</td>
</tr>
<tr>
<td>Synthetic conjugated estrogens, b</td>
<td>Enbyel</td>
<td>0.3, 0.45, 0.625, 0.9, 1.25</td>
</tr>
<tr>
<td>Conjugated estrogens, CED (synthetic)</td>
<td>E.S.E.</td>
<td>0.3, 0.625, 0.9, 1.25</td>
</tr>
<tr>
<td>Esterified estrogens</td>
<td>Norexel</td>
<td>0.3, 0.625, 1.25, 2.5</td>
</tr>
<tr>
<td></td>
<td>Exilene</td>
<td>0.3, 0.625</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Oestrel</td>
<td>0.025, 0.075 estriol; 1.25 (1:5), 2.5 (5:1)</td>
</tr>
<tr>
<td></td>
<td>Estrovet</td>
<td>0.025 (0.75), 1.5 (0.6), 5.0 (0.0)</td>
</tr>
</tbody>
</table>

Oral Estrogens

Pros
- Familiar, easy
- Beneficial effect on HDL, LDL, and total cholesterol
- Relatively low cost
- Large amount of data
- Can measure estradiol levels with some preparations

Cons
- Risk of thrombosis, stroke
- Decreased libido
- Increased triglycerides, CRP, hepatic proteins

When to consider transdermal?

- First Line??
- Obesity
- Diabetes
- Metabolic Syndrome (3 or more)
  - Waist circumference >35 inches
  - Triglycerides >150 mg/dL
  - HDL <40 mg/dL
  - BP >130/95
  - FBS >110 mg/dL

(ATA III National Cholesterol Ed Program 2010)

Transdermal estrogen products

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>Product Name</th>
<th>Dosage (mg Ev/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (E2)</td>
<td>Premarin</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
<tr>
<td></td>
<td>EstroGel</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
<tr>
<td></td>
<td>Estradiol</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
<tr>
<td></td>
<td>Estring</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
<tr>
<td></td>
<td>Ovessa</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
<tr>
<td></td>
<td>Vivelle</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
<tr>
<td></td>
<td>Vivelle-Oral</td>
<td>0.08, 0.16, 0.25, 0.375, 0.75, 1.5, 2 mg/week</td>
</tr>
<tr>
<td></td>
<td>Kroehler</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
<tr>
<td></td>
<td>Various generics</td>
<td>0.025, 0.05, 0.075, 0.1, 0.25/week</td>
</tr>
</tbody>
</table>

Transdermal gel

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>Product Name</th>
<th>Dosage (mg Ev/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (E2)</td>
<td>Ovessa</td>
<td>0.25, 0.5, 1.0, 1.5</td>
</tr>
<tr>
<td></td>
<td>Empress</td>
<td>0.75 (use lowest effective)</td>
</tr>
<tr>
<td></td>
<td>Progynon Gel</td>
<td>0.52 (use lowest effective)</td>
</tr>
</tbody>
</table>

Transdermal patch

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>Product Name</th>
<th>Dosage (mg Ev/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (E2)</td>
<td>Estraderm</td>
<td>0.010 (6 mg patch/8 hours, use lowest effective)</td>
</tr>
</tbody>
</table>

Transdermal spray

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>Product Name</th>
<th>Dosage (mg Ev/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (E2)</td>
<td>Estraceal</td>
<td>1.50 (1std init. adjust dosage by response)</td>
</tr>
</tbody>
</table>
Transdermal

**Pros**
- Avoids hepatic first-pass effect
- Less increase of triglycerides than oral ET
- Less effect on C-reactive protein than oral ET
- Less risk of reducing libido than oral ET
- Topical emulsion is moisturizing
- Perhaps less risk of thrombosis than oral ET

**Cons**
- Patch-adhesive sensitivity/residue
- Patch is less private
- Usually relatively higher cost
- Gels, creams can possible transfer to others

“Equivalent” Dosing

<table>
<thead>
<tr>
<th>Oral</th>
<th>Transdermal/Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated estrogens</td>
<td>Estradiol patch</td>
</tr>
<tr>
<td>Synthetic conjugated estrogens</td>
<td>1.5 mg/2 metered doses</td>
</tr>
<tr>
<td>Estriol estrogens</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Estradiol (0.75 mg)</td>
<td>0.015 mg</td>
</tr>
<tr>
<td>Estradiol (0.015 mg)</td>
<td>0.3 mg</td>
</tr>
</tbody>
</table>

Vaginal

**Pros**
- Vaginal benefit at lower dose
- Low-dose therapy typically avoids adverse systemic effects

**Cons**
- Increase in vaginal discharge
- Some may consider less convenient to use
- Lack of long-term uterine safety data for low-dose products
Progestogens

**Pros**
- Reduced AEs of estrogen on endometrium
- Some progestogens reduce AEs of oral estrogen on triglycerides
- Progestosterone dosed at night can decrease insomnia, improve sleep

**Cons**
- Some progestogens increase risk of breast cancer
- Some progestogens reduce beneficial effect of oral estrogen on HDL-C
- AEs such as bloating
- Dysphoric effect for some women

HT Starting Dosages

**Lower daily doses used with systemic ET:**
- 0.3 mg oral CE
- 0.5 mg oral micronized 17ß-estradiol
- 0.014-0.025 mg transdermal 17ß-estradiol patch

**Typical lowest doses of progestogen:**
- 1.5 mg oral MPA
- 0.1 mg oral norethindrone acetate
- 0.5 mg oral drospirenone
- 50-100 mg oral micronized progesterone

Osphena

- SERM indicated for dyspareunia
- 3 out of 4 women reported improved symptoms (72% vs. 54%)
- Improved tissue health
- 60mg po qD with food


Copyright 2008

Menopause. 2015;22(7):1-11
www.osphenahcp.com 8/23/15
Oh my......Little Pink Pill
Female Viagra

- Flibanserin (Addyi)
- Alters serotonin, dopamine, norepinephrine
- PREMENOPAUSE
- COMPLETE AVOIDANCE of alcohol
- increased coital episodes per month by 0.5
- 10% experienced increase satisfaction
- Prescriber certification required

www.addyirems.com, 1/22/16

“Female Viagra”
Addyi® Flibanserin

- Premenopausal HSDD
- 3rd time the charm
- Risk Evaluation and Mitagation Strategy

FDA Approval of Flibanserin — Treating Hypoactive Sexual Desire Disorder

Perspective

Prescriber Certification Confirmation

To: Gordon Bates  
University of Alabama at Birmingham  
Phone: 205-934-1030  
Fax: (205) 996-5070  
Email: gbates@uabmc.edu

From: Addyi REMS Program  
Phone: 1-844-233-0415  
Fax: 1-844-233-0415

Date: 01/19/2016

Dear Gordon Bates,

This correspondence confirms your successful certification in the Addyi REMS Program.

Certification ID: P080604317693
DHEA
Daily 0.5% DHEA (6.5 mg) vaginal supp (n=325) vs placebo (n=157) for 12 weeks.
• pain with sex (0 to 3) decreased 0.36 (P = .0002)
• improved vaginal pH-0.66 lower (P < .0001).
• Patient with mod – severe dryness at baseline experience greatest benefit
• 86% to 121% improvements in vaginal secretions, lining thickness, tissue color
  (P < .0001)

Menopause December 28, 2015

Osteoporosis
• Identify risk factors
  – AGE
  – Postmenopausal (especially POF)
  – Thin, Caucasian
  – Steroid use
  – Smoking, Alcohol
  – Sedentary
  – Previous fracture
  – Family history
• Screen
  – DEXA (T score, Z score)
Management of Osteoporosis

- Lifestyle modification – Weight Bearing Exercise
- Calcium (>1200 mg) and Vitamin D (800 mg)
- Hormone therapy
- Bisphosphonates – Antiresorptives
  (alendronate, ibandronate, risedronate, zoledronate)
- SERMs
- PTH therapy
- Calcitonin
- Combinations

SERM and CEE

- Bazedoxifene 20 mg/CEE 0.45-0.625 daily (Duavee)
- Indicated for Post menopausal osteoporosis and hot flashes
- Take with Calcium and Vit D
- Avoids need for progesterone
- Costly ~3 dollars a pill

Effect of Delayed Initiation of ET on Menopausal Bone Loss
NAMS

Osteoporosis:

HT reduces the risk of postmenopausal osteoporotic fractures including hip fractures (even in women without osteoporosis)

HT approved for prevention of osteoporosis

NAMS

Vaginal Symptoms:

HT is the most effective treatment for vulvar and vaginal atrophy
- Less dyspareunia, more coital satisfaction
- Not recommended for decreased libido
- Improved urge incontinence
- ? Effect on stress incontinence or overactive bladder?
HT: where do we go from here?

- Individualize based on indication
- Inform of risk AND benefits
- Initiate Early