Disclosure

• I am a litigation consultant to a law firm contracted with Bayer Healthcare relating to the Mirena IUD
Consequences of Estrogen Loss

• Vasomotor symptoms → hot flashes, night sweats
• Neuro-behavioral → sleep problems, memory loss
• Genitourinary Syndrome of Menopause (GSM)
  – Vaginal dryness, painful sex
  – Burning on urination; urinary urge incontinence
• Bone loss → increased hip, vertebral fracture risk
• Increased risk of heart attack, stroke (vs. premenopause)
Vasomotor Symptoms (VMS)

- Experienced by 75% percent of menopausal women
  - May start during the peri-menopause
  - Cluster in the 2-year window before and after the FMP
  - 25% have hot flushes > 5 years after menopause
- Smoking and obesity are risk factors
- Ethnic and racial differences
  - More common in African-American women (46%)
  - Less common in Chinese (21%), Japanese (18%)
  - See “SWAN” study for more detail
Duration of Menopausal VMS Over the Menopause Transition

• Avis NE, et. al, for SWAN. JAMA Int Med. Feb 16, 2015
• 3302 women 7 US sites; 1996-2013, median 13 visits
• Findings
  – Median VMS duration was 7.4 years
  – Median post-FMP persistence was 4.5 years
  – Premenopausal or early perimenopausal when they first reported frequent VMS had the longest...
    • Total VMS duration (median, 11.8 years)
    • Post-FMP persistence (median, 9.4 years)

FMP: final menstrual period
Short term Treatment of Menopausal Symptoms

- Lifestyle changes
- Botanicals and PhytoSERMs
- Non-hormonal Rx medications
- Hormone Therapy (MHT)
Hot Flashes: Lifestyle Changes

- Exercise at least 3-4 days/week
- Relaxation therapy (e.g., yoga)
- Cool room temperature, esp. at night
- Dress in layers (easier to remove outer layers if warm)
- Avoid hot and spicy foods
- Avoid cigarettes
- Minimize alcohol
Hot Flashes: Botanicals and PhytoSERMs

*Probably* better than placebo
- Black cohosh

*No evidence of efficacy (no better than placebo)*
- Soy isoflavones
- Red clover isoflavones
- Evening primrose oil
- Dong quai (as monotherapy)
- Ginseng
- Vitamin E
- Chasteberry (Vitex)
Black Cohosh

- Not an estrogen or SERM
- Marketed as a “supplement”, not a prescription drug
- Remifemin, Estroven, or other single or combo products
- Dosage: 40-80 mg daily
- Adverse effects: headaches, stomach discomfort, heaviness in legs
Hot Flashes: Black Cohosh

- Positive effect of black cohosh vs placebo
  - 50-60% of women improve vs 30% with placebo
  - Improvement is less than with estrogen
- Relatively little risk of adverse effects
- Reasonable first-line choice for women
  - With mild menopausal symptoms
  - Who feel strongly about avoiding hormones
  - Who are willing to use medications that are not “proven” effective or regulated by FDA
### Non-Hormonal Hot Flash Therapies

<table>
<thead>
<tr>
<th></th>
<th>% treated patients with &gt;50% ↓HF</th>
<th>% placebo patients with &gt;50% ↓HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>54-70%</td>
<td>30%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>50-76%</td>
<td>35-57%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>40-56%</td>
<td>21-41%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>46-84%</td>
<td>27-47%</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>55%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*J Clinical Oncology 2009*

Paroxetine 7.5 mg (Brisdelle®) is the only SSRI/SNRI that is FDA approved for this indication.
Menopausal hormone therapy is the most effective treatment for vasomotor symptoms

Options include

- Estrogen alone
- Estrogen-progestogen
- Estrogen-bazedoxifene
- Progestogen alone, or
- Combined OCs in women requiring contraception
## NAMS Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td>Estrogen (E) therapy</td>
</tr>
<tr>
<td>EPT</td>
<td>Combined E+P therapy</td>
</tr>
<tr>
<td>HT</td>
<td>Hormone therapy (ET, EPT)</td>
</tr>
<tr>
<td>MHT</td>
<td>Menopausal hormone therapy</td>
</tr>
<tr>
<td>Progestogen</td>
<td>Progesterone or progestin (P)</td>
</tr>
<tr>
<td>CC-EPT</td>
<td>Continuous-combined E+P therapy</td>
</tr>
<tr>
<td>CS-EPT</td>
<td>Continuous-sequential E+P therapy</td>
</tr>
</tbody>
</table>

# Prescription HT Options: ET and EPT

<table>
<thead>
<tr>
<th>Oral</th>
<th>Transdermal</th>
<th>Intravaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Micronized estradiol</td>
<td>• Patches</td>
<td>• Creams</td>
</tr>
<tr>
<td>• Conjugated equine estrogens (CEE)</td>
<td>• Gels</td>
<td>• Intravaginal tablet</td>
</tr>
<tr>
<td>• Synthetic conjugated estrogens</td>
<td>• Emulsion</td>
<td>• Rings</td>
</tr>
<tr>
<td>• Esterified estrogens</td>
<td>• Spray</td>
<td></td>
</tr>
<tr>
<td>• Estropipate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Estradiol acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CC-EPT</td>
<td>• E+P combination patches</td>
<td></td>
</tr>
<tr>
<td>• CS-EPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly Regimens</td>
<td>Month 1</td>
<td>Month 2</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Estrogen Therapy (ET)</td>
<td><img src="#" alt="Red Box" /></td>
<td><img src="#" alt="Red Box" /></td>
</tr>
<tr>
<td>Estrogen</td>
<td><img src="#" alt="Red Box" /></td>
<td><a href="#">Yellow Box</a></td>
</tr>
<tr>
<td>Continuous combined (CC) EPT</td>
<td><img src="#" alt="Red Box" /></td>
<td><img src="#" alt="Red Box" /></td>
</tr>
<tr>
<td>Estrogen</td>
<td><img src="#" alt="Red Box" /></td>
<td><img src="#" alt="Yellow Box" /></td>
</tr>
<tr>
<td>Progestin</td>
<td><img src="#" alt="Yellow Box" /></td>
<td><img src="#" alt="Yellow Box" /></td>
</tr>
<tr>
<td>Continuous-sequential (CS) EPT</td>
<td><img src="#" alt="Red Box" /></td>
<td><img src="#" alt="Yellow Box" /></td>
</tr>
<tr>
<td>Estrogen</td>
<td><img src="#" alt="Red Box" /></td>
<td><img src="#" alt="Yellow Box" /></td>
</tr>
<tr>
<td>Progestin 14d</td>
<td><img src="#" alt="Yellow Box" /></td>
<td><img src="#" alt="Yellow Box" /></td>
</tr>
<tr>
<td>Continuous-pulsed (CP) EPT</td>
<td><img src="#" alt="Red Box" /></td>
<td><img src="#" alt="Yellow Box" /></td>
</tr>
<tr>
<td>3d</td>
<td><img src="#" alt="Yellow Box" /></td>
<td><img src="#" alt="Yellow Box" /></td>
</tr>
</tbody>
</table>

Legend: Red Box indicates Estrogen Therapy, Yellow Box indicates Progestin Therapy.
Choice of HT Regimen

• If no uterus: **estrogen only**
• If uterus present: **estrogen + progestogen**
  – Goal is to avoid vaginal bleeding entirely, or, at least, to make it predictable
• Endometrial activity predicts bleeding pattern
  – **Recent spontaneous or induced bleeding**
    • Use continuous sequential
  – **No bleeding for >2-3 cycles**
    • Use continuous combined
Choice of Estrogens

- Start *low dose* transdermal or oral estrogen
- If suboptimal response, modify by...
  - Change the estrogen dose (upward)
  - Change the estrogen preparation
  - Change delivery systems (oral ↔ transdermal)
  - Consider an estrogen + androgen (Covaryx)
- Injectable estrogen not recommended
  - Dosage equivalencies are not known
  - Estrogen cannot be discontinued easily
Hormone Therapy Dosages

• Therapeutic goal is lowest effective estrogen dose (plus low dose progestogen) c/w goals, benefits, risks

• Lower doses better tolerated, may have more favorable benefit-risk ratio than standard doses

• Additional local ET may be needed for persistent vaginal symptoms

HT Starting Dosages

- **Estrogen therapy (ET)**
  - 0.3 mg oral conjugated estrogen (CE)
  - 0.5 mg oral micronized 17ß-estradiol
  - 0.014-0.025 mg transdermal 17ß-estradiol patch

- **Progestogen therapy (PT)**
  - 1.5 mg oral MPA
  - 0.1 mg oral norethindrone acetate
  - 0.5 mg oral drospirenone
  - 50-100 mg oral micronized progesterone

HT Standard Dosages

- **Estrogen therapy**
  - 0.625 mg oral conjugated estrogen (CE)
  - 1.0 mg oral micronized 17β-estradiol
  - 0.0375-0.050 mg transdermal 17β-estradiol patch

- **Progestogen therapy**
  - 2.5 mg oral MPA (CC) or 5.0 mg MPA (CS)
  - 100 mg oral micronized progesterone (CC) or 200 mg PO at bedtime (CS)

Kaunitz AM, Manson JE. Obstet Gynecol 2015;126(4):859
HT Routes of Administration

- No clear benefit of one route of administration
- Transdermal ET has lower DVT/PE risk than oral ET
- Local ET preferred when solely vaginal symptoms
- With either route, progestogen is required for endometrial protection from unopposed systemic ET

Bazedoxifene 10mg with CE 0.45 mg
Duavee®

- FDA approved tissue selective estrogen receptor modulator (SERM) plus conjugated estrogen
- Progestin-free
- Reduces VMS frequency and severity
- Prevents loss of bone mass; treats GSM
- No increase in endometrial hyperplasia
- Breast tenderness and overall safety similar to placebo
- **USE:** Combined HT in women who don’t tolerate progestins

Hormonal Contraceptives in Perimenopause

- Low-dose OCs ($\leq 30$ mcg EE) prescribed for relief menopausal symptoms and prevention of pregnancy
  - Other benefits: cycle control, fewer ovarian cancers
- Patch or ring may be helpful, but no studies
- LNG-IUS used with oral, transdermal, or vaginal estrogen prevents endometrial hyperplasia
- LNG-IUS and DMPA alone will not address VMS

Compounded Hormone Therapy

• The *marketing* of compounded hormonal therapy
  – Only bioidentical hormones are used
  – Combination of 2 or 3 estrogens is more “natural”
  – Dosage is tailored to the individual
  – More “pure” than commercial products
  – Safer delivery systems (no dyes, etc)

• The reality
  – The *same* hormones are used in commercial and compounded 17b-E₂ and progesterone
Compounded Hormone Therapy

Compounded hormones will probably work about as well as commercial HT products, but...

- The value of adding $E_1 + E_3$ has not been evaluated
- Progesterone skin cream is not absorbed
- Compounded hormone doses are not standardized
- Salivary hormone levels are not useful
- FDA-approved HT products will offer
  - Bioidentical hormones
  - Choice of delivery systems
  - Formulary coverage/ lower out-of-pocket costs
Treatment of Hot Flashes

• If mild symptoms, try lifestyle, CAM therapy
• Indications for hormone therapy
  – Moderate or severe symptoms
  – Non-hormonal treatments have failed
  – No interest in non-hormonal therapy
• When estrogen can’t be used, offer
  – SSRI or SNRI
  – Gabapentin
  – Progestins alone
• Attempt discontinuation after 2 years
Treatment of Sleep/ Irritability Symptoms

- Evaluate other causes of sleep disturbances
  - Insomnia, sleep apnea, restless leg syndrome, depression
- If mild symptoms
  - Lifestyle change, CAM therapy
- If severe symptoms or no response to above
  - Low dose HT, then titrate upward
  - If mood swings, transdermal E preferred
- Depression component, or no response to HT
  - SNRI or SSRI
Genitourinary Syndrome of Menopause (GSM)

- **Vaginal changes**
  - Vaginal spotting or bleeding
  - Vaginal dryness
  - Dyspareunia: poor lubrication, less vaginal elasticity, skin irritation, introital shrinkage
  - Negative impact on sexual function, relationships, QOL

- **Bladder and urethra changes**
  - Urgency, frequency, dysuria, urge incontinence
  - Often misdiagnosed as bladder infection; tests negative
  - No effect on stress incontinence or pelvic organ prolapse
GSM: Treatment

- OTC lubricants
  - Intimate lubricants: Astroglide, Sliquid, etc
  - Vaginal moisturizers: Replens
- Local estrogen therapy
  - Cream, vaginal tablet, vaginal ring
- Systemic HT (when prescribed for VMS)
- Oral ospemiphene
# Topical (Vaginal) Estrogen

<table>
<thead>
<tr>
<th>Composition</th>
<th>Brand Name</th>
<th>Dose and sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal cream 17β-Estradiol</td>
<td>Estrace® Vaginal Cream</td>
<td>Initial: 2.0-4.0g/d for 1-2 wk Maintenance: 1.0g/d (0.1 mg/g)</td>
</tr>
<tr>
<td>Vaginal cream conj estrogens</td>
<td>Premarin® Vaginal Cream</td>
<td>0.5-2.0 g/d or twice/wk (0.625 mg/g)</td>
</tr>
<tr>
<td>Vaginal ring 17β-estradiol</td>
<td>Estring®</td>
<td>Ring contains 2 mg releases 7.5 mcg/d for 90 d</td>
</tr>
<tr>
<td>Vaginal ring Estradiol acetate</td>
<td>Femring® (Systemic dose and indication)</td>
<td>Systemic dose ring for 90 d 12.4mg releases 50mcg/d 24.8mg releases 100mcg/d</td>
</tr>
<tr>
<td>Vaginal tablet E2 hemihydrate</td>
<td>Vagifem® 10mcg</td>
<td>Initial: 1 tablet/d for 2 wk Maintenance: 1 tab 2x /wk</td>
</tr>
</tbody>
</table>

NAMS Position Statement Menopause. 2013:20(9)
GSM and Hormone Therapy

• When HT is considered solely for this indication, vaginal estrogen is recommended
• Progestogen generally *not indicated* with low-dose, local vaginal estrogen
• Vaginal lubricants often improve vaginal dryness and painful intercourse

Ospemiphene (Osphena®)

- Selective estrogen-receptor modulator (SERM)
  - No direct estrogen effect
  - Only FDA approved SERM for mod-severe dyspareunia

- **Improvement in...**
  - Dyspareunia
  - Vaginal maturation index
  - Vaginal pH
  - Vaginal dryness

- **USE:** alternative to topical vaginal estrogen for GSM

Urinary Tract Symptoms: Vaginal Estrogen

- Provides greater benefit than non-hormonal treatments
- Improves, may cure
  - Overactive bladder
  - Urge incontinence
  - Recurrent urinary tract infections
  - Urethritis (irritative) symptoms
- No effect on stress incontinence (oral ET may worsen it!)
- No HT product FDA approved for urinary health in US

Moderate-Severe Hot Flashes (inadequate response to lifestyle modifications)

GSM sx?

Yes

Free of CI?

Yes

Try vaginal E₂ or ospemiphene

No

No

Avoid HT

No

Yes

Intimate lubricants + moisturizers

Yes

Wants HT? No CI?

CV risk
Low (5%)
Mod (5-10%)
High (>10%)

Yrs since MP
<5Y
6-10Y
>10Y

HT OK
HT OK*
Avoid

Avoid
Avoid
Avoid

Wants SSRI? No CI?

Yes

Yes

Try SSRI

No

Try GBP

CI: Contra-Indication
HT: Hormone therapy


* Consider transdermal hormone therapy
HT and Fracture Prevention

Pros
- Good data on fracture prevention (mainly 2º prevention)
- Relatively lower cost than bisphosphonates
- Less concern of adverse effects with ET alone (vs EPT)

Cons
- Requires long term use and surveillance
- Post-menopausal bleeding can be troublesome
- Increased risk of breast cancer after 5 years of use

Utility
- Fracture prophylaxis if using HT for another indication
- Otherwise, consider bisphosphonates as first line
HT and “Quality of Life”

• RCTs and retrospective studies show that HT has no effect on “quality of life” measures

• Many woman who wean from HT state that they “feel worse”...even after 20 years after menopause!

• Conventional wisdom
  – In women who “feel better on/ worse off” of HT, continue low dose HT if few or no risk factors
  – When (& how often) to re-attempt wean uncertain
  – Don’t start HT for solely for improving QOL
HT Discontinuance and Symptom Recurrence

• After 2 years of use, recommend drug vacation to determine whether HT is still needed
• Vasomotor symptom recurrence similar whether tapered or abrupt discontinuance
  – 25-50% chance of symptoms recurring when HT discontinued
• Decision to resume HT must be individualized

A decade after the Women's Health Initiative—the experts do agree

Cynthia A. Stuenkel, M.D., N.C.M.P., Margery L. S. Gass, M.D., N.C.M.P.,
JoAnn E. Manson, M.D., Dr.PH., N.C.M.P., Rogerio A. Lobo, M.D.,

- Systemic HT is an acceptable option for healthy women up to age 59 or <10 years of menopause and who are bothered by moderate to severe menopausal symptoms
- Individualization is key in the decision to use HT