What’s New in Management of the Menopause?

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Menopause Terms

- Menopause
  - The date of a woman’s final menstrual period (FMP)
  - After the FMP, must have 12 months without vaginal bleeding to establish the diagnosis of menopause
- Due to depletion of eggs in the ovaries
  - No longer at risk of pregnancy
  - Loss of estrogen production from the ovary
  - Reduction in testosterone production

Menopause Terms

- Perimenopause
  - Interval from the onset of menopausal symptoms until 1 year after the final menstrual period
- Menopausal Transition (MT)
  - The time before the FMP when menstrual cycles exhibit variability between cycles

Causes of Menopause

- Natural menopause
  - Menopause symptoms + no menses for 12 months
  - Biochemical markers of menopause
    - > 45 years old: FSH elevated, estrogen reduced
    - < 45 years old: FSH and LH elevated
- Induced menopause
  - Surgical removal of the ovaries
  - Ovarian failure due to drugs or radiation therapy
- Premature menopause
  - Ovarian failure before 40 years of age
Age of Menopause

- Average age in US: 51.4 years old; range: 40-58 y.o.
- Largely genetically determined
- Not related to race, number of pregnancies, height, weight, socioeconomic status, or age at first period
- Cigarette smoking lowers age of menopause by 1-2 years

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)

- Hot flushes (aka: hot flash)
  - Sudden sense of intense body heat
    - Start in trunk → neck → face
  - Skin flush (redness of face due to vessel dilation)
  - Sweating
  - Seconds to several minutes; up to 20-30 minutes
  - Worse at night, but may occur at any time

Vasomotor Symptoms

- Experienced by 75% percent of menopausal women
  - May start during the peri-menopause
  - Most women experience for 2 years, then wane
  - 25% have hot flushes > 5 years after menopause
- Ethnic and racial differences
  - More common in African-American women
  - Less common in Chinese, Japanese women
- Smoking and obesity are risk factors

Neuro-behavioral Changes

- Restful sleep disturbances
  - Insomnia, easy awakening
  - Less deep (REM) sleep due to awakening from hot flashes
- Irritability, fatigue, poor concentration
  - Probably due to sleep disturbances

Neuro-behavioral Changes

- Short-term memory problems
  - Forgetfulness, reduced computational skills
- Emotional swings; anxiety
  - But, depression is not related to estrogen deficiency
- Changes in sex-drive
  - Often less: reduced testosterone, sexual pain
  - Can be more: no pregnancy risk, new partner
- Difficult to separate psychological effects due to estrogen loss, aging, social changes, poor sleep
Genitourinary Syndrome of Menopause (GSM)

- Vaginal changes
  - Vaginal spotting or bleeding
  - Vaginal dryness
  - Painful sex: less lubrication, less vaginal elasticity
  - Orgasm may take longer and be less intense
- Bladder and urethra changes
  - Urgency, frequency, burning, urge incontinence
  - Often misdiagnosed as bladder infection; tests negative
  - No effect on stress incontinence or pelvic organ prolapse

Bone Loss and Fracture Risk

- Low estrogen causes loss of calcium from bone
  - Decreased absorption of calcium from intestine
  - Increased bone resorption (formation same)
- 75% bone loss 15 yrs post-MP due to estrogen deficiency
- “Dowager’s Hump” results from vertebral fractures
- 20% menopausal women will have a hip fracture
  - One-sixth are fatal within 3 months
  - 25% of women with hip fracture require long term care

Acceleration of Cardiac Disease Risk

- Women lag men are about 20 years older when they experience an initial myocardial infarction (MI)
- However, by age 72
  - Risk of MI is about equal for men and women
  - Number one cause of death for women in the United States

Short term Treatment of Menopausal Symptoms
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


Lifestyle Changes

- Not shown to reduce hot flashes
- Homeopathy
- Acupuncture (compared to sham acupuncture)
- Magnetic therapy

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
- 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

<table>
<thead>
<tr>
<th>Supplement Facts</th>
<th></th>
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<tbody>
<tr>
<td>Dosage</td>
<td></td>
</tr>
<tr>
<td>Serving</td>
<td>Total</td>
</tr>
<tr>
<td>1 Tablet</td>
<td></td>
</tr>
<tr>
<td>Black Cohosh</td>
<td>30 mg</td>
</tr>
<tr>
<td>Red Clover</td>
<td>1 mg</td>
</tr>
<tr>
<td>Dong Quai</td>
<td>5 mg</td>
</tr>
<tr>
<td>Ginseng</td>
<td>10 mg</td>
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<tr>
<td>Chasteberry</td>
<td>5 mg</td>
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<tr>
<td>Vitamin E</td>
<td>1 mg</td>
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<tr>
<td>Magnesium</td>
<td>1 mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>100 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>10 mg</td>
</tr>
<tr>
<td>Zinc</td>
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<tr>
<td>Manganese</td>
<td>1 mg</td>
</tr>
<tr>
<td>Copper</td>
<td>1 mg</td>
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<tr>
<td>Other Nutrients</td>
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</table>
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>Therapy</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>
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</table>

Paroxetine 7.5 mg (Brisdelle) is the only SSRI approved by FDA for this indication.

NAMS Recommendations For Clinical Care

Menopause 2014, 21 (10): 125

- Menopausal hormone therapy is the most effective treatment for vasomotor symptoms
- Options include
  - Estrogen alone
  - Estrogen-progesterone
  - Estrogen-bazedoxifene
  - Progestogen alone, or
  - Combined OCs in women requiring contraception

NAMS Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full name</th>
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<tbody>
<tr>
<td>ET</td>
<td>Estrogen (E) therapy</td>
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<tr>
<td>EPT</td>
<td>Combined E+P therapy</td>
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<tr>
<td>HT</td>
<td>Hormone therapy (ET, EPT)</td>
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<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>
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</table>

**Prescription HT Options: ET and EPT**

<table>
<thead>
<tr>
<th>Oral</th>
<th>Transdermal</th>
<th>Intravaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Micronized estradiol</td>
<td>• Patches</td>
<td>• Creams</td>
</tr>
<tr>
<td>• Conjugated equine</td>
<td>• Gels</td>
<td>• Intravaginal tablet</td>
</tr>
<tr>
<td>estrogens (CEE)</td>
<td>• Emulsion</td>
<td>• Rings</td>
</tr>
<tr>
<td>• Synthetic conjugated</td>
<td>• Spray</td>
<td></td>
</tr>
<tr>
<td>estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Esterified estrogens</td>
<td></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>EPT</td>
<td>• CC-EPT</td>
<td>• E+P combination patches</td>
</tr>
<tr>
<td>• CS-EPT</td>
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</tr>
</tbody>
</table>

**Choice of HT Regimen**

- If no uterus: estrogen only
- If uterus present: estrogen + progestogen
  - Progestogen prevents endometrial cancer
  - Goal is to avoid vaginal bleeding entirely, or 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

**Hormone Therapy Dosages**

- Goal is lowest effective estrogen (± progestogen) dose consistent with treatment goals, benefits, risks
- Lower doses better tolerated and are safer than standard doses
- Additional local ET may be needed for persistent vaginal symptoms


**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
Routes of HT Administration

- No clear benefit of one route over another
- Transdermal ET has lower blood clot risk than oral ET
- Local ET preferred when solely vaginal symptoms
- With either route, progestogen is required for protection from endometrial cancer


Bazedoxifene 10mg with CE 0.45 mg Duavee®

- FDA approved tissue selective estrogen receptor modulator (SERM) plus conjugated estrogen
- Progestin-free
- Reduces hot flash frequency and severity
- Prevents loss of bone mass
- Treats GSM symptoms
- No increase in endometrial cancer
- Vaginal bleeding and breast tenderness adverse event rates and overall safety similar to placebo

Taylor HS. Menopause; 2012 (19);4:479-485.

Birth Control Pills in Perimenopause

- Low-dose OCs (< 30 mcg estrogen) are commonly prescribed for perimenopausal women because they relieve menopausal symptoms and prevent pregnancy
  - Other benefits: cycle control, fewer ovarian cancers
- Contraceptive patch, ring also may be helpful
- Progestin IUD (Mirena, Skyla) and DepoProvera will not address vasomotor symptoms

NAMS position statement. Menopause 2007

Compounded Bioidentical Hormones

“Then, suddenly, the Seven Dwarfs of Menopause arrived at my door without warning: Bitchy, Sweaty, Sleepy, Bloated, Forgetful, and All-Dried-Up….What was it that sent those wretched dwarfs packing? Natural bioidentical hormones.”

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...
- 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

Risks: Venous Thromboembolism (VTE)

- VTE: blood clot in a leg vein; can travel to lungs
- Oral HT increases VTE risk in menopausal women
- VTE risk starts after HT initiation; decreases over time
- Lower VTE risk with EPT or ET in women <60 y.o.
- Lower ET doses may be safer than higher doses
- Lower VTE risk with transdermal than with oral ET
- Risks fall into the “rare” category


Risks: Breast Cancer

- Conventional wisdom
  - Estrogen may be weak promoter, but not an initiator, of breast cancer
  - Based on finding of the Women’s Health Initiative, progestogens may add a further degree of risk
  - Women with a history of breast cancer should not use estrogen or progestin as it may cause recurrence of tumor
Risks: HT & Breast Cancer

• EPT use >4-5 years increased breast cancer risk
  – Increased absolute risk of EPT in WHI: “rare”
  – 4-6 additional cases/10,000/yr of EPT for ≥ 5 yrs
• Estrogen only regimens
  – WHI ET trial showed no increased risk after 7.1 yrs
    • 6 fewer cases/10,000 women/yr of ET use
  – Other studies showed that ET for < 5 yrs has little or no impact on breast cancer risk


Individualization of Therapy

• An individual risk profile is essential
• Each woman must be informed of her known risks
• Acceptance of HT risks varies with indication for use
• Benefit-risk ratio more acceptable for short-term symptom relief in younger women
• Long-term HT or use in older women less acceptable
• Women with premature menopause have increased symptoms and risks if not treated


Treatment of Hot Flashes

• If mild symptoms, try lifestyle, botanical therapy
• Indications for hormone therapy
  – Moderate or severe hot flashes
  – Non-hormonal treatments have failed
  – No interest in non-hormonal therapy
• When estrogen can’t be used, offer
  – Anti-depressant drugs
  – Gabapentin
  – Progestins alone
• Attempt discontinuation after 2 years

Treatment of Sleep/ Irritability Symptoms

• If mild symptoms
  – Lifestyle change, botanicals
• If severe symptoms or no response to above
  – Low dose HT, then titrate upward
  – If mood swings, transdermal estrogen preferred
• Depression component, or no response to HT
  – Antidepressant medications
GSM: Treatment Options

- OTC lubricants
  - Intimate lubricants: Astroglide, Sliquid, etc
  - Vaginal moisturizers: Replens
- Vaginal estrogen therapy
- Systemic HT (when prescribed for VMS)
- Oral ospemiphene

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


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Topical (Vaginal) Estrogen

<table>
<thead>
<tr>
<th>Composition</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>17β-estradiol Vaginal Cream</td>
<td>Estrace® Vaginal Cream</td>
</tr>
<tr>
<td>Conjugated estrogen Vaginal Crm</td>
<td>Premarin® Vaginal Cream</td>
</tr>
<tr>
<td>17β-estradiol Vaginal Ring</td>
<td>Estring®</td>
</tr>
<tr>
<td>Estradiol Acetate Vaginal Ring (<strong>Systemic Dose And Indication</strong>)</td>
<td>Femring®</td>
</tr>
<tr>
<td>E2 Hemihydrate Vaginal Tablet</td>
<td>Vagifem®</td>
</tr>
</tbody>
</table>


Ospemiphene (Osphena)

- Selective estrogen-receptor modulator (SERM)
  - No direct estrogen effect
  - Only oral SERM approved in the US to treat moderate to severe dyspareunia
- Improvement in...
  - Painful intercourse (dyspareunia)
  - Vaginal dryness
  - Vaginal pH

NAMS, *Menopause*. 2013
Urinary Tract Symptoms: Vaginal Estrogen

- Provides greater benefit than non-hormonal treatments
- Improves, may cure
  - Overactive bladder
  - Urge incontinence
  - 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


HT & Sexual Function

- Treatment of moderate to severe vaginal atrophy with systemic ET/EPT or local ET can relieve dyspareunia
- One oral systemic ET product FDA is approved for dyspareunia
- HT is not recommended as sole treatment of other sexual function problems (e.g., diminished libido)


HT and Fracture Prevention

Pros
- Good data on fracture prevention (mainly 2nd 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