Update on Managing Menopausal Symptoms

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Disclosures

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Guidelines & Developments in Menopause Management

Nomenclature and criteria in reproductive aging
• 2012 STRAW +10
Symptom management
• 2014 (2016) ACOG Pract Bulletin Mgt of Menopausal Sx
• 2017 + earlier NAMS Position Statements – June 20th
GSM
• 2014 ISSWSH-NAMS Consensus Statement
• 2015 Petition to remove black box

Stages of Reproductive Aging Workshop (STRAW)

FMP
Reproductive phase
Menopausal Transition
Post-Menopause
AMH, inhibin B
decline in late repro
Perimenopause
< 40: Primary ovarian insufficiency (1%)
40-45 yo or surgical: Early Menopause (5%)
Vasomotor Symptoms (VMS)

- Experienced by 75% of menopausal women
  - May start during the peri-menopause
  - Cluster in 2-year window before and after 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
  - Less common in Chinese, Japanese

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; urge incontinence
- **Bone loss** → increased hip, vertebral fracture risk
- **Increased risk of MI, stroke** (vs. premenopause)

Duration of Menopausal VMS

- 3302 women 7 US sites; 1996-2013, median 13 visits
- Findings:
  - **Duration** 7.4 yrs (median)
  - **Persistence post-FMP** 4.5 yrs (median)
  - **Both** longer if premenopausal or early perimenopausal when first reported frequent VMS Duration 11.8 yrs Persistence post-FMP 9.4 yrs

FMP: final menstrual period

Avis NE, et. al, for SWAN. JAMA Int Med. 2015
2017 NAMS Hormone Therapy Position Statement

- Benefit-risk ratio appears favorable for vasomotor symptoms (VMS) and elevated risk of bone loss or fracture if starting treatment:
  - Younger than 60yo
  - Within 10 yrs of menopause
  - No contraindications
- Risks for above groups: CHD, stroke, DVT, dementia
- Do NOT need to routinely D/C at any age
- Longer duration more favorable for estrogen alone

Case Study

- Ms S is a 53 year old woman with moderate-severe hot flashes and difficulty getting to sleep
- Her menses were regular until two years ago, became irregular, and then stopped 16 months ago
- She has tried a number of herbal remedies, each of which helped for only a few months
- Her medical history, BP, physical exam are normal
- The hot flashes affect her work productivity and she wants to try something else

In addition to sleep hygiene and stimulus control, Would you recommend.....

1. a sleep/insomnia medication
2. a trial of SSRI or SNRI medication
3. lowest dose of estrogen and progestin
4. a “mid-range” dose of estrogen and progestin
5. a consultation visit with an ObGyn
Explaining HT Benefit and Risk

HT risk is related to
- A woman’s baseline disease risks
- Her age
- Age at menopause
- Cause of menopause
- Time since menopause
- Prior use of any hormone
- HT types, route of administration, doses used
- Emerging medical conditions during treatment

Contraindications for Systemic HT

- Unexplained vaginal bleeding
- Severe active liver disease
- Prior estrogen-sensitive breast or endometrial ca
- CVD, stroke
- Dementia
- History of or high risk for thromboembolic disease
- Hypertriglyceridemia

Concerns: endometriosis or migraine may worsen, fibroids may grow

Systemic HT & CV Risk (and All-Cause Mortality)

- Initiation <10 yrs after menopause and < 60yo
  - CVD lower and reduction in all-cause mortality
  - Likely no increased risk of stroke
  - Increased risk VTE (RR=1.74)
- Initiation > 10yrs or over 60yo
  - Increased stroke (RR=1.21) and VTE (RR=1.96)
- Across all ages: Stroke ↑6 per 10K, VTE ↑8 per 10K
- Transdermal estrogen: lower risk in obs studies

Systemic HT & Breast Cancer

- Effect of HT on breast cancer risk depends on
  - Type of HT, regimen, dose, duration and route
  - Prior exposure and individual characteristics
- Nonsignificant reduction in risk w CEE alone
  (in RCTs but not all obs studies. 7 fewer in 10,000)
- Increased risk with CEE+MPA. <1 more in 1000
  (in some RCTs and many obs studies)
- Fewer breast changes w CEE+bazedoxifene
- Survivors: systemic generally not recommended;
  Local “may be considered” if fails non-hormonal tx
Nonhormonal Management of Menopause-associated Vasomotor Symptoms (VMS)

Key points from the 2015 NAMS Position Statement

Cognitive-behavioral therapy (insomnia > hot flashes)

Prescription Therapies
- FDA-approved low-dose paroxetine salt (the only FDA-approved non-hormonal Rx)
- Gabapentin and pregabalin
- Other SSRIs and SNRIs yielding significant VMS reductions in large RCTs

VMS: Non-Hormonal Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% treated patients with &gt;50% ↓HF</th>
<th>% placebo patients with &gt;50% ↓HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine 75 mg</td>
<td>54-70%</td>
<td>30% (ok on tamoxifen)</td>
</tr>
<tr>
<td>Paroxetine 10 mg</td>
<td>50-76%</td>
<td>35-57%</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>40-56%</td>
<td>21-41% (non signif)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>46-84%</td>
<td>27-47%</td>
</tr>
</tbody>
</table>

Recommend With Caution

Level II evidence suggests these may be beneficial
- Weight loss
  - AND have other health benefits
- Mindfulness-based stress reduction
- S-equol derivative of soy
- Stellate ganglion block (SGB)
  - Image-guided anesthetic block at C-6 level
  - 45-90% HF reduction for 6 weeks-3 months
  - No significant HF reduction at 6 months
Do Not Recommend at This Time
(No benefit or no studies)

- Over-the-counter supplements
- Herbal therapies
- Vitamins
- Relaxation
- Calibration of neural oscillations
- Chiropractic intervention
- Cooling techniques
- Avoiding “triggers”

Do Not Recommend

Level I evidence shows these are unlikely to alleviate VMS; may have other health benefits

- Exercise
- Yoga
- Paced respiration
- Acupuncture

NAMS Recommendations For Clinical Care of Midlife Women

- Hormone therapy is the most effective treatment for vasomotor symptoms
- “The benefits outweigh the risks for most healthy, symptomatic women aged younger than 60 years or within 10 years of the final menstrual period”
- Options include:
  - Estrogen alone (no uterus)
  - Estrogen-progesterone
  - Estragon-bazedoxifene
  - Progestogen alone (300mg MP qhs, DMPA)
  - Combined OCs in women requiring contraception

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 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>
</tbody>
</table>

| EPT                          |                   |                         |
| CC-EPT                       |                   |                         |
| CS-EPT                       | E+P combo patch    |                         |

NAMS Menopause, 2015 © 2015
Hormone Therapy Regimens

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogen Therapy (ET)</strong></td>
<td><strong>Estrogen</strong></td>
</tr>
<tr>
<td>Estrogen</td>
<td></td>
</tr>
<tr>
<td>Continuous combined (CC) EPT</td>
<td>Continuous sequential (CS) EPT</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Progestin</td>
</tr>
<tr>
<td>Progestin 14d</td>
<td>Off for 14d</td>
</tr>
<tr>
<td>Continuous-pulsed (CP) EPT</td>
<td>Off for 14d</td>
</tr>
</tbody>
</table>

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

Hormone Therapy Dosages

“Appropriate, often lowest” appropriate

- The lowest dose of HT should be used for the shortest duration needed to manage menopausal symptoms
- Lower doses better tolerated, may have more favorable benefit-risk ratio 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

*NAMS position statement. Menopause 2015 → 2017

Bazedoxifene 10 mg + CE 0.45 mg

- Tissue selective estrogen receptor modulator (SERM)
- Progestin-free
- Reduces VMS frequency and severity
- Prevents loss of bone mass
- Treats GSM
- No increase in endometrial hyperplasia
- Amenorrhea, breast tenderness adverse event rates and overall safety similar to placebo

Taylor HS. Menopause; 2012

HT: Routes of Administration

- No clear benefit of one route of administration
- Non-oral systemic ET:
  - Lower DVT/PE risk
  - Less effect on SHBG (bioavailability of testosterone)
- With either route, progestogen required for endometrial protection
- Local ET preferred when solely vaginal symptoms


Systemic HT and Other Health Issues: Benefits

- Indicated ONLY for: fracture prevention, VMS and premature hypoestrogenism
- Improves chronic insomnia
- Improves skin: thickness, collagen, elastin, moisture, fewer wrinkles. No change in hair found.
- Sig decrease in diagnosis of type 2 DM (40%)
- No change or decrease in weight
- Decreases dizziness, vertigo (small trials)
- May decrease cataracts and open-angle glaucoma
- Unclear effect on joint pain/osteoarthritis

NAMS 2017
**Systemic HT and Other Health Issues: AEs/Risks**

- CVD and breast cancer as discussed above
- AE’s: nausea, bloating, mood swings (prog), HA, breast tenderness
- Increased GSUI (vaginal ET improves incontinence)
- Cholelithiasis, cholecysitis (more w oral ET) ~50 per 10K

**Systemic HT and Other Health Issues: Dementia**

- Timing of initiation likely significant determinant
- Initiated 65yo+:
  - Dementia risk doubled with EPT (23 per 10K)
  - No change with CEE alone
- Initiated within 10 years:
  - Likely lowers Alzheimer’s risk
- After surgical menopause: possibly beneficial
- More favorable when initiated at the time of normal cognitive function. Does not improve function.

**Case Study**

- Betty is a 53 year old G4 P3 Vietnamese American with severe vulvovaginal irritation, burning, and watery yellow discharge
- Not sexually active for 10 years
- Multiple courses of OTC topical antifungal drugs and topical vulvar 1% cortisone with no relief

**Physical Exam with No Evidence of: (Differential Diagnosis)**

- Candidiasis
- Bacterial vaginosis
- Desquamative inflammatory vaginitis
- Contact dermatitis (irritant or allergic)
- Lichen sclerosis
- Lichen planus
- Lichen simplex chronicus
- Vulvar intraepithelial neoplasms
- Vulvar cancer
- Other benign and malignant tumors
- Other medical disorder (e.g., diabetes, lupus)
- Psychological causes
- Trauma/Foreign body
  - “Vulvodynia”
Would you ..... 

Advise her that she has vulvar and vaginal signs of genitourinary syndrome of menopause (GSM) and offer:

1. Prebiotics
2. Topical estrogen treatment
3. Vaginal moisturizer
4. Systemic low-dose transdermal estrogen

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 Epidemiology

- 64 million postmenopausal women in the US
- GSM symptoms will affect at least 50% of postmenopausal women at some point in their lives
  - 4% during perimenopause and 47% 3 years post FMP
  - Chronic, progressive
  - Symptoms do not improve without treatment
- Many women unaware that changes can be a direct result of menopause
- Less than 1 in 10 symptomatic women are being treated

Expert consensus that vulvovaginal atrophy (VVA) needed improved nomenclature

- Atrophy has negative connotations
- Vagina: some patients consider inappropriate for discussion
- Further, VVA does not encompass sx of lower genital tract

Precedent established for how medical lexicon has changed and increased comfort in patient discussions: “impotence” has fully transitioned to “ED”
GSM: Treatment

- OTC lubricants
  - Water based: Astroglide®, KY Jelly®, Sliquid®
  - Silicone based: K-Y intrigue®, Astroglide X®
  - Oil based: Elegance®, olive oil, coconut oil
- Vaginal moisturizers: Luvena®, Vagisil®, Replens®
- Local estrogen therapy (preferred over systemic)
- Systemic HT (when prescribed for VMS)
- Oral ospemifene

"Estrogen therapy is the most effective treatment for GSM." - NAMS 2017

- Estrogen lowers vaginal pH, increases subepithelial capillary growth, thickens epithelium
- Raises level of vaginal secretions
- VMI increases reflecting higher percentage of superficial cells relative to parabasal cells
- Estrogen therapy alleviates subjective vaginal symptoms
  - Dryness, soreness, irritation, pruritus, and dyspareunia

Vaginal Histology

Premenopause
Epithelium well-estrogenized, multi-layered with good blood supply, superficial cells rich in glycogen

Postmenopause
Estrogen-deficiency atrophy with marked thinning of epithelium, blood supply reduced, and loss of glycogen

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</td>
<td>Estring® Ring</td>
<td>Ring contains 2 mg releases 7.5 mcg/d for 90 d</td>
</tr>
<tr>
<td>17β-Estradiol</td>
<td>Estrace® Vaginal Cream</td>
<td>Initial: 2.0-4.0g/d for 1-2 wk Maint: 1.0g/d (0.1 mg/g)</td>
</tr>
<tr>
<td>Vaginal cream conj</td>
<td>Premarin® Vaginal Cream</td>
<td>0.5-2.0 g/d or twice/wk (0.6 mg/g)</td>
</tr>
<tr>
<td>estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>Estrace® Cream</td>
<td>Initial: 12.4mg releases 50mcg/d Maint: 24.8mg releases 100mcg/d</td>
</tr>
<tr>
<td>17β-estradiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>Femring® (Systemic dose and indication)</td>
<td>Systemic dose ring for 90 d</td>
</tr>
<tr>
<td>E2 acetate</td>
<td></td>
<td>12.4mg releases 50mcg/d</td>
</tr>
<tr>
<td>Vaginal tablet</td>
<td>Vagifem® 10mcg</td>
<td>Initial: 1 tablet/d for 2 wk</td>
</tr>
<tr>
<td>E2 hemihydrate</td>
<td></td>
<td>Maintenance: 1 tab 2x/wk</td>
</tr>
</tbody>
</table>

NAMS Position Statement Menopause. 2013
Onset of Action of Vaginal Estrogens

- Improvements in VMI reported as early as 2 to 4 weeks after initiation of vaginal CEE cream or estradiol vaginal tablets
- Vaginal pH falls to lowest levels by 3rd week of vaginal estrogen treatment (number of superficial cells in the vagina has increased by that time)
- Superficial cells continue to increase during 12-weeks of therapy
- Atrophic vaginal epithelium absorbs locally applied estrogen faster than after the epithelium has been estrogenized

CEE, conjugated equine estrogen

GSM: Vaginal vs. Systemic Estrogen

- Topical therapy is preferred when vaginal symptoms are the only complaint
- Topical more effective than systemic oral ET
- Presumed lower risk, progestin NOT needed for most
- 10%-15% of women on systemic HT may also need local estrogen therapy
- Systemic ET may worsen or provoke stress incontinence—Ultralow-dose transdermal ET has no effect on incontinence
- Only vaginal ET is effective for urinary tract infection
- ACOG committee opinion and NAMS 2017 endorsed vaginal use in breast cancer survivors

Ospemifene
Approved 2013 for Vulvovaginal Sx of Menopause

- Daily 60mg oral tablet, administer with food
- Selective estrogen-receptor modulator (SERM)
  - Preclinical data: antiestrogen effects on breast tissue and agonistic effects on bone
- Improvement in...
  - Dyspareunia
  - Vaginal maturation index
  - Vaginal pH
  - Vaginal dryness

Ospemifene

- VMS: most common AE 7.2% vs 2% in placebo
- Prescribing information similar to estrogens and other SERMs
- Contraindicated in
  - Genital bleeding unknown etiology
  - Estrogen-dependent neoplasia
  - DVT, PE, CVA, MI history or current
Vaginal Prasterone (DHEA/Dehydroepiandrosterone)

- FDA Approved Nov 2016
- 4 Phase 3 trials - 665 women, dyspareunia as MBS of VVA
- Prasterone - 6.5 mg (0.5%)
- Daily vaginal suppository
- Slight increase in serum DHEA, estradiol, testosterone secondary to aromatization –in PMP range
- No Box Warning
- AEs: 5.7% discharge vs. 3.66% placebo

Urinary Tract Symptoms: Vaginal Estrogen

- Provides greater benefit than non-hormonal tx
- Improves, may cure:
  - Overactive bladder
  - Urge incontinence
  - Recurrent urinary tract infections
  - Urethritis (irritative) symptoms
- No effect on SUI (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 is FDA approved for dyspareunia
- HT is not recommended as sole treatment of other sexual function problems (e.g., diminished libido)

Day-to-Day Impact of Vaginal Aging Questionnaire (DIVA)

- Self-report questionnaire: 23 items in 4 domains
  1. activities of daily living
  2. emotional well-being
  3. sexual functioning
  4. self-concept and body image
- Evaluation of the impact of GSM symptoms on QOL for women of diverse backgrounds
- Valid for researchers and clinicians
Black Box Warning for Low-Dose Vaginal Estrogen

Low-Dose Vaginal Estrogen: Safe for Nearly All

“WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA”

Citizen’s Petition supported by ACOG, AMWA, Endoc Soc. ++. Awaiting decision about label change.

NAMS sponsored initiative- FDA scientific workshop November 2015

Value emojis from Risa Kagan, MD (past president of NAMS)

Black Box Warning

This commentary summarizes the activities of several initiatives and research to encourage identification of adverse events associated with low-dose vaginal estrogen use. The panel of experts convened by consensus of reaching consensus that the lack of definitive data on the safety and efficacy merits for these products should be redefined.

Black Box Warning for Low-Dose Vaginal Estrogen

Why the product labeling for low-dose vaginal estrogen should be changed.

Low-Dose Vaginal Estrogen: Safe for Nearly All

“WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA”

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