Update in Menopausal Hormone Therapy

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Learning in the Olympics
March 2, 2019
Objectives

• Review current data and guidelines for prescribing menopausal hormone therapy, including special populations

• Review current data and guidelines regarding “bioidentical” hormone therapy

• Review alternative medications and strategies for treatment of menopausal symptoms
Let’s start with the most overlooked organs: the vagina and vulva
Vaginal Atrophy: Pathophysiology

Vaginal environment before menopause:
- Ovaries produce estrogen
- The vaginal lining is thick and moist
- There is good blood flow to vaginal tissues
- Vaginal walls are elastic
- Vaginal fluid is secreted during sexual activity

Vaginal environment after estrogen loss:
- Ovaries produce less estrogen (or none at all)
- The vaginal lining becomes thin and dry
- There is decreased blood flow to vaginal tissues
- Vaginal elasticity decreases
- There is less secretion of fluids during sexual activity
- The vagina narrows and shortens

Vaginal Epithelium

Layers
- superficial
- intermediate
- parabasal
- basal

Estrogenized

Atrophic

Three Types (Or Stages) of Vaginal Epithelial Cells

All scored to quantify estrogenization in the Vaginal Maturation Index

The Vaginal Maturation Index quantifies the relative proportion of the vaginal parabasal (P), intermediate (I), and superficial (S) cells presented as % P / % I / % S.

Vaginal histology

Vaginal lining with estrogen

Vaginal lining in low-estrogen state
Vaginal symptoms

• May lag behind vasomotor symptoms by several years
• Most common complaints are dryness and pain with penetration
• Reduced thickness of vaginal epithelium increases susceptibility to infection
• Dyspareunia frequently leads to diminished libido
### TABLE 2. Genitourinary Syndrome of Menopause (GSM): symptoms and signs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital dryness</td>
<td>Decreased moisture</td>
</tr>
<tr>
<td>Decreased lubrication with sexual activity</td>
<td>Decreased elasticity</td>
</tr>
<tr>
<td>Discomfort or pain with sexual activity</td>
<td>Labia minora resorption</td>
</tr>
<tr>
<td>Post-coital bleeding</td>
<td>Pallor/Erythema</td>
</tr>
<tr>
<td>Decreased arousal, orgasm, desire</td>
<td>Loss of vaginal rugae</td>
</tr>
<tr>
<td>Irritation/Burning/Itching of vulva or vagina</td>
<td>Tissue fragility/fissures/</td>
</tr>
<tr>
<td>Dysuria</td>
<td>petechiae</td>
</tr>
<tr>
<td>Urinary frequency/urgency</td>
<td>Urethral eversion or prolapse</td>
</tr>
<tr>
<td></td>
<td>Loss of hymenal remnants</td>
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<tr>
<td></td>
<td>Prominence of</td>
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<td></td>
<td>urethral meatus</td>
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<td></td>
<td>Introital retraction</td>
</tr>
<tr>
<td></td>
<td>Recurrent urinary tract</td>
</tr>
<tr>
<td></td>
<td>infections</td>
</tr>
</tbody>
</table>

Supportive findings: pH >5, increased parabasal cells on maturation index, and decreased superficial cells on wet mount or maturation index.
Scope of the problem

• 40-60% of postmenopausal women have GSM but only 6-7% treated
• Many unaware that symptoms worsen over time
• When sex is good it adds \(~15-20\%) value to relationship but when it is bad, it diminishes the relationship by 50-75\%
Nonprescription therapies

- Vaginal lubricants and moisturizers
  - Should be considered first-line therapies
  - Over-the-counter products can significantly decrease or eliminate symptoms for many women

- Herbal products have not demonstrated any beneficial effect in clinical trials

Nonpharmacologic treatment strategies: Initial and mainstay treatments

• Lubricants
  • Used as needed for sexual activity to increase comfort/pleasure
  • Can be used with other therapies
  • Water/Silicone/Oil-based
  • Avoid potential irritants

• Moisturizers
  • Used daily or every few days to maintain moisture
  • Can be used with other therapies
  • Mimics normal vaginal secretions
  • Does not reverse cellular/pH changes or GSM
Non-Rx therapies for vaginal sx

- Vaginal moisturizers effective; also produce low pH to guard against infection
- Vaginal lubricants ease penetration
- Avoid use of petroleum-based products
- Douches may worsen condition; antihistamines may have drying effect
- Continued sexual activity and/or stimulation may benefit vaginal health
Vaginal Symptoms

- ET is most effective treatment of moderate to severe symptoms of vulvar and vaginal atrophy.
- Many systemic HT and local vaginal ET products are available for treating one or both of these symptoms.

Prescription therapies

- Low-dose vaginal estrogen therapy (ET)
- Ospemifene (Osphena) which is indicated for dyspareunia
- Prasterone (Intrarosa)
Bothersome GSM symptoms—consideration of low- dose vaginal ET

- Low-dose vaginal ET used for the GSM has minimal systemic absorption (blood levels in the post- menopause range) and, on the basis of limited observational data, appears to hold minimal to no demonstrated risk for recurrence of endometrial or breast cancer. (Level II)

- For women with early endometrial cancer who have completed successful treatment, including hysterectomy, consideration may be given for low-dose vaginal ET for relief of GSM if non- hormone options are not successful, based on limited short- term safety trials. (Level II)

- For women who are survivors of breast cancer, decisions about low-dose vaginal ET should involve the woman’s oncologist, particularly for women using AIs who have lowered overall estradiol levels. (Level III)

*North American Menopause Society position statement, Menopause, 2017*
Vaginal Estrogen Therapy

US FDA-approved vaginal ET products

- Estradiol vaginal cream (Estrace)
- Conjugated estrogen vaginal cream (Premarin)
- Estradiol vaginal ring (Estring)
- Estradiol acetate vaginal ring (Femring)\(^a\)
- Estradiol hemihydrate vaginal tablet 4 mcg (Imvexxy), 10 mcg (Vagifem, Yuvalfem)

- All are effective at recommended doses
- Choice depends on clinical experience and patient preference (including cost)

\(^a\)This product delivers systemic levels of estradiol.
Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women’s Health Initiative Observational Study

Carolyn J. Crandall, MD, MS, 1 Kathleen M. Hovey, MS, 2 Christopher A. Andrews, PhD, 3 Rowan T. Chlebowski, MD, PhD, 4 Marcia L. Stefanick, PhD, 5 Dorothy S. Lane, MD, MPH, 6 Jan Shifren, MD, 7 Chu Chen, PhD, 8 Andrew M. Kaunitz, MD, 9 Jane A. Cauley, DrPH, 10 and JoAnn E. Manson, MD, DrPH 11
Figure 1. Algorithm of Study Participants

Exclusions:
- current HT users (oral, transdermal estrogen and/or progestogen) at baseline or during follow-up (N= 41,630)
- history of breast, ovarian, endometrial cancer (N= 7,079)
- missing HT use data (N= 85)
- missing info hysterectomy status (N= 454)
- no follow-up data (N= 473)

N = 93,676 WHI-Observational Study

N = 45,663

N = 32,433 Intact uterus*

N = 14,133 Hysterectomy*

N = 3,003 Vaginal estrogen users

N = 1,207 Vaginal estrogen users

*numbers don’t add up to 45,663 due to time-varying nature of hysterectomy status: 903 change from no hysterectomy to hysterectomy and are counted in both cells (Crandall et al, Menopause 2017)
• In this large prospective cohort study, compared to nonusers of vaginal estrogen, users had similar risks of:
  • invasive breast cancer
  • stroke
  • colorectal cancer
  • endometrial cancer, and
  • venous thromboembolism

• Did not find evidence for elevated risk of CHD or death in vaginal estrogen users compared with non-users
Vaginal estrogen products

- Estradiol tablets 10 mcg vaginally daily for two weeks, then twice weekly
- Estradiol vaginal ring (Estring) 2mg vaginally every 3 months
- Estradiol or conjugated estrogen cream (Estrace or Premarin)
- Estradiol inserts (Imvexxy) 10 mcg, 4 mcg
Estring vs Vagifem

Randomized controlled trial comparing Estring and Vagifem for 12mos
No difference in efficacy or endometrial thickness
Fewer patients with bleeding in Estring group (0 vs 6%)

Weisberg, Ayton, et.al. Climacteric 2005
Vaginal ET: Effectiveness

- Typically provides greater benefit than nonhormonal interventions
- Preferred mode of delivery when vaginal symptoms are the only complaint
- Shown in clinical trials to be more effective than systemic oral ET
- May also reduce risk of urinary urgency and recurrent urinary tract infections

Presumed lower risk than commonly used doses of systemic ET

Serum estrogen levels reported with use are within postmenopausal range
Vaginal ET: Adverse effects

- Vulvovaginal candidiasis, uterine bleeding, mastalgia, and nausea have been reported; may be dose-related

- Data for women at high risk for venous thromboembolism are lacking

- Endometrial carcinoma can be a concern with use of ET in women who have a uterus
- Improvement in symptoms typically occurs within a few weeks of starting treatment
- Vaginal ET may be continued as long as distressing symptoms remain

Insufficient data to recommend annual endometrial surveillance in asymptomatic women

Closer surveillance may be required if a woman is

- Using a higher dose of vaginal ET
- At high risk for endometrial cancer
- Having symptoms such as spotting, breakthrough bleeding
• Tablet vs.crm – 6 months
  • Estradiol tablet 25 mcg once/wk or CEE cream 1.25 mg/d X 21 days f/b 1 wk off for 6-month intervention
    • Tablet: 1/49 proliferative endometrium;
    • Cream: 7/49 proliferative endometrium, 2/49 endometrial hyperplasia (Rioux et al Menopause 2000)

• Tablet without comparison group – 12 months
  • Estradiol vaginal tablet 10mcg, 2 studies
    • No hyperplasia or endometrial ca (Ulrich Climactieric 2010)
    • 2 events of hyperplasia and carcinoma in 386 evaluable biopsy samples (incidence rate 0.52% per year) (vs. background incidence of 0% - 1%) (Simon Obstet Gynecol 2010)
Cochrane Review 2016

• 30 RCTs comparing vaginal estrogen formulations to each other or placebo
• Poor quality studies
• All approved vaginal therapy products more effective than placebo
• No formulation superior to others

Cochrane Database of Systematic Reviews 2016
Class Labeling

• Low-dose vaginal estrogen preparations approved by the U.S. Food and Drug Administration carry the same boxed warning about health risks as the systemic formulations of estrogen alone and combination estrogen plus progestogen carry.

• This labeling is based on extrapolations of data from clinical trials of systemic hormone therapy, which:
  • involved substantially higher levels of systemic exposure, and
  • were not based on evidence from clinical trials of vaginal estrogen.

On May 29, 2018, the FDA rejected a proposal to modify package labelling of low-dose vaginal estrogen products to accurately reflect evidence-based information for low-dose vaginal estrogen products approved for treating symptoms of vulvovaginal atrophy.

(Docket No. FDA-2016-P-1246)
The North American Menopause Society (NAMS) joins The International Society for the Study of Women’s Sexual Health, the American College of Obstetricians and Gynecologists, and other major organizations in recognizing the Centers for Medicare and Medicaid Services (CMS) for acting on a major health concern for postmenopausal women by **no longer excluding from Medicare Part D coverage drugs for the treatment of moderate to severe dyspareunia due to menopause** when used consistent with this labeling under their “Prescription Drug Benefits” section 1860D-2(e)(2)(A) of the Social Security Act. Postmenopausal women can now receive access to newer, tested, and effective FDA-approved therapies to relieve symptoms and signs of vulvovaginal atrophy (VVA), a component of the genitourinary syndrome of menopause (GSM). **Dyspareunia in postmenopausal women should not be considered sexual dysfunction but rather the most common presenting symptom of GSM**, a chronic, progressive medical condition that is the result of lowered estrogen levels in vaginal and urogenital tissue after menopause, resulting in thinning of the vaginal tissues.
Prasterone (Intrarosa)

- 6.5 mg insert, vaginal, once daily
- DHEA is converted by aromatase activity into testosterone and estradiol
- Approved for treatment of dyspareunia due to GSM
Clinical trial data

• Clinical trials (12 weeks):
  • More effective than placebo in improving vaginal dryness and dyspareunia
  • No significant impact on serum levels of DHEA, DHEA-S, E\textsubscript{2} or T
  • Negligible endometrial effect
• Labeling lists breast cancer as warning, not contraindication
Ospemifene

- Nonhormonal selective estrogen-receptor modulator (SERM)
- Only SERM approved in the United States to treat moderate to severe dyspareunia
Ospemifene: Effectiveness

- Two 12-week studies showed improvements with daily use (60 mg) in:
  - Vaginal maturation index
  - Vaginal pH
  - Most bothersome symptom (vaginal dryness)

- 52-week extension study showed sustained improvements with no cases of VTE, endometrial hyperplasia or carcinoma
Ospemifene: Adverse effects

- Vasomotor symptoms most common
- Prescribing information contains precautions similar to those for estrogens and other SERMs
- Data in women with breast cancer or at high risk of developing breast cancer are lacking so use is not recommended

The techno vagina: The laser and radiofrequency device boom in gynecology

OBG Management, September 2018
Is applying energy to the vagina the answer?

- Women seek non-hormonal treatment, especially breast cancer survivors
- Cost of ongoing therapy may be a factor
- Short-term treatment may be appealing
Clinical Study (30 patients)

Use of a Novel Fractional CO$_2$ Laser for the Treatment of Genitourinary Syndrome of Menopause: 1-Year Outcomes

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$^2$ Advanced Urogynecology and Pelvic Surgery, The Christ Hospital, Cincinnati, Ohio

Menopause. July 2017
Observational Study

All GSM symptoms significantly improved at 12 months
Before and after vaginal laser
Vaginal laser therapy

- FDA cleared for general gynecologic indications
- Not approved specifically for treatment of GSM or dyspareunia
- FDA July 2018: “warns against use of energy based devices to perform vaginal ‘rejuvenation’ or vaginal cosmetic procedures”
- FDA encouraged randomized trials before wide acceptance
Radiofrequency-based devices

- Variable mechanisms of action but generally deliver energy to deeper connective tissue of vaginal wall
- May be monopolar, bipolar, multipolar
- FDA cleared for nonspecific electrocoagulation and hemostasis, not cleared for treatment of any vaginal conditions or symptoms
Radiofrequency-based devices

- Based on small, short term studies, most without placebo arm
- Preliminary data reassuring regarding benefits and risks
- Not compared to standard therapy (local estrogen treatment)
- Experts advise long-term randomized sham-controlled trials
GSM and Breast Cancer

- 3.1 million survivors of breast cancer
- >250,000 women diagnosed with breast cancer each year
  - 11% under 44 years of age
- Add women at high risk for breast cancer
- Most will suffer from GSM and will go undiagnosed and untreated!
Key Points

• High risk women
  • Observational data suggest that local or systemic hormone therapy do not further increase risk for breast cancer in women already at high risk

• Estrogen receptor-positive disease
  • Nonhormonal therapy first line
  • Consider local hormone therapy after discussion with oncologist (women receiving AIs might first consider switching to tamoxifen)
Key Points

• Triple-negative breast cancers
  • Theoretically no increased risk associated with local or systemic hormone therapy, but data are lacking

• Metastatic disease
  • Quality of life, comfort, and sexual intimacy most important
  • Optimal choices will vary with probability of long-term survival
## Factors affecting decision-making regarding local hormone therapy

<table>
<thead>
<tr>
<th></th>
<th>More desirable candidates</th>
<th>Less desirable candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage of disease</strong></td>
<td>Stage 0, 1, and 2 or metastatic with limited life expectancy</td>
<td>Stage 3 or metastatic with extended life expectancy</td>
</tr>
<tr>
<td><strong>Grade of disease</strong></td>
<td>Low or intermediate grade</td>
<td>High grade</td>
</tr>
<tr>
<td><strong>Lymph node involvement</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hormone-receptor status</strong></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Endocrine Therapy</strong></td>
<td>Tamoxifen</td>
<td>Als</td>
</tr>
<tr>
<td><strong>Risk of recurrence</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Time since diagnosis</strong></td>
<td>Remote</td>
<td>Recent</td>
</tr>
<tr>
<td><strong>Symptom severity</strong></td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td><strong>Nonhormone therapies</strong></td>
<td>Failed</td>
<td>Effective</td>
</tr>
<tr>
<td><strong>Effect on QOL</strong></td>
<td>Severe</td>
<td>Mild</td>
</tr>
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</table>

Als: aromatase inhibitor; QOL: quality of life
DHEA (prasterone) and risk

- FDA-approved DHEA not studied in breast cancer survivors; label warns against its use
- No studies directly comparing estrogen to DHEA in levels or efficacy
- One cannot be recommended over the other in this population

• **Ospemifene**
  
  • Systemically administered SERM FDA-approved for treatment of moderate to severe dyspareunia
  • Anti-estrogenic breast effects in pre-clinical trials
  • Not studied in breast cancer survivors
  • Not approved by FDA for US women with or at high risk for breast cancer
  • Not contraindicated in Europe in breast cancer survivors who have completed treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Product Name</th>
<th>Initial Diagnosis</th>
<th>Maintenance Dose</th>
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</thead>
<tbody>
<tr>
<td><strong>Vaginal creams</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>17β-estradiol</td>
<td>Estrace; generic</td>
<td>0.5 – 1 gm/d x 2 wks</td>
<td>0.5 – 1 gm 1–3 x wk</td>
</tr>
<tr>
<td>Conjugated estrogens</td>
<td>Premarin</td>
<td>0.5 – 1 gm/d x 2 wks</td>
<td>0.5 – 1 gm 1–3 x wk</td>
</tr>
<tr>
<td><strong>Vaginal inserts</strong></td>
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<td></td>
</tr>
<tr>
<td>Estradiol hemihydrate</td>
<td>Vagifem; Yuvaferm;</td>
<td>10 µg insert 1/d x 2 wk</td>
<td>1 twice wk</td>
</tr>
<tr>
<td></td>
<td>generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHEA (prasterone)</td>
<td>Intrarosa</td>
<td>6.5 mg 1/d</td>
<td>6.5 mg 1/d</td>
</tr>
<tr>
<td><strong>Vaginal ring</strong></td>
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<tr>
<td>17β-estradiol</td>
<td>Estring</td>
<td>2 mg releases about 7.5 µg/d x 90 d</td>
<td>Changed q 90 d</td>
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<tr>
<td><strong>SERM</strong></td>
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<td></td>
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<tr>
<td>Ospemifene</td>
<td>Osphena</td>
<td>60 mg orally/d</td>
<td>60 mg orally/d</td>
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<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lidocaine</td>
<td>4% aqueous lidocaine</td>
<td>Applied to vestibule before sexual</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>activity</td>
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Vasomotor and other Symptoms
ET with or without progestogen is most effective treatment of menopause-related vasomotor symptoms

Almost all systemic HT products are approved for vasomotor symptom relief

Sexual Function

- Low-dose local ET may improve sexual satisfaction by improving lubrication and increasing blood flow and sensation in vaginal tissue.
- HT is not recommended as the sole treatment of other sexual function problems (e.g., diminished libido).

Urinary Tract Health

- Local ET may benefit some women with overactive bladder
- Only vaginal ET is effective for urinary tract infection
- Systemic ET may worsen or provoke stress incontinence
- Ultralow-dose transdermal ET has no effect on incontinence

Mood and Depression

- Evidence is mixed re: effect of HT on mood when no clinical depression
- Progestogens in EPT may worsen mood when history of PMS, PMDD, or clinical depression
- HT should not be recommended as an antidepressant

Although HT is not approved for enhancing QOL, HT can improve health-related QOL in symptomatic women.

Unclear if HT improves health-related QOL in asymptomatic women.

Osteoporosis

- HT reduced the risk for fracture (e.g., hip, spine, non-spine) in postmenopausal women in the Women’s Health Initiative (WHI) who were not selected on basis of osteoporosis or bone density.

- Many systemic HT products are approved for preventing postmenopausal osteoporosis.

- No HT product is approved for treating osteoporosis.

Extended use of HT is option for women at high risk of osteoporotic fracture when alternate therapies aren’t appropriate.

Risks of long-term HT use should be considered.

Benefits of HT on bone mass dissipate quickly after discontinuation.

ET may reduce CHD and coronary artery risk when initiated in younger and more recently postmenopausal women without a uterus.

HT is currently not recommended for coronary protection in women of any age.

Diabetes Mellitus

- HT reduces new-onset DM, although no HT product approved for prevention
- Inadequate evidence to recommend HT for sole or primary indication for DM prevention in peri- or postmenopausal women

Both ET and EPT appear to increase ischemic stroke risk and have no effect on hemorrhagic stroke risk.

Venous Thromboembolism

- Oral HT increases the risk of VTE
- VTE risk emerges soon after HT initiation (1-2 y) and decreases over time
- Lower VTE risk with either EPT or ET in women before age 60
- Possible lower VTE risk with transdermal and lower oral HT doses. No RCT evidence

Risk of blood clots/stroke

Both estrogen therapy and E+P therapy increase the risk of blood clots in the legs and lungs.

Although the risks of blood clots and strokes increase with either type of HT, the risk is rare in the 50-59-year-old age group.
Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to dose and duration of use.

HT not recommended with history of endometrial cancer

Diagnosis of breast cancer increases with EPT use beyond 3-5 years

Unclear whether EPT risk differs between continuous and sequential progestogen

EPT and, to a lesser extent, ET increase breast cell proliferation, breast pain, and mammographic density

EPT may impede diagnostic interpretation of mammograms

Increase in breast cancer diagnosis dissipated 3 years post EPT cessation

Breast cancer mortality higher in women assigned to EPT compared to placebo

Women starting EPT shortly after menopause experience increased breast cancer risk, but those with a gap time greater than 5 years do not
ET arm of WHI showed no increased cancer risk after mean 7.1 years on study

ET and EPT use in breast cancer survivors may increase recurrence risk

Ovarian Cancer

- Data on HT and risk of ovarian cancer are conflicting

- There were increases of ovarian cancer in those using EPT in WHI but the numbers did not reach statistical significance

No significant increase in incidence of non-small-cell lung cancer with EPT over 7.1 years in WHI

Lung cancer mortality was higher with EPT use

No increase in incidence or mortality was seen with ET

Evidence is mixed on effect of HT on cognition at time of menopause

No effect on episodic memory or executive function with ET at time of menopause

WHI Memory Study reported an increase in dementia with HT use at ages 65-79

HT not recommended at any age for preventing or treating cognitive aging or dementia
Data regarding HT in women over age 50 should not be extrapolated to younger postmenopausal women.

Likely that risks attributable to HT are smaller and benefits greater in these younger women.

Recommend use of HT or oral contraceptives until median age of menopause, then reevaluate continued use.

HT may reduce total mortality when initiated soon after menopause

Both ET and EPT may reduce total mortality by 30% when initiated in women younger than age 60

A Decade After The Women’s Health Initiative—The Experts Do Agree

The statement was published in the journals of
The North American Menopause Society
(Menopause),
the American Society for Reproductive Medicine
(Fertility and Sterility), and The Endocrine Society
(Journal of Clinical Endocrinology and Metabolism)
July 9, 2002, the first report from the Women’s Health Initiative (WHI)—the largest and longest trial of postmenopausal women using hormone therapy (HT)

Debate ensued with the one consistent theme:
“Even the experts don’t agree”

This statement of agreement on the use of HT for symptomatic menopausal women was published on the 10-year anniversary of the first report from the WHI
This solidarity statement was prepared by The North American Menopause Society, the American Society for Reproductive Medicine, and The Endocrine Society. 12 other leading organizations in women’s health endorsed the statement.
HT for treatment of menopausal symptoms:

“Individualization is key in the decision to use hormone therapy. Consideration should be given to the woman's quality-of-life priorities as well as her personal risk factors such as age, time since menopause, and her risk of blood clots, heart disease, stroke, and breast cancer.”
For younger women

HT is an acceptable option for treating moderate to severe menopausal symptoms in relatively young (up to age 59 or within 10 years of menopause) and healthy women.
Women with a uterus

- Women who still have a uterus need to take a progestogen (progesterone or a similar product) along with estrogen to prevent cancer of the uterus
- Women who have had their uterus removed can take estrogen alone
Practical Therapeutic Issues
Estrogen formulations

- Conjugated estrogens...0.3, 0.45, 0.625, 0.9, 1.25mg (Premarin, Cenestin)
- Estradiol...0.5, 1.0, 2.0 mg
- Esterified estrogens...0.3, 0.625, 1.25mg (Menest)
- Estropipate...0.625, 1.25mg (Ogen, Ortho-est)
- Esterified estrogens 1.25mg/methyltestosterone 2.5mg , 0.625/1.25 (EstraTest)
Estrogen options

• Transdermal
  – Estradiol (weekly): 0.014, 0.025, 0.05, 0.075, 0.1mg
    • (Climara)
  – Estradiol (twice weekly): 0.025, 0.0375, 0.05, 0.075, 0.1mg (Vivelle-Dot, Minivelle)

• Transdermal combinations
  – Combipatch: 0.05mg estradiol/0.14mg or 0.25mg norethindrone acetate, twice weekly
  – ClimaraPro: 0.045mg estradiol/0.014mg levonorgestrel weekly
Non-oral estrogen formulations

- **Ring:** Femring 0.05mg or 0.1mg *vaginally* every 3 mos
- **Topical:** Estrogel 0.06% gel, 1.25 grams applied to *arm* daily (one pump), Divigel packets
- **Topical:** Estrasorb 1.74g/packet emulsion, one packet applied to *each thigh* daily = 0.05mg estradiol
- **Topical:** Evamist 1-3 sprays applied to *arm*
Progestogen options

- Norethindrone (only available in 5mg dose)
- Micronized progesterone (Prometrium) 100mg, 200mg
- Medroxyprogesterone acetate 2.5, 5, 10mg
- Mirena or Skyla (levonorgestrel intrauterine system)...replace every 3-5 yrs
Primary indication for progestogen use is endometrial protection from systemic ET

Adequate progestogen recommended for women with an intact uterus using systemic ET

Progestogen generally not indicated with low-dose local ET for vaginal atrophy
Progestogen choices

• Progesterone is more difficult molecule than estradiol making it difficult to get into the circulation
• Micronized progesterone only oral form: suspended in peanut oil: only available in 100 and 200mg doses
• Norethindrone has long history of safety in oral contraceptives for over 50 years
• Medroxyprogesterone acetate rejected for OCs due to breast proliferative effect
• Progesterone creams unreliable
Progestogen options

- KEEPS trial used micronized progesterone 200mg for 12 days per month
- No RCT evidence to support extended cycle progestin use (e.g. every 3 months) but widely used
- Combined synthetic progestin (norethindrone or levonorgestrel) with estradiol in transdermal patch
Intrauterine progestin

• Levonorgestrel (Mirena or Skyla)
• Intuitively satisfying as endometrium is the only tissue in the body that benefits from the progestin as part of combined hormone therapy
• not FDA-approved for this indication
• Well tolerated, must be replaced q 3 or 5 yrs
Continuous combined products

- Estradiol 1mg/NETA 0.5mg, 0.5mg/0.1mg (Activella)
- Ethinyl estradiol 5 µg/NETA 1mg, 2.5mcg/0.5mg (Femhrt)
- CEE 0.625/MPA 2.5 or 5mg, 0.3/1.5, 0.45/1.5 (Prempro)
- CEE 0.625/MPA 5 for 14/28 days
- Estradiol 1mg/norgestimate 0.09mg (Prefest)
- Estradiol 1mg/drospirenone 0.5mg (Angeliq)
Estrogen plus SERM

- **DuaVee**: conjugated estrogen 0.45 mg/bazedoxifene 20 mg one po qd
- Indicated for women with a uterus
- Treatment of vasomotor symptoms without effect on endometrium
All estrogens share some common features but may have unique properties as well

Same is true for progestogens

Without RCTs, data for one agent should be generalized to all agents within same hormonal family

More research required

Dosage and Route

- Therapeutic goal is lowest effective estrogen dose consistent with individual treatment goals, benefits, and risks, plus appropriate progestogen dose for women with a uterus.

- Lower doses have fewer side effects and may have more favorable benefit-risk ratio than standard doses but lower doses not been tested in long-term trials.

Dose & Route of Administration

- All routes of administration of ET can effectively treat menopausal symptoms
- Nonoral routes may offer both advantages and disadvantages compared with oral route (but no RCT outcomes)
- Transdermal ET may be associated with lower risk of DVT, stroke, and MI
- Multiple progestogen options for endometrial protection

Duration of Use

Extending EPT use is acceptable for:

- Women who request it and are well aware of potential risks and benefits
- Prevention of further osteoporosis-related fracture and bone loss when alternate therapies are not appropriate or cause unacceptable adverse effects

Discontinuation

After 3 years of EPT discontinuation:
- Rate of cardiovascular events, fractures, and colon cancer same as placebo group
- Increase in rate of all cancers and mortality from breast cancer

After 3 years of ET discontinuation:
- No increase in CHD, DVT, stroke, hip fracture, colorectal cancer, or total mortality
- Decrease in breast cancer persisted
Discontinuation

- HRs for all-cause mortality neutral for both
- 50% chance of vasomotor symptoms recurring when HT discontinued
- Symptom recurrence similar whether tapered or abruptly discontinued
- Decision to continue HT should be individualized
Persistent symptoms

“It is inappropriate to withhold hormone therapy from persistently symptomatic women who prefer to continue or who do not derive relief from currently available alternatives” (ACOG)

Disease prevention may be appropriate as a secondary benefit for women who are already taking hormones for vasomotor symptoms
Women over 65

“The decision to continue HT should be individualized and be based on a woman’s symptoms and the risk-benefit ration, regardless of age. Because some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms, ACOG recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of HT and estrogen therapy should be individualized based on each woman’s risk-benefit ratio and clinical presentation.”

ACOG Practice Bulletin #141, January 2014
What are “bioidenticals”?

• Not a scientific term, and no uniform definition in any medical dictionary
• Molecularly very similar or identical to endogenous hormones; plant-derived from soybean or yam
• “Individualized exact doses” to replicate homeostatic hormone levels of Estrogen, Progesterone, Testosterone
• Dosage is adjusted according to salivary or blood hormone levels, unlike commercial HT which is adjusted based on symptom relief
• Purported anti-aging, sexual vibrancy and energizing effects are similar to structure/function claims made for dietary supplements rather than disease treatment/prevention claims made for drugs
Bioidentical Hormone Therapy

• Many well-tested, government-approved, brand-name HT products contain hormones chemically identical to those made by ovaries

• “BHT” usually refers to custom-compounded formulations

• Custom BHT may combine several hormones and use nonstandard routes of administration

• Use of compounded BHT and salivary hormone testing are not recommended
Bioidentical Hormone Therapy

- BHT is not tested for efficacy, safety, batch standardization, or purity
- FDA says compounding pharmacies make false and misleading claims about safety and effectiveness of BHT
- BHT should include package inserts explaining benefits & risks just like government-approved HT products
- Compounded HT should only be used by women allergic to ingredients in approved products

<table>
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<th>Traditional</th>
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<td>Molecular structure</td>
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Endocrine Society Position Statement

Supports FDA regulation and oversight of all hormones, regardless of chemical structure or method of manufacture. This should include:

• surveys for purity and dosage accuracy
• mandatory reporting by drug manufacturers of adverse events
• a registry of adverse events related to the use of hormone preparations
• inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products
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  • mandatory reporting by drug manufacturers of adverse events
  • a registry of adverse events related to the use of hormone preparations
  • inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products
Common compounded products

Tri-Est: 80% estriol, 10% estradiol, 10% estrone
Bi-est: 80-90% estriol, 10-20% estradiol
Micronized progesterone
Micronized testosterone
No drug containing estriol has been approved by FDA and the safety and effectiveness of estriol is unknown. Pharmacies may not compound drugs containing estriol unless they have an FDA-sanctioned investigational new drug application.
Hormone testing

• No scientific basis for testing of hormone levels before or during treatment
• No “target” value or ratio of hormone levels that is correlated with symptom relief or safety
• Levels may be useful in certain women, such as young surgically menopausal
• Salivary levels not validated
Testosterone for women?

- It works to improve hypoactive sexual desire disorder
- Associated with reduction in total cholesterol, TGs, HDL
- Increase in LDL, acne and hirsutism
- Long term safety data sparse, and quality of evidence low
- No well-defined syndrome of androgen deficiency in women, data correlating androgen levels with specific signs and symptoms are unavailable
• Recommend against dx of androgen deficiency syndrome
• Recommend against use of Testosterone for sexual dysfunction other than hypoactive sexual desire disorder, or for infertility, cognitive, metabolic or bone health or general well-being
• Recommend against routine use of DHEA due to limited data for efficacy and safety
Endocrine Society clinical practice guideline

- Recommend against routine use of T or DHEA for low androgen levels due to hypopituitarism, adrenal insufficiency, surgical menopause, pharmacological glucocorticoid administration
- Endogenous T levels do not predict response to therapy
- If testosterone used for treatment of HSDD, monitoring recommended
NAMS Position Statement

- No T level has been clearly linked to a syndrome of hypoandrogenism
- Lab assays are not accurate at low levels in postmenopausal women
- Labs should be used only to monitor for supraphysiologic levels during therapy, not to diagnose insufficiency
- Salivary testing not reliable
Conclusions

- Individualization is key in decision to use HT and should incorporate the woman’s health and QOL priorities as well as her personal risk factors for VTE, CHD, stroke, and breast cancer

Conclusions & Recommendations

Duration of use recommendations differ for EPT and ET:

- For EPT, duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3-5 years of use.
- For ET, more favorable benefit-risk profile during mean of 7 years of use and 4 years of follow-up, a finding that allows more flexibility in duration of use.
Conclusions & Recommendations

- Although ET did not increase breast cancer risk in WHI, there is lack of safety data for breast cancer survivors, and one RCT reported higher increase in recurrence rates.

- Both transdermal and low-dose oral estrogen associated with lower risks of VTE and stroke but RCT evidence not yet available.
Non-hormonal Therapies for Menopausal Symptoms
50% to 80% of North American women use nonhormonal therapies for VMS at midlife
Most midlife women don’t feel fully informed or have concerns

75% don’t feel fully informed about herbals

64% have concerns or are unsure about herb-drug interactions

61% are not confident about herbal product dosing
Uncertainty leads to

- Use of inappropriate or ineffective therapies
- Delay in use of effective therapies
- Underuse of effective therapies
Two mind-body therapies have level I evidence showing positive effects

- Cognitive behavioral therapy (CBT) protocols (MENOS 1 and MENOS 2)
- Clinical hypnosis: Elkins protocol
Other SSRIs, SNRIs

Large RCTs show significant VMS reductions with

– Paroxetine
– Escitalopram
– Citalopram
– Venlafaxine
– Desvenlafaxine
Prescription therapies: Choice

Depends on

- Prior effective therapy
- Patient history
- Adverse events profile and tolerance of adverse effects
- Coadministered medications
Prescription therapies:

Depends on
- Coexistence of mood disorder
- VMS more bothersome day or night
- Medication sensitivity
- Pharmacogenetic testing
- Patient preference
Prescription therapies

- Start lowest dose first; titrate up to effect, tolerance
- When stopping, taper therapy over 1-2 wk
- Re-evaluate carefully and regularly (eg, every 6-12 mo)
Level II evidence suggests these may be beneficial

- Weight loss
- Mindfulness-based stress reduction
- S-equol derivative of soy
- Stellate ganglion block
Do not recommend at this time

- Over-the-counter supplements
- Herbal therapies
- Vitamins
- Relaxation
- Calibration of neural oscillations
- Chiropractic intervention
These therapies appear risk free but have no evidence testing effects on VMS
- Cooling techniques
- Avoiding “triggers”
Level I evidence shows these are unlikely to alleviate VMS, although they may have other health benefits

- Exercise
- Yoga
- Paced respiration
- Acupuncture
The 2017 hormone therapy position statement of the North American Menopause Society (*Menopause, vol. 24, no.7*)

- Endorsed or supported by American Association of Nurse Practitioners, National Association of Nurse Practitioners in Women’s Health and 32 other US and global organizations