Disclosures

No disclosures within the past 12 months

Prior disclosures past 3 years
Consultant for Pfizer
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Menopause Management
Where do we stand?

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Despite the fact that published evidence from the WHI suggests that hormone therapy is a relatively safe, viable solution for symptomatic menopausal women under age 60 or who are within 10 years postmenopause, the number of women being prescribed and using hormones continues to decline.
Fear has been driving the conversation about hormone therapy.

Women’s Health Initiative study 2002
Breast cancer
Heart disease
Stroke
Probable Dementia

Fear has been driving the conversation about hormone therapy.
The 2017 NAMS Hormone Therapy Position Statement published in July 2017 issue of *Menopause*

- Hormone therapy remains the most effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture,” says Dr. JoAnn V. Pinkerton, NAMS Executive Director and Chair of the Position Statement Advisory Panel.
HT, CHD and the ‘Timing Hypothesis’

• If initiated **early** in the menopausal transition, HT does not increase coronary heart disease risk
  • HT may reduce morbidity/mortality risk if initiated early

• **‘Early’**: Age 50-59 years, or < 10 years after menopause onset

• HT increases CHD risk if initiated later

• Findings congruent with other human, as well as non-human primate data

Stram DO, et al. Menopause 2011
JE Rossouw et al. JAMA 2007
The timing hypothesis refers to **initiation**, not **continuation**, of hormone therapy...
WHI: Women’s Health Initiative

- Multicenter, double-blind, placebo-controlled trial of women age 50-79 years at baseline, designed to assess HT’s impact on cardiovascular disease
- Mean age at screening 63-64 years
- Planned 10-year trial of standard dose HT; stopped early
  - CEE/MPA v. placebo: N= 16,608, stopped Summer ’02, mean follow-up 5.2 years
  - CEE v. placebo: N = 10,739, stopped Spring ’04, mean follow-up 6.8 years

Writing Group WHI. JAMA 2002
WHI Steering Committee. JAMA 2004
All-cause Pooled (EPT+ET) Mortality Hazard Ratios at 18 Years
Cumulative f/u by Age at Randomization

50-59 years 0.89
60-69 years 0.98
70-79 years 1.03

Risks with age at randomization

JE Manson, et al. JAMA October, 2013 & September 2017
EPT: Breast Cancer

Invasive Breast Cancer

26% ↑*

*95% nominal CI Hazard Ratio = 1.26 (1.00-1.59)

Adapted from: Writing Group WHI. JAMA 2002
Risk of Breast Cancer @13 Years Cumulative f/u in Participants OVERALL (all ages at randomization)

- EPT Hazard Ratios (HRs):
  - Persistent, significant but modest ↑ risk breast cancer: 1.28

- ET Hazard Ratios:
  - Significant ↓ risk breast cancer: 0.79

JE Manson, et al. JAMA October 2, 2013
EPT and Elevated Risk of Breast Cancer

- What does an 1.28 HR for breast cancer mean?
  - <1 additional case per 1,000 EPT users annually can be attributed to HT (WHI)
  - HR with EPT slightly higher than that seen with one daily glass of wine; less than HR with 2 daily glasses (Nurses Health Study)
  - 1 in 5 breast cancers occurring in women using EPT can be attributed to HT (WHI)

JE Manson, et al. 2013
WY Chen, et al. 2011
Meta-analysis of CHD in RCTs

• HT initiated < 10 years after the menopause in postmenopausal women reduced CHD
  – RR of 0.52 (CI 0.29 to 0.96)

• Significant increased risk of VTE
  – RR 1.74 (1.11 to 2.73)

• Death was significantly reduced
  – RR 0.70 (0.52 to 0.95)
Risks which increase with age or time from menopause

• In meta-analysis of RCTS, absolute risks which increased with age or time from menopause included stroke, venous thromboembolism and pulmonary embolism
EPT: Pulmonary Embolism

Kaplan-Meier

Cumulative Hazard

Follow-Up Year

Pulmonary Embolism

113% \(*\)

Estrogen + Progestin

Placebo

Oral HT used in WHI - might transdermal HT be safer? No comparative RCTs...

*95% nominal CI Hazard Ratio = 2.13 (1.39-3.25)

Writing Group WHI. JAMA  2002
Transdermal HT

- Based on observational data only, the use of lower doses and transdermal therapy appear to be associated with lower VTE and stroke risk.

- But…. the lack of comparative RCT data limit recommendations.
Lowering doses or transdermal

- May be appropriate as women age
- For those with metabolic syndrome
  - Hypertriglyceridemia with risk of pancreatitis
  - Fatty liver (Level III)
Endometrial protection

- For systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination CEE with bazedoxifene (TSEC) (Level I)

- Progestogen therapy is not recommended with low-dose vaginal estrogen—1-year safety data

- Appropriate evaluation of the endometrium for vaginal bleeding (Level I)
Hormone Therapy and Specific Areas

Vasomotor symptoms
Sleep
Bone and joints
Cognition and mood
Diabetes mellitus
Gallbladder and liver
Quality of life
Hormone therapy is the most effective treatment for hot flashes.

During the menopause transition, women with hot flashes are more likely to report reduced sleep.

Hormone therapy improves sleep in women with bothersome nighttime hot flashes:
- Reduces nighttime awakenings
- Improves duration, disruption, latency, and sleep cycles

Hormone therapy effectively prevents postmenopause osteoporosis and fractures

Women in the estrogen-alone and estrogen-progestogen therapy overall cohorts in the WHI had significant 33% reductions in hip fracture

After treatment discontinuation in the WHI, beneficial effects on bone dissipated rapidly, but no rebound was seen

Women in the WHI showed less joint pain or stiffness

HT & Cognition

• HT not recommended at any age to prevent or treat cognition or dementia.

• CEE/ MPA initiated >65
  – rare increase in risk for dementia (WHI)

• ET may have positive cognitive benefits if initiated immediately after early surgical menopause

• Early postmenopause period - neutral effects

• Tentative support (observational critical window hypothesis of HT in Alzheimer disease prevention

NAMS position statement. *Menopause* 2017
HT & Mood

- Evidence is insufficient to support HT in the treatment of clinical depression

In small RCTs, ET improved clinical depression in perimenopausal, but not postmenopausal women

- Progestins may contribute to mood disturbance

- If depression improves with HT, more likely to experience a worsening of mood after estrogen withdrawal
Hormone therapy & diabetes mellitus

- HT significantly reduces the diagnosis of new-onset type 2 DM but not FDA approved for this purpose
- HT may help attenuate abdominal adipose accumulation and the weight gain that is often associated with the menopause transition

The 2017 hormone therapy position statement of The North American Menopause Society.
Risk of gallstones, cholecystitis, and cholecystectomy increased with oral ET and EPT.

Lower risk with transdermal HT than with oral and with oral estradiol vs CEE (lacking RCT data).

Association of HT with slower fibrosis progression in hepatitis C and with fatty liver observed, but no RCTs benefits/risks of HT in postmenopausal women with liver disease.
Hormone Therapy and Cancer

Breast
Lung (neutral)
Ovarian
Colon

© 2017
HT & Breast

• The effect of HT on breast cancer risk is complex and conflicting
• The effect of HT on breast cancer risk may depend on
  – Type of HT (Less risk estrogen alone)
  – Dose, duration of use
  – Regimen, route of administration
  – Prior exposure to HT
  – Individual characteristics
Hormone therapy and family history of breast cancer

- Observational evidence shows use of HT does not alter risk for breast cancer in women with a FH of breast cancer
- FH is one risk among many that should be assessed when counseling women on the use of HT (Level II)
HT & Ovarian Cancer

- If an association between hormone therapy and ovarian cancer exists, the absolute risk is likely to be rare (< 1/1,000) and possibly only with long duration of use.

- Based on limited observational data:
  - no increased risk of ovarian cancer in women with a FH or a BRCA mutation using EPT.
HT & Colon Cancer

• Observational studies suggest a preventive benefit of HT on colorectal cancer incidence, particularly if initiated early in menopause

• WHI data and post intervention data found no strong evidence of a protective effect of either estrogen-progestin therapy or estrogen therapy on risk of colorectal cancer
The Symptoms of VA can include:

- Burning (urinating or not)
- Itching
- Dryness
- Vaginal irritation
- Painful intercourse (sex)
- Light bleeding after sex
- A clear or watery discharge
- Urgency with urination
- Urinary leakage
- Frequent bladder infections

As though hot flashes are not bad enough!
HT & Sexual Function

- Both systemic HT and low-dose vaginal ET provide effective treatment for increasing lubrication, blood flow and sensation of vaginal tissues.
- HT increases sexual function scores primarily in symptomatic, but not asymptomatic women.
- HT not recommended as the sole treatment of other sexual function problems (eg, diminished libido) but may be an adjunct.
Bothersome GMS (VVA) and HT

• Low-dose vaginal estrogen preparations are safe and effective - cream, tablet, ring
• Minimal systemic absorption
• Advised when ET is considered only for symptoms of the genitourinary syndrome of menopause
Ospemifene and VVA
60 mg Approved FDA for Dyspareunia

- Increased superficial cells 4 + 12 weeks
- Vaginal pH decreased 4 and 12 weeks relative to placebo
- Vaginal dryness decreased 30 and 60 mg 12wks
- *Dyspareunia decreased in the 60 mg group*

- Hot flushes: placebo 3.4%, ospemifene 30 mg (9.6%); 60 mg (8.3%)
- *Boxed warning*
  - estrogen on vaginal tissues and lining of the uterus
  - **VTE** (1.45/1000 women)

Prohormone DHEA converts to local vaginal estrogen and testosterone—keeping within normal postmenopausal hormone range.

Warnings and Precautions

- Current or past history of breast cancer
- Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. Intravaginal DHEA has not been studied in women with breast cancer.
ESTROGEN SENSITIVE CANCER SURVIVORS

Endometrial Cancers
Breast Cancers

“Having cancer does make you try to be better at everything you do and enjoy every moment. It changes you forever. But it can be a positive change.”

-Jaclyn Smith on how breast cancer changed her life

Some people don’t need hair to look beautiful.
Low-dose vaginal ET & survivors of endometrial cancer

- Consideration given for low-dose vaginal estrogen therapy for relief of the GSM
  - early endometrial cancer who have completed successful treatment, including hysterectomy
  - If nonhormone options are not successful
  - On the basis of limited short-term safety trials (Level II)

Breast Cancer Survivors & GSM—low dose vaginal ET

Minimal systemic absorption

- Blood levels in postmenopause range
- Based on limited data, **minimal risk** for recurrence of breast cancer  
  (Level II)

Decisions should involve the woman’s oncologist

Concern raised for aromatase inhibitors with lowered overall estradiol levels  
  (Level III)
Special Populations

Early menopause
Primary ovarian insufficiency
Age older than 65 years
HT & Premature Menopause & POI

• Don’t extrapolate WHI Data to younger postmenopausal women

• Observational studies benefits on bone, heart, cognition, GSM, sexual function, and mood

• HT recommended until at least the median age of menopause (51.4 y)

• Higher doses of estrogen with adequate endometrial protection may be needed to protect bone
Prolonged duration- no good data

- Prolonged Duration- there is a lack of good quality information about prolonged duration with lower doses, transdermal products, in women who initiate hormone therapy at younger ages or closer to menopause

- Observational data is positive including recent Finnish Database (less heart disease, no increase breast cancer, but may include “healthy user bias”
No general rule to discontinue HT >65

- The recommendation to routinely discontinue systemic HT after age 65 is **NOT** supported by data
- Decisions regarding whether to continue HT beyond the age of 60 should be individualized
  - After appropriate evaluation
  - Counseling about potential benefits/risks
  - Ongoing surveillance (Level III)
Tissue selective estrogen complex

• Pairs selective estrogen receptor modulator bazedoxifene with conjugated estrogens
• Effectively treats VMS and Preserves BMD
• Protects the endometrium in postmenopausal women with a uterus
• Does not stimulate the breast;
• High rates of amenorrhea
• Improvements in sleep parameters and QOL

1Pickar JH, Mirkin S. Menopause Int. 2010;16(3):121-128.
Pinkerton JV et al Menopause 2010
Uterus intact—endometrial protection

- Consider TSEC over conventional EPT
  - Breast tenderness
  - Increased breast density on mammogram
  - Concerned about breast cancer
  - Bleeding

- Can switch from EPT to TSEC
- Early preclinical data on endometriosis, fibroids and DCIS
Medications approved by the FDA for treating depression and seizures may help to VMS shown in RCTs effective in treating hot flashes include the following off label except Brisdelle:

- **Venlafaxine** (Effexor®)
- **Desvenlafaxine** (Pristiq®)
- **Paroxetine** (Paxil®)
- **Fluoxetine** (Prozac®)
- **Citalopram** (Celexa®); **Escitalopram** (Lexapro)
- **Gabapentin** (Neurontin®)
- **Pregabalin** (Lyrica®)
- **Low dose paroxetine salt** (Brisdelle)***FDA approved VMS
Conclusion—

OVERALL BENEFIT-TO-RISK RATIO
The Experts Agree About Hormone Therapy

- Benefits are likely to outweigh risks for symptomatic women who initiate HT when aged younger than 60 years and within 10 years of menopause.
The Experts Agree about who SHOULDN’T TAKE Hormone Therapy

• For women who initiate HT > than 10 or 20 years from menopause or 60 yrs or older, the benefit-risk ratio appears less favorable than for younger women

• Greater absolute risks
  • CHD, stroke, VTE, & dementia
Change the message about Hormone Therapy

- Post WHI “Lowest dose for shortest period of time”
- Change “Appropriate hormone therapy to meet treatment objectives (goals)
  - Type, dose and formulation
  - Route of administration
  - Duration
55 year old recently postmenopausal woman complains of VMS moderate to severe hot flashes and night sweats with sleep disruption. According to the NAMS Hormone Therapy Position Statement study published in 2017, which is best statement based on current knowledge of hormone therapy for menopausal women?

1. HT should be used at the lowest dose for the shortest period of time.
2. The most favorable benefit-risk ratio is for postmenopausal women with bothersome VMS and without contraindications who are under age 60 or within 10 years of menopause.
3. Women who start HT more than 10-20 years from menopause onset or who are 60 years or older should use HT for the primary indication to lower their risk of dementia.
4. Women with an intact uterus may be given estrogen alone for relief of their VMS without concern of endometrial proliferation.