Disclosures

- Consultant (Fees to UVA)
  - Pfizer, DepoMed, Noven, Shionogi, NovoNordisk, TherapeuticsMD

- Multicenter Research (Fees to UVA)
  - DepoMed, Endoceutics, Bionova, TherapeuticsMD

- Travel fees: Pfizer, DepoMed, Noven, Shionogi, NovoNordisk, TherapeuticsMD
Hormone Therapy: Conventional and Novel

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Director, Midlife Health Center
University of Virginia
NAMS, Past President

Individualized Treatment Options Available—Appropriate Candidates, Clinical Pearls

Marriott Gaylord National Hotel—Washington, DC Thurs.—October 16, 2014
At the conclusion of this presentation, participants should be able to:

- Understand new option compared to traditional HT
  - Tissue Selective Estrogen Compound (TSEC)
    - Conjugated Estrogens/Bazedoxefine
- Compare traditional and novel hormone therapy
- Choose the best therapy for the individual symptomatic menopausal woman
- Differentiate on basis of bleeding and breast tenderness between CE/BZA (TSEC) and CE/MPA (EPT)
The Women’s Health Initiative (WHI)\textsuperscript{1} study

Women who took estrogen plus a progestin (CEE/MPA, EPT) for more than 5 years were at increased risk for coronary heart disease, stroke, venous thromboembolism, and breast cancer.

Estrogen alone, for women without a uterus, did not increase the risk of coronary heart disease or breast cancer.
**WHI Re-analysis**

**Effect of Estrogen Alone on Major Outcomes for Women <60 Years vs 70-79 Years**

### Differences in Outcomes in Women Who Received CEE*

<table>
<thead>
<tr>
<th></th>
<th>50-59 Years</th>
<th>70-79 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>-12</td>
<td>+16</td>
</tr>
<tr>
<td>Death</td>
<td>-13</td>
<td>+19</td>
</tr>
<tr>
<td>Adverse events</td>
<td>-18</td>
<td>+48</td>
</tr>
<tr>
<td>(Global index of</td>
<td></td>
<td></td>
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<tr>
<td>chronic diseases)</td>
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</tbody>
</table>

*Expressed as absolute rates per 10,000 women annualized over the average follow-up period of 10.7 years.*

Reanalysis in 2007 found less risk for women under 60 and higher risks for women 70 and over.
NAMS and IMS Guidelines

“New data and re-analyses of older studies by women’s age show that, for most women, the potential benefits of HT given for a clear indication are many and the risks are few when initiated within a few years of menopause”

“Benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause”.

A Decade After The Women’s Health Initiative—The Experts Do Agree
Menopause
Stuenkel, Cynthia A.; Gass, Margery L.S.; Manson, JoAnn E.; More
RD Langer JA Manson, MA Allison WHI Investigators Climacteric June 2012
De Villiers TJ. Climacteric 2013:16:203-204
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
- Individualization is key in the decision to use HT
Women taking menopausal estrogen

- Women with a uterus need endometrial protection
  - Either combined with a progestogen
  - TSEC- combined with SERM
- Women without a uterus can take estrogen alone

Adapted Pinkerton
A Decade After The Women’s Health Initiative—The Experts Do Agree
Window of Opportunity for Cardio-Protection

Tom Clarkson: monkey model first suggested timing hypothesis

Limited RCT data support cardioprotective effect and the timing hypothesis:

- Danish Osteoporosis Prevention Study (DOPS)
- Early versus Late Intervention Trial with Estradiol (ELITE)

Similar cardioprotective effect as HT meta-analysis

Confirmed the “Timing hypothesis”

Concordance with observational studies: Young postmenopausal women who use HRT for long periods of time have lower rates of CHD and mortality than comparable postmenopausal women who do not use HRT.

Risk of blood clots/stroke

- Both estrogen therapy and estrogen with progestogen therapy increase the risk of VTE and PE

- Although the risks of VTE and strokes increase with HT, the risk is rare in the 50-59-year-old age group

- In 50-59 yr olds in WHI the attributable risks were:
  - Combined MHT - 1/2,000 WY
  - Estrogen alone – no increase

- Is route or dosage more important? Less risk with low dose transdermal in observational studies

Adapted Pinkerton A Decade After The Women’s Health Initiative—The Experts Do Agree
Risk of breast cancer

- An increased risk in breast cancer is seen in 3-5 years of continuous estrogen/progestogen therapy
- The risk decreases after HT is stopped
Safe to use EPT or ET long term?

The WHI did not address the long term effects of EPT or ET when started in newly menopausal women!

See Dr. Kaunitz’s talk
Thursday Plenary 4
Women with vaginal symptoms only

- The preferred treatments are low doses of vaginal estrogen
- Another option is new SERM, ospemifene which improved dyspareunia

Adapted Pinkerton
A Decade After The Women’s Health Initiative—The Experts Do Agree
HT is an FDA-approved option for relief of menopausal symptoms and VVA and prevention of osteoporosis

- Many FDA approved HT options including bioidentical oral and transdermal
- Compounded HT is not FDA approved

Adapted Pinkerton: A Decade After The Women’s Health Initiative—The Experts Do Agree
Concerns about Custom Compounded Bioidentical Hormone Therapy

- Not FDA APPROVED, regulated or monitored
- Manufacturing not overseen by FDA
  - What exactly is in it? Quality, purity?
  - 70-200% estradiol, 70% progesterone
- No large clinical trials to test safety and effectiveness
- Meningitis and deaths from compounded non sterile steroid injections
- Myths abound that it is safer or prevents breast cancer
- Potential medicolegal risks for provider

NAMS. Website. ACOG. Website.  
//www.acog.org//Committee_on_Gynecologic_Practice/Compounded_Bioidentical_Hormones
HT tolerability issues

- HT associated with poor compliance due to tolerability of progestogen
  - Irregular bleeding
    - May increase unnecessary interventions/anxiety
  - Breast pain/tenderness
    - May cause anxiety
  - Increase on breast density
    - May reduce sensitivity of screening mammograms
    - Independent risk factor for breast cancer
New hormonal option - CEE/BZA (TSEC)

CEE/BZA is a tissue-selective estrogen complex (TSEC) pairing CE with the selective estrogen receptor modulator (SERM) BZA.

Unlike other SERMs, BZA possesses sufficient antagonist effect on uterine tissue to be paired with an estrogen.

**CEE/BZA**
- Endometrial protection
- Prevents hot flushes
- Preserves vaginal health
- Neutral breast
- Prevents bone loss
- Favorable lipid profile
In October 2013, the FDA approved a novel hormone therapy, conjugated estrogens paired with the SERM bazedoxefine (CE/BZA) for symptomatic postmenopausal women with a uterus to relieve hot flashes and prevent osteoporosis without the need for a progestogen.

Incidence of endometrial hyperplasia at year one was low, <1% and similar to placebo with rates comparable to placebo for cardiovascular and cerebrovascular events, and cancer. VTE rates were low.
SMART 2: Daily # Mod-Severe Hot Flushes (LOCF) - Reduction in HF number up 80%

Pinkerton et al. Menopause. 2009;16:1116-1124
SMART 2 Hot Flush Daily Severity Score
Reduction in HF severity up to 54%

Pinkerton et al. Menopause. 2009;16:1116-1124
SMART 3: Vaginal Maturation Index

SMART 3:
Superficial cells

*P<0.05 vs. placebo; †P<0.05 vs. BZA alone.
*Kagan et al. Menopause. 2010;17:281-289

*P<0.05 vs. placebo; †P<0.05 vs. BZA alone.
SMART 3 Adjusted Mean Change From Baseline in Vaginal pH

Week 4

- Placebo: 0.101
- CE 0.45/BZA 20: <0.001
- CE 0.625/BZA 20: -0.4
- BZA 20: -0.6

Week 12

- Placebo: 0.116
- CE 0.45/BZA 20: <0.001
- CE 0.625/BZA 20: -0.8
- BZA 20: -1

Both CE/BZA groups statistically different from BZA 20 at both time points

Lumbar Spine BMD Adjusted Mean % Change

Months of Therapy

- CE 0.625/BZA 20 (n=139)
- CE 0.45/BZA 20 (n=119)
- BZA 20 (n=56)
- Placebo (n=139)
- CE 0.45/MPA 1.5 (n=59)

BMD change relative to PBO:
- CE 0.625/BZA 20: ↑ 1.87% at 1y
- CE 0.45/BZA 20: ↑ 1.51% at 1y
- BZA 20: ↑ 1.34% at 1y
- CE 0.45/MPA 1.5: ↑ 2.57% at 1y

P-value vs Placebo ≤ 0.001 (both CE/BZA groups, BZA and CE/MPA)

Data on file, Pfizer Inc.
Prevention Osteoporosis Summary

- Increase from baseline in LS and total hip BMD at year 1 and 2
  - Significantly higher than placebo
  - Comparable or superior to raloxifene
  - Comparable to BZA
  - Comparable or inferior to CE/MPA
  - Persistence of effect up to 2 years
  - Effective regardless of the sub-population evaluated
Endometrial Safety

- Incidence of endometrial hyperplasia < 1%, as required by regulatory agencies
- Low incidence of endometrial proliferation
- Low incidence of asymptomatic endometrial polyps
- Asymptomatic increase in endometrial thickness (< 1mm)
- Amenorrhea similar to placebo and consistently lower than CE/MPA
Breast Tenderness and Density

- Breast density -independent risk factor for breast cancer
  2.
  - EPT associated with increased breast density 1
  - New onset of tenderness with EPT linked to increase in mammographic density 3-5

- CEE-alone no increased breast tenderness or mammographic density 5-6

Percentage of subjects ≥1 day of breast tenderness during 4-week cycles over Year 1

BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate.

a\[P <0.001 vs placebo.

b\[P <0.01 vs BZA 20 mg/CE 0.45 and 0.625 mg and BZA 20 mg.

Data on file, Pfizer Inc.
SMART 5 Adjusted Change From Baseline in Breast Density (PP)

Adjusted Change From Baseline in Percent Breast Density at Year 1†

†Includes all women enrolled in the breast density substudy who took at least 1 dose of study drug, had a baseline breast density evaluation, and had at least 1 post-baseline evaluation.

*P <0.001 vs placebo.

CE 0.45 mg/BZA 20 mg (n = 186)
CE 0.625 mg/BZA 20 mg (n=191)
BZA 20 mg (n=98)
CE 0.45 mg/MPA 1.5 mg (n=68)
Placebo (n=182)

Pinkerton et al. Obstet Gynecol. 2013. 121:959-68
## Cumulative Incidence of Breast Cancer*

<table>
<thead>
<tr>
<th></th>
<th>BZA 20 mg/CE 0.45 mg (n = 1,585)</th>
<th>BZA 20 mg/CE 0.625 mg (n = 1,583)</th>
<th>Placebo (n = 1,241)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events</strong></td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Incidence rate per 1000 women-years (95% CI)</strong></td>
<td>1.0 (0.0, 3.2)</td>
<td>0.0 (0.0, 1.5)</td>
<td>1.4 (0.0, 4.2)</td>
</tr>
<tr>
<td><strong>Relative risk (95% CI)</strong></td>
<td>1.1 (0.3, 3.8)</td>
<td>0.4 (0.1, 2.0)</td>
<td></td>
</tr>
</tbody>
</table>

BZA, bazedoxifene; CE, conjugated estrogens; CI, confidence interval.
*Includes cumulative data (up to 2 years) from SMART-1, SMART-2, SMART-3, SMART-4, and SMART-5.
SUMMARY: CEE 0.45 and 0.625 mg/ BZA 20

- Significant reduction in menopausal symptoms,
  - Improvements in VMS\(^1,5,6\)
  - Improvement in measures of VVA\(^1,7,8\)
- Significant increases in BMD and decreased bone turnover\(^2\)
- Low incidences of breast pain/tenderness\(^1\)
- High rates of amenorrhea, similar to placebo\(^4\)
- Low incidences of endometrial hyperplasia\(^3\)
- No changes in mammographic breast density\(^9\)

Maximize Benefits and Minimize Risks of HT

- Lowest risk if begun w/in 1st 10 yrs of menopause or < age 60
- Primary indication is bothersome hot flashes and night sweats
  - Other indications include high risk osteoporosis, depression not responding to antidepressants, sleep disruption due to VMS, Somatic pains, migraines worsening with lowered estrogen
  - Benefit for CVD protection intriguing-
- Not contraindicated for symptomatic women >60
  - If evaluate risk factors for CAD, treat medical issues
  - If continuing hormone therapy for women who began in their 50’s
- Consider low dose transdermal- lower VTE and stroke risk
- Reassess regularly. For many, treatment can be tapered down or stopped after a few years of use.

Adapted Robert Reid SOCG
Clinical Pearls - Traditional or TSEC? Individualizing Therapy

No uterus - Estrogen alone
- *No data/ indication* for TSEC if hysterectomized

Uterus intact - need endometrial protection
- Requires progestogen or TSEC

Consider TSEC over conventional EPT
- Breast tenderness,
- Increased breast density
- Concerned about breast cancer risk
- Bleeding
- Possibly after 3-5 years of EPT - *no data* on switching from EPT to TSEC
Suggested References


### Table 1 | Current major indications and contraindications for PMHT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Evidence and recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential indications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe climacteric symptoms</td>
<td>High-quality evidence, strong recommendation</td>
<td>Systematic PMHT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oestrogen therapy in case of hysterectomy</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>High-quality evidence, strong recommendation</td>
<td>Local oestrogen therapy</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Moderate-quality evidence, weak recommendation</td>
<td>Systematic PMHT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment for a limited period of time, before shifting to other drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>when non-oestrogen therapies are unsuitable or when climacteric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>symptoms are also present</td>
</tr>
<tr>
<td>Overactive bladder</td>
<td>Moderate-quality evidence, weak recommendation</td>
<td>Local oestrogen therapy</td>
</tr>
<tr>
<td>Recurrent urinary tract infection</td>
<td>Moderate-quality evidence, weak recommendation</td>
<td>Local oestrogen therapy</td>
</tr>
<tr>
<td><strong>Not indicated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genuine stress incontinence</td>
<td>High-quality evidence, weak recommendation</td>
<td>Condition might be worsened by systemic PMHT, and improved by vaginal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oestrogen therapy</td>
</tr>
<tr>
<td>Prevention of coronary heart disease</td>
<td>High-quality evidence, weak recommendation</td>
<td>Oestrogen therapy might reduce the risk of atherosclerosis in young</td>
</tr>
<tr>
<td></td>
<td></td>
<td>women early after menopause, but risk of coronary heart disease might</td>
</tr>
<tr>
<td></td>
<td></td>
<td>be worsened as a result of thrombosis in at-risk patients</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>High-quality evidence, weak recommendation</td>
<td>Some studies suggest a reduced risk among users of hormone replacement</td>
</tr>
<tr>
<td>Prevention of dementia</td>
<td>Moderate-quality evidence, weak recommendation</td>
<td>Oestrogen therapy might decrease risk of cognition impairment in early</td>
</tr>
<tr>
<td></td>
<td></td>
<td>menopause and oophorectomised patients, but PMHT might worsen dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in elderly patients</td>
</tr>
<tr>
<td><strong>Potential contraindicated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer survivors</td>
<td>Moderate-quality evidence, strong recommendation</td>
<td>Increased risk of recurrence</td>
</tr>
<tr>
<td>Endometrial cancer survivors</td>
<td>Low-quality evidence, weak recommendation</td>
<td>Few studies show no increase in recurrence of endometrial and ovarian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cancer</td>
</tr>
<tr>
<td>Ovarian cancer survivors</td>
<td>Low-quality evidence, weak recommendation</td>
<td>Low-dose PMHT and transdermal therapy might be preferred in high-risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients</td>
</tr>
<tr>
<td>Stroke</td>
<td>High-quality evidence, strong recommendation</td>
<td>NA</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>High-quality evidence, strong recommendation</td>
<td>The risk might not be increased using transdermal therapy</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, not available; PMHT, postmenopausal hormone therapy.
Demographics & Baseline Characteristics

- Pooled demographics for all 4 trials generally balanced across treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>SMART-1 (PM)</th>
<th>SMART-2 (VMS)</th>
<th>SMART-3 (VVA)</th>
<th>SMART-5 (VMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Mean (SD)</strong></td>
<td>56.33 (5.94)</td>
<td>53.39 (4.76)</td>
<td>56.33 (4.47)</td>
<td>53.53 (3.72)</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>81.2</td>
<td>81.4</td>
<td>88.4</td>
<td>84.1</td>
</tr>
<tr>
<td>Black</td>
<td>13.6</td>
<td>10.7</td>
<td>3.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.8</td>
<td>3.8</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Asian</td>
<td>0.8</td>
<td>0.9</td>
<td>1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>0.7</td>
<td>3.1</td>
<td>3.1</td>
<td>0.6</td>
</tr>
<tr>
<td><em><em>BMI</em> Mean (SD)</em>*</td>
<td>25.93 (3.51)</td>
<td>26.20 (4.00)</td>
<td>25.39 (3.84)</td>
<td>26.08 (3.83)</td>
</tr>
<tr>
<td><strong>Yrs Since LMP</strong></td>
<td>8.20 (5.73)</td>
<td>4.54 (4.09)</td>
<td>7.44 (4.84)</td>
<td>3.59 (3.09)</td>
</tr>
</tbody>
</table>

*BMI – Body Mass Index
**LMP – Last Menstrual Period