Nuts & Bolts of Menopausal Hormone Therapy

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Disclosure Consultant, Merck
Learning Objectives

At the conclusion of this presentation, participants should be able to:

- Identify the spectrum of benefits & risks relating to menopausal hormone therapy (MHT)
- Compare & contrast the efficacy, safety & side effects of available therapies (hormonal & non-hormonal)
- Individualize risk assessment and management strategies
Case Studies

Case 1
- 51 year old, LMP 9 months, frequent bothersome night sweats, difficulty concentrating.
- Otherwise healthy, nonsmoker, BMI 28Kg/m²
- Exercises regularly.
- Mom fractured hip at 72

Case 2
- 65 year old, menopausal since age 53 presents with disturbed sleep, bothersome VMS
- BMI 32Kg/m²
- WC 95 cm.
- History of HTN
- Mom had stroke at 63.
Case 3

- 49 year old, irregular cycles, hot flashes, poor sleep
- History of wrist # at 45
- Maternal h/o Br. Ca at 50
- Nonsmoker, BMI 25Kg/m²
- Dense breasts on mammography

Case 4

- 55 year old, menopausal since age 53 presents with progressively worsening dyspareunia & insomnia
- BMI 34Kg/m²
- WC 98 cm.
- History of type II DM
- Father died at 52 of MI.
Pre-WHI Perceptions

Risks
- Endometrial Ca-E alone
- VTE
- Stroke
- Breast Cancer

Benefits
- Cognition
- CVD Risk
- QOL
- Skeletal Benefit
- Symptom Control

Weighing Risks vs Benefits

WHI

E+P

WHI HRT Study
Effect of E plus P on Event Rates

<table>
<thead>
<tr>
<th>Event</th>
<th>Additional Events</th>
<th>Reduced Events</th>
<th>Neutral</th>
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<tbody>
<tr>
<td>CHD</td>
<td>7</td>
<td>6</td>
<td>E+P</td>
</tr>
<tr>
<td>Stroke</td>
<td>8</td>
<td>5</td>
<td>Placebo</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

E-Alone

Annual Risks & Benefits after 7 years of E

<table>
<thead>
<tr>
<th>Event</th>
<th>Increase</th>
<th>Decrease</th>
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<tbody>
<tr>
<td>Stroke</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>VTE*</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Breast cancer*</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>CVD*</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hip fractures</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>All fractures</td>
<td></td>
<td>57</td>
</tr>
</tbody>
</table>


Adapted from JAMA 2004;291:1701–12
MacLean A, Sturdee D. Climacteric 2004
WHI- Take Home Message

**WHI HRT Study**

<table>
<thead>
<tr>
<th>Event</th>
<th>Number Needed To Harm</th>
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</thead>
<tbody>
<tr>
<td>CHD</td>
<td>237</td>
</tr>
<tr>
<td>Stroke</td>
<td>225</td>
</tr>
<tr>
<td>CV- All (CHD or Stroke)</td>
<td>115</td>
</tr>
<tr>
<td>VTE</td>
<td>105</td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td>237</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>336</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>403</td>
</tr>
<tr>
<td>Vertebral Fracture</td>
<td>387</td>
</tr>
</tbody>
</table>

*Based on an average exposure of 52 years

**Lessons of Past Decade.....**

- MHT Does NOT retard aging
- MHT is NOT risk free
- MHT CAN harm some...
  - Aged
  - Remote from last menstrual period
  - Overweight/ obese
  - Existing pre morbidities
MHT ...... Why Consider?

- VMS
- Poor Sleep
- Cognition
- Mood & Affect
- Urogenital Symptoms
- Musculoskeletal
- Hair & Skin
Symptom Burden..... *When*?

- >75% of women report hot flushes within the 2-year period around menopause
- Primary reason women seek medical treatment
- 25% remain symptomatic for >5 years

*Prevalence of Hot Flushes*

Menopause

Years Before | Years After
--- | ---
3 | 1
2 | 2
1 | 3

Symptom Burden.....Who?

- Perimenopause
  - VMS
  - Sleep
  - Mood/affect/cognition
  - Hair
- Obese
- Race
- Remote from LMP
  - Urogenital
- Unique
  - PMS
  - HIV
  - Surgical menopause
MHT – Is the Most Efficacious of Available Rx Options for Common Menopausal Symptoms

**Hot Flashes**

- HF ITT-OCEE
- HF ITT-t-E2
- HF ITT-PBO

**Night Sweats**

- HF ITT-OCEE
- HF ITT-t-E2
- HF ITT-PBO

**KEEPS Trial**

727 early postmenopausal women within 3 years of final menses

OCEE-0.45mg/d; t-E2: 50mcg/d + cyclic micronized P 200mgx12 days/month vs. Placebo
# Placing MHT in Perspective

<table>
<thead>
<tr>
<th><strong>Risks</strong></th>
<th><strong>vs.</strong></th>
<th><strong>Benefits</strong></th>
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</thead>
<tbody>
<tr>
<td>- Vascular (VTE, stroke, MI)</td>
<td></td>
<td>- Symptom control</td>
</tr>
<tr>
<td>- Age</td>
<td></td>
<td>- Improved QOL</td>
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<tr>
<td>- Obesity</td>
<td></td>
<td>- Skeletal benefit</td>
</tr>
<tr>
<td>- Comorbidities</td>
<td></td>
<td>- Breast cancer risk reduction with E alone?</td>
</tr>
<tr>
<td>- Family history</td>
<td></td>
<td></td>
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<tr>
<td>- Lifestyle</td>
<td></td>
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</tr>
</tbody>
</table>

| **Breast Cancer** | | |
| - Age | | |
| - Obesity | | |
| - Parity | | |
| - Comorbidities | | |
| - Lifestyle | | |
MHT & Breast Cancer Risk

MHT & Breast Ca Risk

- WHI EP (6.2 yr)
  - 1.26 (1.0-1.6) – ITT
  - 1.49 (1.13-1.96) – Adherent

- WHI E (7.1 yr)
  - 0.8 (CI, 0.6-1.2) – ITT
  - 0.67 (CI, 0.47-0.97) – Adherent

- HERS II (EP - 6.8 yr)
  - 1.27 (0.8-1.9)

OR (95% CI)


WHI- Estrogen Alone & Invasive Breast Ca
Extended Follow Up

(median 11.8 [9.1-12.9] years follow up after median 5.9 years of E use)

- Intent to Treat
- Adherence adjusted risk

151 cases of invasive Br Ca in E users vs. 199 in Placebo, HR 0.77, 95% CI 0.62-0.95

MHT & VTE Risk

Age

Age-specific incidence of venous thrombosis
WHI EP: 16,608 PM women

50-59
Events: 132 versus 13
Annualized rate: 1.9 in E+P vs 0.8/1,000 person-yr

60-69
Events: 76 versus 38
Annualized rate: 3.5 in E+P vs 1.9/1,000 person-yr

70-79
Events: 60 versus 25
Annualized rate: 6.2 in E+P vs 2.7/1,000 person-yr

Placebo ▲
E+P ○

BMI-Specific Incidence of Venous Thrombosis
WHI study: RCT 16,008 women

< 25 kg/m²
Events: 24 versus 13
Annualized rate: 1.6 in E+P vs 0.9/1,000 person-yr

25-30 kg/m²
Events: 59 versus 24
Annualized rate: 3.5 in E+P vs 1.5/1,000 person-yr

> 30 kg/m²
Events: 83 versus 38
Annualized rate: 5.1 in E+P vs 2.5/1,000 person-yr

Placebo ▲
E+P ○

VTE Risk: *Drug & Route*

**Route of HT & Progestin**

**Oral vs. Transdermal E**

**VTE & CVA Risk and Route of ET:**

Five Observational Studies

- **France:** ESTHER case-control study and E3N cohort study
- **UK:** GP Research Database: VTE and CVA
- **US:** Claims-based cohort study
- **Dutch (Leiden)** case-control study

- **Oral estrogen therapy:** ↑ risk VTE & CVA
- **Transdermal ET:** no ↑ risk

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Case-control study (271 cases and 610 controls, postmenopausal women 45-70 yrs)  
Age, MHT & Stroke Risk

Rate of total stroke among never users of HT: Nurses’ Health Study.

Quantifying risk of stroke with HT use

If 10,000 women aged 50-54 years used HT for 1 year—applying the RR of 1.4 for HT and stroke seen in the overall cohort to all, 1.5 extra cases of stroke may be expected compared with an extra 7.2 cases for women aged >65.

Stroke Risk & HT in Nurses Health Study (1980-2004)
Risk for *current* versus *never* users by dose of CE

**CEE Dose**

0.3mg/day
(33,391 women yr, n=25)

0.625mg/day
(233,249 women yr, n=268)

1.25mg/day
(59,373 women yr, n=60)

Reference: No estrogen (452,957 women-years; n=349)
Adjusted: age, BMI, high cholesterol, high BP, DM, smoking, husband’s education, FH MI

Progestin *only* Option?

- **Who for?**
  - When E is contraindicated
    - Prior DVT
    - Underlying CVD
    - *History of severe endometriosis?*

- **What for?**
  - Symptoms
    - VMS
    - Sleep
  - Skeleton?

**Considerations?**
- Type-natural vs. synthetic?
- Dose

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The *art* of medicine must not be rendered a victim to our overzealous quest through obscurities of *evidence*.

- Therapeutic benefits of MHT far exceed purported risks for a substantial proportion of the most symptomatic population, i.e. early menopausal women.
- It is my/our responsibility to ensure that I/we minimize risks while helping alleviate symptom/s.
Individualize MHT Decision for Each Woman

Her Risks?
- Underlying atherosclerosis?
  - Stroke/MI
- VTE?
- Breast cancer? … does she have a uterus and therefore will need E+P

Her Gain?
- Symptom control?
  - What symptoms?
- Skeletal benefit
Symptom Specific Management

**VMS**

- **MHT** is highly efficacious
  - Right patient
  - Right dose
  - Right formulation
- Non-hormonal regimens
  - 1st line for at risk women
  - Combinations MAY be individualized
- Lifestyle interventions
  - Do work!

**Sexual**

- Psychological wellbeing?
- Relationship
  - Counseling?
- Vaginal estrogen for atrophy
- Lubricants, moisturizers and dilators have a role!
- Androgen Rx
  - Surgical menopause
Symptom Specific Management

Skeleton

• Prevention vs. Rx
• Calcium 1000-1200mg/d
• Vitamin D
  – 800-2000U D3 per day
• Exercise
  – Weight bearing
  – Impact sport
  – Walking
• Physical therapy

Sleep Disturbances

• Co morbidities
  – Apnoea
  – Restless leg syndrome
  – Depression
• Sleep Hygiene
• MHT
• Sedative/hypnotics
• Anxiolytics
• Antiseizure – Neurontin/Gabapentin
• Environment
MHT Considerations

**Formulation**

- **Estrogen**
  - Bioavailable-E2
  - CEE
  - EE
- **Progesterone**
  - Natural
  - Synthetic
- **TSEC**
  - Oral E + oral SERM

**Route**

- Oral
- TD
- Vaginal
- Intrauterine
- Parenteral

**Regimens**

- Continuous
- Cyclic / Sequential
- Long Regimens
  - Infrequent P dosing
Long Cycle MHT

Sequential Regimens

• **Infrequent P dosing**
  – Alternate month P
  – Every third month P
  – Every 6 months
  – Biweekly P

• **Rationale?**
  – Minimize P related SE’s
  – Breast Ca risk mitigation?

Considerations

• **Progesterone**
  – Formulation
  – Dose
  – Duration
  – Interval

• **Estrogen dose**

• **Patient’s Risk Profile**
  – Risk for Endometrial Ca?

• **Endometrial surveillance?**

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## Future of MHT... *the Future is NOW!*

<table>
<thead>
<tr>
<th>Target</th>
<th>SERMs</th>
<th>Estrogens</th>
<th>TSECs</th>
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## Non-Hormonal Rx options

<table>
<thead>
<tr>
<th>Class</th>
<th>Commonly used agents</th>
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</thead>
<tbody>
<tr>
<td><strong>Anti depressants</strong></td>
<td><strong>SSRI’s:</strong></td>
</tr>
<tr>
<td></td>
<td>Paroxitene (Paxil, 12.5-25mg/day)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine (Prozac, 20mg/day)</td>
</tr>
<tr>
<td></td>
<td>Escitalopram (Lexapro, 10-20mg/day); Citalopram (Celexa, 10-30mg/day)</td>
</tr>
<tr>
<td></td>
<td><strong>SNRI’s:</strong></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine (Effexor, 37.5-75mg/day) Daloxetine (Cymbalta 60-120mg/day)</td>
</tr>
<tr>
<td><strong>Hypnotic</strong></td>
<td>Eszopiclone (Lunesta, 3mg/day)</td>
</tr>
<tr>
<td><strong>Antiseizure</strong></td>
<td>Gabapentin (100-300mg starting dose, increasing to 900mg/day)</td>
</tr>
<tr>
<td><strong>Antihypertensive</strong></td>
<td>Clonidine (0.05mg twice daily orally or 0.1mg/day patch)</td>
</tr>
<tr>
<td></td>
<td>Methyldopa (250mg three times/day)</td>
</tr>
<tr>
<td><strong>Natural products</strong></td>
<td>Vitamin E/Herbals/ Phytoestrogens</td>
</tr>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Relaxation/Exercise/Yoga/Weight reduction</td>
</tr>
<tr>
<td><strong>Acupuncture</strong></td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Lubricants &amp; moisturizers</strong></td>
<td>Water based lubricants; bio-adhesive moisturizers</td>
</tr>
<tr>
<td><strong>Steallate ganglion blockade</strong></td>
<td></td>
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</table>
Take Home Points

- Management strategies **MUST** be individualized to:
  - address nature and severity of symptoms
  - while maintaining individualized risk/s in perspective
- For early menopausal women, MHT is the **MOST** efficacious of available strategies.
- Non-hormonal therapies **SHOULD** be 1st line Rx for symptomatic women who are deemed “at risk” for MHT related adverse effects.
- Estrogen dose reduction, TD administration, choice of progestin & regimen **CAN** offer risk reduction.
Case Study

Case 1

- 51 year old, LMP 9 months, frequent bothersome night sweats, difficulty concentrating.
- Mom fractured hip at 72.

- MHT OFFERS SYMPTOM CONTROL & SKELETAL BENEFIT
- MHT 1ST LINE APPROACH
- TRANSDERMAL E ROUTE PREFERRED

Case 2

- 65 year old, menopausal since age 53 presents with disturbed sleep, bothersome VMS.
- Mom had stroke at 63.
- AT INCREASED RISK FOR VASCULAR EVENTS (AGE, OBESITY, HISTORY)
- NON-HORMONAL OPTIONS SHOULD BE FIRST LINE CONSIDERATION
Case Study

Case 3

• 49 year old, irregular cycles, hot flashes, poor sleep
• History of wrist # at 45
• Maternal h/o Br. Ca at 50
• Nonsmoker, BMI 25Kg/m2
• Dense breasts on mammography

Case 4

• 55 year old, menopausal since age 53 presents with progressively worsening dyspareunia & insomnia
• BMI 34Kg/m2
• WC 98 cm.
• History of type II DM
• Father died at 52 of MI.

TSEC
• SYMPTOM CONTROL
• SKELETAL BENEFIT
• NO NEED FOR P
• REDUCED RISK FOR BR CA?

TD E2 + PROGESTERONE IUD
• SYMPTOM CONTROL
• SKELETAL BENEFIT
• ENDOMETRIAL PROTECTION
• MINIMAL BREAST TISSUE EFFECT?

AT INCREASED RISK FOR VASCULAR EVENTS (AGE, OBESITY, HISTORY)
• DOES NOT NEED SYSTEMIC MHT!
• VAGINAL ESTROGEN
• NONHORMONAL RX

Father died at 52 of MI.
Long Cycle MHT

• **Take Home Points: Risk for Endometrial Ca**
  • Duration of P use matters
    • >10 days (12-14)
  • Dose of P matters
    • 200-400mg micronized P
    • 10mg MPA
    • 1mg NETA
  • Dose of E matters
    • higher risk with higher E dose
  • Length of MHT use matters
    • *Increased risk with >5 year use*
  • Type of P matters
    • *Progestins are superior to natural P in antagonizing endometrial effects of E*