A New Menopause Generation
What Have We Learned in the 13 Years Since the WHI?: Case Reviews
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Disclosures

- **Speaker**
  - Bayer Pharmaceuticals

- **Editorial Advisory Board**
  - Bayer Pharmaceuticals
  - Actavis
  - Sharecare Inc.

- Off label discussion will be included and identified in this discussion.
Objectives

- Apply stage specific menopause symptom management.
- Counsel women across age groups regarding the variation of risks of menopause hormone therapy. Use evidence to support or correct the patient's understanding of menopause management, including the topic of bio-identical hormones.
- Identify women with special medical considerations and apply individualized management plans.
Women’s Health Initiative 2002

Randomized Controlled Trial

- CEE 0.625 mg/MPA 2.5 mg vs. placebo
  - 16,608 women aged 50-79 years, median age 63 years
  - E+P arm stopped at 5.2 years
- CEE 0.0625 mg vs. placebo if no uterus
  - 10,739 women aged 50-79 years, median age 63 years
  - E only arm stopped at 7.1 years

The Menopausal Hormone Therapy Controversy is Over

15 Major Medical Organizations Joint Statement 2012

- The North American Menopause Society: [www.menopause.org](http://www.menopause.org)
- The American Society for Reproductive Medicine: [www.asrm.org](http://www.asrm.org)
- The Endocrine Society: [www.endocrine.org](http://www.endocrine.org)

Manage the Symptoms
“My periods are different. Is this Menopause?”

- Random cycling, sometimes early, sometimes late.
- Flow variable with prodromal spotting, a long taper, or stopping and starting.
- She has a day of very heavy flow.

- What is the longest interval without bleeding?
- Does she have any other symptoms?
Hormones Control the Cycle

- Messages
- Produced by the pituitary and developing follicles
A Well Controlled Conversation

Harvard Women’s Health Watch. Perimenopause. September 1999
As The Follicles Age

Perimenopause (180° φ)

True Menopause: Cessation of Menses

Harvard Women’s Health Watch. Perimenopause. September 1999
Predicting Menopause

- Salivary hormone levels not reflective of serum levels - no role in monitoring therapy
- Blood tests of little value

Stages of Reproductive Aging Workshop

- Best indicator of approaching last menses (FMP) is 60 days without menses
  - Last menses will occur within 1 to 3 years

What Was Not Useful

- Antimüllerian Hormone
- Inhibin-B
- FSH
- Antral Follicle Count

Perimenopause

- Menstrual cycle irregularities appear first
  - Persistent ≥ 7 day variance in cycle length
  - Onset time frame variable

- STRAW stages -1 and +1a characterized by vasomotor and other symptoms
  - One to three years before and 2 years after FMP

Managing Cycle Irregularities

- Combined Hormonal Contraceptives
  - Only intervention that provides cycle control
  - Exposes patient to known risks of CHC
- Progestin-Only Contraceptives
- Levonorgestrel IUS
- Endometrial Ablation
- Hysterectomy
“If Only I Could Sleep.”

- Vasomotor/hot flashes (85% incidence)
- Sleep disturbances
- Vulvovaginal atrophy and urinary incontinence
- PMS - new or worsened
- Decreased libido
- Arthralgias/Myalgias
- Increased body mass

“My hot flashes are so bad I can’t even go to the gym.”

- Frequency and severity of hot flashes and night sweats
- Insomnia primary or secondary?
- Mood changes cyclical? Longer duration? “Foggy brain?”
“I’m eating the same, exercising the same. I’m still gaining weight”

- 25% of women aged 35-47 gained ≥ 10 lb. in 4 years
  - Women in the 35-39y and 40-44y cohorts were more likely to gain ≥ 10 lb than women in the 45-49y cohort
  - Women who were normal weight at baseline were more likely to gain ≥ 10 lb than overweight or obese women

Joint Statement

The North American Menopause Society (www.menopause.org)
The American Society for Reproductive Medicine (www.asrm.org)
The Endocrine Society (www.endo-society.org)

- Hormone therapy is an acceptable option up to age 59 or within 10 years of menopause for moderate to severe symptoms

- Women need progestogen along with estrogen if uterus is intact
Indications for Hormones

- Systemic estrogen therapy is FDA approved for the treatment of:
  - Vasomotor Symptoms
  - Vulvovaginal Atrophy
  - Osteoporosis Prevention
- Variable effectiveness in treating other sx
- No protection from pregnancy
Vasomotor Symptom Response

- 60-80% patients ↓ frequency and severity of hot flashes by 4 to 8 weeks treatment
- Lowest effective dose of estrogen theoretical reduction in risks of HT

Estrogen Lowest Effective Doses

- 17β-estradiol orally as conjugated equine or synthetic (0.3-0.45 mg)
- Estradiol (0.5 mg)
- Ethinyl Estradiol (5 mcg)
- Estradiol transdermally
  - osteoporosis prevention 0.014 mg
  - vaginal atrophy 0.025 mg
  - vasomotor symptom relief 0.0375 mg
Adding Progestogen

- Unopposed estrogen stimulates endometrial cancer
  - Relative risk endometrial cancer 2.3
  - RR 9.5 after 10 years use
- Risk persists several years after ET discontinuance

Lowest Effective Progestogen Doses

- Medroxyprogesterone 2.5 mg
- Micronized progesterone 100 mg
- Progestins oral
  - Norethindrone acetate 0.1 mg
  - Drosperinone 0.5 mg
- Progestins transdermal
  - Norethindrone acetate 0.14 mg
  - Levonorgestrel 0.015 mg
Best Endometrial Protection

- Continuous combined E + P
- No hormones
- E with long cycle sequential P

Off Label Progestogen

- Vaginal administration progestogen and LNG-IUS not FDA approved in postmenopausal women
  - Progestin IUS protection equivalent to continuous E+P and superior to sequential E+P in one small study
  - Close monitoring of endometrium recommended

Secondary Insomnia

- Behavioral Interventions
  - Thought stopping
  - Exercise
  - Cognitive Behavioral Therapy

- Caution re pharmaceutical sleep aids
  - FDA approved only for short term use.
“I’m Miserable with Night Sweats but Hormones Are Dangerous.”

Putting the Risks in Perspective

- Both estrogen alone and estrogen with progestin increase the risk of blood clots
  - The risk is rare in women aged 50-59

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Stroke and VTE

- Risk VTE doubled over baseline for all age groups
  - Women with BMI > 30 risk VTE almost triples
- Risk stroke age 50-59 not significant
- Elevated risks both VTE and stroke dissipate soon after therapy discontinuation.

Lowering the Risk VTE

- Transdermal estrogen does not increase VTE risk in 4 case controlled studies
  - Oral estrogen 2.5 (1.9, 3.4)
  - Transdermal estrogen 1.2 (0.9, 1.7)

- Limited data comparing progestins
  - ESTHER study no increased risk with micronized progesterone.

Breast Cancer and the Joint Guidelines

- Breast cancer risk increases with 5 or more years of continuous estrogen with progestin therapy, possibly earlier.
- The risk decreases after hormone therapy is stopped.

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Beyond the Headlines: WHI Breast Cancer

- E+P absolute risk: 8 additional cases per 10,000 women/year use
  - E+P increase node positive cancer at 11 years
  - Absolute risk increase: 2 deaths per 10,000 women/year at 11 years

- E+P no increased risk: <5 years use

- ET no increase risk persists at 11 years
  - Absolute risk: 7 fewer cases per 10,000 women/year; not statistically significant

Women who initiate E+P use soon after menopause, and continue for many years, appear to be at particularly high risk.

- 5-Year Estimated hazard ratio 1.64 (1.00, 2.68)
- 10-year estimated HR 2.19 (1.56, 3.08)
Conjugated estrogen/bazedoxifene 0.45 mg/20 mg (Duavee®)

- “Purposely paired” with non-progesterone
  - Yet still protects endometrium
- For women with a uterus and should have risk osteoporosis
- 4% trial population age 65 – 74 years
- 74% reduced severity/freq vasomotor sx 12 wks
- No incidence VTE clinical trials
- Unknown risk for breast cancer

NEW PRODUCT
Prescribing Considerations

- Counseling on benefits vs. risks
- Choose product
  - Estrogen component
  - Endometrial protection component
- Regimen
- Route of administration
- Dose
“I Want a Natural Menopause.”
“I Want Bioidentical Hormones”

- Molecular structure identical to endogenous hormones
  - 17-β-estradiol (E₂)
  - Estrone (E₁)
  - Estriol (E₃)

- Progesterone
  - Micronized in oil to improve absorption in gut
  - No creams have demonstrated efficacy in endometrial protection¹

Misconceptions Plentiful

- All pharmaceutical hormones, FDA approved or custom compounded, are synthesized.
- Regardless of origin, yams or horses, extensive modification occurs.
- Bioidentical products available from both FDA approved and custom compounded sources.

Pattimakiel L, Thacker H. Cleveland Clinic Journal of Medicine December 2011 vol. 78:12 829-36. [www.ccjm.org/content/78/12/829.full](www.ccjm.org/content/78/12/829.full) accessed 17 Feb 2015.
Avoid Unsubstantiated Claims

- Custom compounded formulations
  - No rigorous evidence of safety or superiority
  - May lack patient information
- Role for custom compounded hormones
  - Allergies to inert ingredients
  - Market available doses unsatisfactory
She has no vasomotor symptoms but her mother and her grandmother both had osteoporosis.

She is very concerned
Assessing Risks for Fracture

- Look for secondary causes of bone loss
- Bone density scan (DXA) only validated on women post-menopause
- Implement lifestyle interventions
  - Adequate calcium and D
  - Physical activity
  - Fall prevention
Hormones and Bone Health

- First line therapy are bisphosphonates
- Hormones reduce hip, spine, and non-spine fractures
  - 60-70% Reduction in Case Controlled Data
  - 24% Reduction in WHI
    - Hip 5-6 fewer fractures/10,000 women/year
    - risk all fractures 45-56 fewer per 10,000 women per year HT

Benefits Dissipate When Hormones Stopped

- 3 years post MHT no difference fractures past users and never users
- If alternate osteoporosis therapies not tolerated or safe, consider extended HT in high risk women

Micro Dose Estradiol Protects BMD

- Transdermal 0.014 mg/d (Menostar®)
  - Indicated for osteoporosis prevention only*
  - No data on women <55 yrs age

- *Evidence mild effect on vasomotor symptoms and histological vaginal epithelium improvement.

Berlex, Inc. Menostar package insert. 2004
Micro Dose E₂ vs. Raloxifene

- Similarly effective
- Prevents bone loss at lumbar spine in 2 yr study
  - 77.3% of E₂ recipients
  - 80.5% of raloxifene recipients

Microdose E₂ Safety Profile

- No histological evidence of endometrial stimulation
  - 99% in the E₂ group
  - 100% in the raloxifene group
- No difference mean dense area in breast mammograms
  - 19.8% in the E₂ group
  - 19.0% in the raloxifene group

“I Think I Keep Getting Yeast Infections”

- Genitourinary Syndrome of Menopause* (GSM) reported by 50% postmenopausal women.
  - Dryness
  - Itching
  - Burning
  - Pain with intercourse

*Previously called Vulvovaginal Atrophy

Portman DJ, Gass MLS. Menopause 2014; 21(10): DOI: 10.1097/gme.0000000000000329
Using Topical Vaginal Estrogen

- **Vaginal Dryness & Joint Statement**
  - Local topical estrogen if only vaginal symptoms

- **Patient education is key to success**
  - Creates estrogen rich environment
  - New cells restore elasticity and lubrication
  - Package insert is class labelling
  - Progestogen generally not indicated but no data beyond one year.

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Systemic Treatment for Genitourinary Syndrome of Menopause

 Estradiol agonist/antagonist ospemifene 60mg (Osphena®)
  
  > Significant changes in histology, pH, and dyspareunia in 12-week trial
  
  > Contraindicated in
  
  > 1. Genital bleeding of unknown etiology
  > 2. Estrogen-dependent neoplasia
  > 3. DVT or PE history or current
  > 4. Arterial thromboembolic disease s/a stroke, MI

  > May increase hot flashes. Also saw increase in UTI

Challenging Case Studies

- Hx Vascular Event or Breast Cancer
- Prolonged Use
  - E+P vs E
- Premature menopause
- Libido issues
50 year old with history of cerebral venous thrombosis

- Hot flashes and night sweats “constant”
  - Worsened over last 12 months
- Insomnia awakens at 2AM and is awake >1 hour
- “Foggy” brain
- No vaginal dryness
Non-hormonal Agents for Hot Flashes

- SSRI, SNRI and clonidine all reduced 1 hot flash/day
  - Paroxetine 10-20 mg/d*
  - Paroxetine controlled release 12.5-25 mg/d*
  - Venlafaxine 75 mg/d
  - Desvenlafaxine 100mg /d
    - 64% ↓ frequency, 31% ↓ severity vs. placebo
  - Clonidine 0.1 mg/d
    - More likely to report sleep problems 41% vs 21%

*Paroxetine decreases effectiveness of Tamoxifan

Setraline no effect
Fluoxetine modest effect
All of the previous protocols are off label.

Brisdelle ©/Paroxetine 7.5 mg
Reduced frequency VMS -1.7 @ 12 weeks
Reduced severity VMS @ 4 weeks
Same warnings as all SSRI - suicidal thoughts, serotonin syndrome

Product Information.
Gabapentin 300 mg TID

- More effective than placebo in 3 studies.
- Gabapentin 2400 mg/d or CEE 0.625 mg
  - Hot flash composite score reduction
    - Gabapentin 71%
    - Estrogen 72%
    - Placebo 54%
  - Gabapentin 25% complain of headaches, dryness, disorientation
  - Titrate dose up

Follow-up 2 Months Later

- Titrated up to gabapentin 300 mg bid after one week.
  - Stayed at this dose for 7 weeks.
- Hot flashes baseline 25/day now 3-4/day
  - Tolerable
- Feels so much better, she asks if gabapentin also has antidepressant effect.
77 year old using combination estradiol/progestin patch

- No vasomotor symptoms or vaginal dryness on therapy
- Multiple trials weaning, last 3 yrs ago
- Exercise water aerobics
- Adequate calcium, vitamin D
- “The quality of my life is worth a lot.”
2012 NAMS Position Statement
- Individualization is of key importance in the decision to use HT and should incorporate the woman’s health and quality of life priorities as well as her personal risk factors, such as risk of venous thrombosis, CHD, stroke, and breast cancer.
Consider non-hormonal product
Consider estrogen/bazedoxifene
Evidence says ameliorate risk VTE with transdermal route
8/10,000/WY cases breast cancer from WHI probable underestimate
Patient “self-managed” risk reduction by using one patch weekly vs. on-label use of bi-weekly dosing.
Vertebral fractures in 66 year old

- Osteoporosis not responsive to bisphosphonates
  - Has 3 months Forteo therapy remaining
- Painful kyphosis now progressed to 93°
- Had uterus removed
- Using estradiol patch 0.0375 mg
Breast Cancer Risk with Estrogen Only

- WHI non-significant decreased risk in all age groups (50-59, 60-69, 70-79)
- Observational studies showed risk lower than with E+P but present after long duration use

44 year-old with amenorrhea for 12 months and AMH 0.1 ng/ml

- She has vasomotor symptoms, secondary insomnia and some vaginal dryness
- She is worried about starting menopausal hormone therapy so young
Early Menopause is a Distinct Risk Group

- Acutely induced menopause from surgical removal of ovaries or chemotherapy
- Premature ovarian failure (<40y)
- Early menopause, whether spontaneous or induced, occurs before 45y
NHS Oophorectomy Data

- Estimate 1 additional death for every 9 oophorectomies if a 35-year lifespan expected

- Women hysterectomy for benign disease, n > 29,000
  - 55.6% Hysterectomy and oophorectomy
  - 44.4% Hysterectomy and ovarian conservation
  - Followed > 24 years

NHS Oophorectomy Cancer Data

- **Lung Cancer**
  - HR 1.25 (1.02, 1.56)

- **All Cancer Mortality**
  - HR 1.17 (1.04, 1.32)

- **Breast Cancer**
  - HR 0.75 (0.68, 0.84)

- **Ovarian Cancer**
  - HR 0.04 (0.01, 0.09)

Research identifying risks associated with HT is on older women.

Biologically plausible that risks are reduced for women using HT during ages typically included in reproductive years.

“I’m just not interested in sex.”

- Assess for interest/arousal/orgasm issues
- Assess for confounding variables
- Research is very limited
  - Every discipline gets to have a theory
Natural Testosterone

- No evidence enhanced vasomotor relief
- Meta-analysis systemic T (n=5053)
  - Improved sexual function and personal distress
  - Lowered total cholesterol, triglyceride, HDL; increased LDL
  - Long term safety sparse evidence of low quality
- Testosterone 300 mcg transdermal patch

Federal Register
Side Effects & Concerns

- Potential negative side effects dose related
  - Virilization (acne, deepened voice and hair growth) only with supraphysiologic levels

- Breast and cardiovascular health concerns
  - USA trial >3600 women stopped year 4 with no increase adverse events¹
  - Is RCT large enough for conclusions?

¹Biosante Pharmaceutical Libigel clinical trials.