Managing Menopause in the Presence of Chronic Disease: Exploring Options

Patricia Geraghty FNP-BC, WHNP
Disclosures

- AbbVie: Speaker, Advisory Board
- Bayer: Device Proctor
- Therapeutics MD: Speaker, Advisory Board
- Sharecare: Advisory Board

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

- Review the physiology of menopause and the risks and benefits of menopause symptom management options
- Explain the bi-directional interaction of chronic disease conditions and the menopause transition
- Identify the appropriate patient and describe the effect of menopause hormone therapy and other management options on chronic disease
Menopause Through the Ages

Aristotle describes transition

322 BC

Hypothesis & Observation

“Throw them away!”

Deficiency disease

1821

French physician DeGardanne calls it “Menopause

Treated with plants s/a cohash, cannabis, opium

1942

Premarin” copyright

1960’s

“Politics of Menopause” by Robert Wilson MD

1980’s-1990’s

WHI - First large randomized control trial

2002


Median Lifespan

34 yr

Adult lifespan

53-55 yr
Menopause Key Points

• Lifetime supply of primordial oocytes present in the fetus
  • From birth to menopause oocyte loss d/t natural cell death
• Median age of final menstrual period 51.3 yr.
  • 60-85% women have symptoms; most prevalent sleep and vasomotor issues
• Median duration of menopause symptoms 7.4 yr
  • 10.1 yr American women of African descent
  • 11.1 yr women with symptoms before final menses

Sex Steroid Formation

CHOLESTEROL

- Pregnenolone
- Dehydroepiandrosterone (DHEA)

PROGESTERONE

- 60%
- Androstenedione
- Androstenediol

PROGESTERONE

- Aldosterone
- Cortisol

Androstenedione

- 5α-Reductase
- Dihydrotestosterone (DHT)

TESTOSTERONE

- Aromatase CYP-19

ESTRADIOL

- Estradiol
- Estrone
- Estriol
Estrogen at the Cellular Level

• Three main receptors:
  • ERα and ERβ in the nucleus and, recently discovered, in the plasma membrane.
  • GPER uncertain location- plasma membrane and endoplasmic reticulum.

• Tissue specific co-activators and co-repressors
• Up regulate and down regulate DNA transcription in nucleus
• Independent activity in plasma membrane
• Action is tissue, sex, age, and disease specific
Selective Estrogen Receptor Modulators

- Tissue selective and unique by design
- Products developed for a target often have effect in non-target tissue
  - Tamoxifen- decrease breast cancer related ER, stimulates endometrial ER
  - Ospemifene- increase vulvovaginal ER and bone ER
Estrogen Target Organs

- **Estrogen Target Organs**

  - **Vulvovaginal Atrophy**
  - **Collagen loss**
  - **Decrease HDL, Increase LDL & triglycerides**
  - **Decrease arterial compliance, increase BP, Endothelial change**
  - **Decrease osteoporosis, Osteoarthritis**
  - **Vulvovaginal Atrophy**
  - **Bronchoconstriction, Vasospasm, Endothelial change**
  - **Decrease HDL, Increase LDL & triglycerides**
  - **Vasomotor symptoms, Cognition, Mood?**
  - **Decrease arterial compliance, increase BP, Endothelial change**
  - **Collagen loss**
“If Only I Could Sleep.”

Vaginal Atrophy & Urine Leaking

GSM

Muscle Aches & Pains

Hot Flashes Vasomotor

Heavy Periods

Decreased Libido

Weight Gain

Sleep Disturbances

Consequences of Failure to Treat

- 60% of women with severe symptoms seek treatment but >70% remain untreated
- Increased direct healthcare costs and indirect costs
  - Office visits, ED visits, pharmacy and hospitalization increased in women with untreated vasomotor symptoms

Iatrogenic Menopause
Premature Ovarian Failure-
Mayo Clinic Study of Oophorectomy and Aging (MOA-2)

• Surgery 45 yr
  • Increased composite 18 tracked conditions over 15-yr
• Surgery 46-49 yr
• Healthcare Costs and Utilization Project “Top 20” costly diagnoses*

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.

http://dx.doi.org/10.1016/j.fertnstert.2012.05.051
Adding Progestin

- Endometrial Cancer
  - If she has a uterus, use progestin with estrogen
    - Cancer risk r/t dose and duration unopposed E
    - Cancer risk persists after discontinuing HT
  - Hx endometrial cancer w/menopause symptoms
    - Low grade, early stage, surgically treated: benefits may outweigh risks particularly in younger women
    - Higher grade, more advanced: HT not recommended

Leading Causes Chronic Disease

1. Diseases of the heart
2. Malignant neoplasms
3. Obstructive lower respiratory disease
4. Accidents
5. Cerebrovascular disease
6. Alzheimers
7. Diabetes
8. Influenza and pneumonia
9. Kidney disease
10. Intentional self harm
11. Septicemia
12. Chronic liver disease
13. Hypertension
14. Parkinsons
15. Pneumonitis due to solids and liquids

FRAILTY

National Vital Statistics Reports, Vol. 65 No. 4, June 30, 2016
Age-adjusted Death Rate
Selected Leading Causes in USA

NOTES: ICD is the International Classification of Diseases. Circled numbers indicate ranking of conditions as leading causes of death in 2014.
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National Vital Statistics Reports, Vol. 65 No. 4, June 30, 2016
Risk Assessment: Relative or Absolute?

- Relative - WHI 26% Increased risk
- Absolute - WHI E+P: 8 additional cases per 10,000 w/y use
  - E+P increase node positive cancer at 11 years with absolute risk 2 deaths per 10,000 women/year at 11 years

BREAST CANCER and HT Duration of Use

- E+P: no increased risk < 5 years use
  - Women who initiate E+P use soon after menopause, and continue for many years, appear to be at particularly high risk.
    - 5-Year Estimated HR 1.64 (1.00, 2.68)
    - 10-year estimated HR 2.19 (1.56, 3.08)

- Personal History Breast Cancer (ER positive) ❌
- Dense breasts mammogram and biopsy but not cancer ✓
- Genetic risk breast cancer not further increased ✓

Other Cancers and HT

- **Ovarian Cancer**
  - If association exists it is *rare* (<1/1000) or *very rare* (<0.01/1000)
  - Only RCT (WHI) no association persists at 13 y follow up
  - From limited data, no association with family history or BRCA

- **Colorectal Cancer**
  - Observational studies suggest *reduced* risk
  - WHI showed protection only during treatment

- **Lung Cancer**
  - Overall *neutral* effect HT
  - 5 meta-analyses showed reduction risk or no association
  - WHI past and current smokers, > 60 y had increased deaths on CEE+MPA

The 2017 Position Statement of the North American Menopause Society
Menopause. 2017 Nov;24(7):728-753
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Mechanism of Action: Hormones & Hearts

• Cardiovascular effects seem estrogen mediated, not altered by progesterone
• Vascular endothelial cells
  • Increase vasodilation and cell migration
• Smooth muscle cells
  • Decrease cell proliferation and cell migration
• Cardiomyocyte
  • Decrease LDL cholesterol oxidation, resistance to insulin, ischemic reperfusion injury, cardiac hypertrophy

Menazza S, Murphy E. Circulation Research. 2016; 118:994-1007
Differentiated Cardiac Estrogen Receptor Roles

<table>
<thead>
<tr>
<th><strong>ERα</strong></th>
<th><strong>ERβ</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases left ventricular mass and volume</td>
<td>Reduces pathological cardiac hypertrophy</td>
</tr>
<tr>
<td>Reductions of infarct size after myocardial infarction</td>
<td>Prevents increases mortality in chronic heart failure</td>
</tr>
<tr>
<td>Cardioprotection against ischemia– reperfusion injury</td>
<td>Cardioprotection against ischemia– reperfusion injury</td>
</tr>
<tr>
<td>Regulates glucose transporter type 4 expression</td>
<td>Regulation of vascular function and blood pressure</td>
</tr>
<tr>
<td>Regulates cardiac growth</td>
<td>Modulates sex-specific response of the heart to exercise</td>
</tr>
<tr>
<td></td>
<td>Decreases inflammatory response</td>
</tr>
</tbody>
</table>

Menazza S, Murphy E. Circulation Research. 2016; 118:994-1007
HEART DISEASE: Age of HT Initiation

<table>
<thead>
<tr>
<th>Across All Ages</th>
<th>Close to menopause or &lt; 60 y age</th>
<th>&gt; 10 y since menopause or &gt; 60 y age</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Change:</td>
<td>Decrease:</td>
<td>No Change:</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>All-cause Mortality</td>
<td>All-cause Mortality</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>Cardiovascular Disease</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>Surrogate markers (carotid artery intima-media thickness) mixed</td>
<td></td>
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<tr>
<td>Angina</td>
<td></td>
<td></td>
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<tr>
<td>Revascularization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑ Stroke 6/1000
↑ VTE

↑ No increase stroke
↑ VTE

Pre-existing CVD

VTE

• Strong evidence increased risk all ages
  • Cochrane Review RR 1.74; CI 1.11-2.73
  • Do not use with hx VTE or inherited ↑ risk

• Ameliorate risk
  • Transdermal estrogen (II+++)
  • Lower dose estrogen (I+)
  • Micronized progesterone (I+)

• Vaginal estrogen no excess risk VTE or CVD

Largely Observational Data; few RCTs

2012 Joint Statement:
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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LUNG DISEASE

• Gender differences from fetus to adult
  • ERα and ERβ receptors, progesterone receptors, DHEA, and aromatase all present in lung tissue of both men and women

• Women have unique lung disease, higher incidences of asthma, more sensitivity to carcinogens s/a tobacco
  • Women have higher incidence COPD but less likely to have accurate diagnosis
    • Primary care correct diagnosis 49.9% in women and 64% in men

Lung Disease and Menopause

• Menopause transition associated with more rapid lung function decline than premenopause age-controlled women
  • FVC -10.2 ml/yr perimenopause and -12.9 ml/yr postmenopause
  • FEV1 -3.8 ml/yr perimenopause and -5.8 ml/yr postmenopause
• Hormone connection poorly defined
  • Low-dose estrogen resistance to bronchoconstriction
  • High-dose sensitivity to vasoconstrictive stimulus

Leading Causes Chronic Disease

① Diseases of the heart
② Malignant neoplasms
③ Obstructive lower respiratory disease
④ Accidents
⑤ Cerebrovascular disease
⑥ Alzheimer's
⑦ Diabetes
⑧ Influenza and pneumonia
⑨ Kidney disease
⑩ Intentional self harm
⑪ Septicemia
⑫ Chronic liver disease
⑬ Hypertension
⑭ Parkinson's
⑮ Pneumonitis due to solids and liquids

National Vital Statistics Reports, Vol. 65 No. 4, June 30, 2016
ALZHEIMERS

- WHI Memory Study initiated CEE+MPA > 65 y with 23/10,000 increased dementia indicates need for caution initiating HT this age group.
- Kuopio prospective longitudinal study showed decreased risk ALZ with early initiation and > 10 years duration HT (HR 0.47; 0.28-0.80).
- ET may help cognition initiated early after surgical menopause but effect neutral in early natural menopause.
  - In WHI ET alone did not increase ALZ in women > 65y.
- Hormone therapy not for preventing or treating decline in cognition or dementia.

MOOD DISORDERS

• Inconsistent results in use of HT to improve mood in women without clinical depression
• Women with perimenopause depression responsive to HT may experience recurrence when estradiol stopped
• Women may experience mood swings with progesterone

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KIDNEY DISEASE

• Women with mild, moderate CKD and women on dialysis experience menopause earlier than women without CKD
  • WHI cohort mild to moderate CKD 26% incidence of menopause < 45 yr
  • Anovulatory profile and hyperprolactinemia reported in dialysis patients
• Early menopause may exacerbate health risks associated with CKD: bone, cardiovascular, sexual function
• Women with CKD report less vasomotor symptoms
  • Vascular calcification and impaired endothelial function, lower body temperature?

Leading Causes Chronic Disease

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DIABETES

• Diabetes prevalence increases from 4.5% in 20-44 yr to 24.7% age 65
  • Menopause at natural age not a risk for diabetes
  • Increase of 57% with oophorectomy or early menopause- shortened reproductive life span
• Metanalysis show 47% reduction DM2 with E+P
  • WHI reduction in both E+P (19%; AR 16/10,00) and E alone (14%; AR 21/10.000)
  • Benefit reverses when HT discontinued

Effect of MHT on Diabetes

- Women with diabetes: 2 meta-analysis of studies 1966-2004 and 1997-2011, effect of E alone or E+P is either advantageous (oral) or neutral (oral and transdermal).
  - Need data and attention to safety, particularly CVD
  - AHA 2011 guidelines call diabetes CHD risk equivalent and imply not to use
  - Most guidelines do not address the issue

Effect of MHT on Diabetes Risk

- MHT not recommended as a treatment to prevent diabetes
- MHT does not have an adverse effect on blood glucose control

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ARTHRITIS

• Joints and muscles have estrogen receptors
  • Estrogen/Progesterone have demonstrated protection of joint structure and function
  • Significant reduction arthralgia in Women’s Health Initiative both arms

• Link to osteoarthritis less clear: Obesity? Cardiovascular Disease? Diabetes?

Menopause Accelerates Symptoms

- Osteoarthritis predominant females (18% to 10% in one cohort) and post menopause age
  - Hand symptoms developed within 4 years of menopause or stopping HT
- Rheumatoid arthritis functional decline accelerates after menopause
  - Ameliorated by hormone therapy use and longer reproductive age span

Bone

- ET and HT both reduce bone loss via inhibition of osteoclast resorption
  - Results in ↑ BMD and ↓ fractures hip, spine, all fractures
  - @Lower doses no sufficiently powered studies to demonstrate fracture reduction

- Protection BMD dissipates rapidly when HT stopped
  - Some residual fracture protection WHI CEE+MPA 13 y f/u

- No head-to-head studies with other bone agents

- “For women with VMS aged < 60 y or within 10 y of menopause,...ET, EPT or CEE + baxedoxifene... is probably the most appropriate bone-active therapy...”

  The 2017 Position Statement of the North American Menopause Society
  *Menopause. 2017 Nov;24(7):728-753*
Addressing the Needs of All Women, Individually

- Symptom Management
- Health Promotion
  - USPSTF says NO role postmenopause
    - Ignores QOL and associated risks of GSM
- Risk Assessment
  - <10 y since menopause, <60 y age
  - >10 y since menopause, >60 y age

https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/menopausal-hormone-therapy-preventive-medication1
No General Rule Stop Age 65y

- 42% of women aged 60-65 have moderate/severe vasomotor symptoms
- 16% of women > 85 y have VMS several times weekly
- Beers Criteria recommendation **routinely** stop systemic HT by 65 years not supported by data
- Continued use in women who started HT < 60 y & w/o new health risk more favorable safety profile
- Care w/ initiation or restart hormones after age 65 y
  - Counsel risks/benefits, potentially change to transdermal route
  - Annual reevaluation reviewing co-morbidities
  - Periodic trials lowering dose or discontinuing

The 2017 Position Statement of the North American Menopause Society
*Menopause*. 2017 Nov;24(7):728-753
Do estrogen formulations differ?

- Conjugated Equine Estrogen (CEE) or Estradiol (E2)

<table>
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<tr>
<th>Risks CEE differs from E2</th>
<th>Benefits CEE differs from E2</th>
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<tbody>
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<td>CVD</td>
<td>Vasomotor</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>GSM</td>
</tr>
<tr>
<td>Stroke</td>
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<td>Sleep</td>
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<table>
<thead>
<tr>
<th>CVD Risk¹* or No difference²</th>
<th>Vasomotor</th>
<th>No data⁴</th>
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¹Not head-to-head studies

Does Route of Administration Differ?

- Oral or Transdermal

<table>
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<th>Oral v Transdermal</th>
<th>Benefits</th>
<th>Oral v Transdermal</th>
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<td>No difference¹</td>
<td>Vasomotor</td>
<td>No data</td>
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<tr>
<td>Breast Cancer</td>
<td>No difference¹</td>
<td>GSM</td>
<td>↓ efficacy</td>
</tr>
<tr>
<td>Stroke</td>
<td>No difference¹</td>
<td>Sexual Function</td>
<td>↓ efficacy²</td>
</tr>
<tr>
<td>PE</td>
<td>↑ Risk²</td>
<td>Weight</td>
<td>No data</td>
</tr>
<tr>
<td>VTE</td>
<td>↑ Risk²</td>
<td>Bones</td>
<td>No data</td>
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<td>↑ Risk³</td>
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Role of Compounded Hormones

• Only consider if FDA approved therapy not tolerated for reasons s/a allergies to inert ingredients, or dose or formulation not available.

  • Document medical indication

  • Salivary testing unreliable

  • “Bio-identical” (similar to endogenous) FDA approved hormones available including estradiol, micronized progesterone

    • Have package inserts, including black box warnings

    • Monitored for safety in production and use

    • Supplied in tested combinations and routes of administration


• 1 – 2.5 million women use CHT
• Accounts for 68% hormone use
• 86% users unaware not FDA approved
Women Who Can’t or Won’t Use HT

- Pharmacological alternatives
- OTC and the evidence
- Lifestyle and behavioral
Pharmacological Alternatives

- SSRI, SNRI and clonidine all reduced 1 hot flash/day
  - Paroxetine 10-25 mg/d*
  - Paroxetine salt 7.5mg/d*
  - Citalopram 10-20 mg/d
  - Escitalopram 10-20 mg/d
  - Venlafaxine 37.5-150 mg/d
  - Desvenlafaxine 100-150 mg /d
    - 64% ↓ frequency, 31% ↓ severity vs. placebo
  - Clonidine 0.1 mg/d
    - More likely to report sleep problems 41% vs 21%

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
- Start at 900 mg/d. Titrate dose up

Botanicals: Fine Tuning the Isoflavone Data

- Major sources are soy and red clover
  - Genistein
  - Daidzein- converted to equol by intestinal bacteria
    - Only 30% North American women metabolize
- S(-)-equol is biologic ER-β agonist
- Intense scrutiny-no more effective than placebo in VMS
- Japanese studies of s-equol supplement

Menopause Botanicals
Ineffective (Level II Evidence)

- Black cohosh (Actaea racemosa) 40 mg
- Crinum- no studies
- Dioscorea (wild yam)-
  - D. villosa aka D. mexicana contain disogenin a sterol precursor used in manufacture synthetic steroids
  - no in vivo conversion of diosgenin to progesterone
- Dong quai aka Angelica sinensis, dang gui, tang kuei- high doses & combination products not tested
- Flaxseed- lignans in cell wall
  - Gut microbiota convert to weakly estrogenic sterols
- Ginseng
- Hops
- Maca- in vitro but not in vivo estrogen effects, decreased VMS in small but poorly designed studies
- Peurpuria (Peuraria mirifica)- a source of isoflavones but small studies with poor reporting
- Siberian Rhubarb- hydrostilbenes with weak ER-α and stronger ER-β affinity; small clinical trial with very poor retention

Botanicals Possibly Effective

- **Pine Bark** source of proanthocyanidins trademarked as Pycnogenol
  - RCT’s of 200 mg, 100 mg, 30 mg
  - Small studies
  - VMS measurements by questionnaire
  - Safety of other pine bark preparations unknown
- **Omega-3 fatty acids** - conflicting results
  - EPA 1,100 mg and DHA 150 mg
- **Pollen extract** (Relizen®) only RCT n=324, unblinded

Botanicals Potential for Harm

- *Wild Yam Creams* - often lacked yam extract and were adulterated with estrogens, progesterones, MPA
- *Dong quai* - possible photosensitization, anticoagulation, possible carcinogen; reports of uterine bleeding
- *Siberian Rhubarb* - laxative properties similar to senna

Lifestyle & Menopause Symptoms

- Recommendations without evidence:
  - Cooling techniques s/a clothing choices, environmental controls
  - Avoiding triggers s/a alcohol, spicy foods, hot foods

- Ineffective
  - Exercise
  - Yoga
  - Acupuncture
    - More effective than wait group
    - No more effective than sham acupuncture

Effective Lifestyle Interventions

• Weight Loss
  • Reported effective with 10 lb, 8.9 kg, and 10% losses
• Clinical hypnosis
• Cognitive Behavioral Therapy (CBT)
  • Reduces bother but not frequency
  • Intervention included self-guided or group education and relaxation technique training.
  • Control given only instructions
  • Group and self-guided manuals are available: Myra Hunter and Melanie Smith., Managing Hot Flushes and Night Sweats... East Sussex, NY: Routledge, 2015

Individualize

- Duration of use
- Benefits/risks
- Dosage
- Estrogen
- Progesterone
- Route of administration
- Lifestyle
- Symptoms
- Pharmacokinetics
- Treatment population
- Non-hormonal pharmacological management
Menopause in Chronic Disease Key Points

• Untreated menopause symptoms increase healthcare costs
• Menopause is associated with worsening of several chronic disease states
• Menopause Hormone Therapy is acceptable in the symptomatic woman at risk for, but without current disease
• Menopause Hormone Therapy interacts with existing chronic disease, with paucity of data to drive clinical decisions
• Alternative management protocols can give satisfactory results