Menopause Management
Current Recommendations

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Conflict of Interest Disclosure
Beth M. Lalande, MD has no significant relationships with industry to report.

OBJECTIVES
• Define menopause and associated terms
• Discuss symptoms of menopause
• Review absolute risks/benefits for five years of hormone therapy in younger postmenopausal women
• Discuss non hormonal medications to treat menopausal symptoms

Menopause
• Menopause is the final menstrual period (FMP) and is usually confirmed when a woman has missed her period for 12 consecutive months (in the absence of other obvious causes).
• It reflects complete or near complete depletion of ovarian follicles and absence of ovarian estrogen secretion. It marks the permanent end of fertility.
• Average age is 51, but age ranges from 40 to early 60s. (Occurs after age 55 in 5% and between 40-45 in 5%.
• Age of menopause influenced by genetics, ethnicity, smoking, and reproductive history.

Diagnosis of Menopause
• Diagnosis of menopause is based on clinical history
• Measurement of FSH and estradiol is not required in women ≥ 45 yrs
• In women s/p hysterectomy or have inadequate menstrual history to ascertain menopause status, measurement of an elevated FSH and low estradiol (<20 pg/ml) on several occasions supports but does not confirm diagnosis

Definitions
Perimenopause/ Menopausal Transition
• Characterized by variations in menstrual cycle length and bleeding pattern, mood shifts, vasomotor, and vaginal sx
• Rising FSH
• Falling AMH and inhibin B levels
• It can last 6 years or more and ends 1 year after the final menstrual period.

Postmenopause
• All the years beyond menopause

Induced Menopause
• when the menstrual periods stop due to a medical intervention, such as surgical removal of both ovaries or chemotherapy.
Definitions continued

**Premature Ovarian Insufficiency**
- Loss of ovarian function before age 40. Waxing/waning course with potential resumption of menses, conception, and pregnancy
- Women with premature ovarian insufficiency should undergo complete evaluation.
- Causes include: idiopathic, autoimmune (PGA), metabolic, genetic (Fragile X premutation)
- Prevalence approx 1%
- Because women with premature menopause spend more years without the benefit of estrogen, they are at greater risk of health problems later in life such as heart disease and osteoporosis. MHT is recommended to normal natural age

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**Menopausal Symptoms**

<table>
<thead>
<tr>
<th>GOOD Evidence</th>
<th>FAIR Evidence</th>
<th>POOR Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor symptoms (60-85%)</td>
<td>Cognitive dysfunction common, temporary</td>
<td>Body Composition</td>
</tr>
<tr>
<td>Vaginal dryness (30-60%)</td>
<td>Urinary incontinence</td>
<td>Joint aches and pains (up to 50% and assoc with obesity and depression)</td>
</tr>
<tr>
<td>Sleep disturbances (30-50%)</td>
<td>2-fold increase</td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Depression/mood disorders (25-40%)</td>
<td>More common in women with hot flashes</td>
<td>Known PMS</td>
</tr>
<tr>
<td>No mood disorders</td>
<td></td>
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</table>

**Consequences of Estrogen Deficiency in the Postmenopausal Years**
- Increased risk of osteoporosis
- Increased risk of diabetes
- Increased risk of CHD and CVD
- Changes in body composition-increased fat mass and decreased lean mass

**Vasomotor Symptoms: Duration**
- 90% of women typically experience VMS for 1-2 yrs around the time of the FMP.
- Average duration of VMS is 7.4 yrs with median post FMP persistence of 4.5 yrs. Women with earliest onset of sx wrt FMP had longest duration (median >11.8 yrs and post FMP persistence (median 9.4 yrs) (Avis, *JAMA Intern Med* 2015;175:531-539 –SWAN data on 881 women)
- 15% have symptoms into their 60's (Barnabei 2008)
- 9% past age 70 yrs (Huang 2008)
- May recur 10 yrs after menopause

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**Menopause Transition**

Adapted from The Stages of Reproductive Aging Workshop for Reproductive Age Women

**Vasomotor Symptoms (VMS)**

**Menopause Transition**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Late Reproductive</th>
<th>Late Transition</th>
<th>Early Post Menopause</th>
<th>Late Post Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual cycle</td>
<td>Subtle changes in flow</td>
<td>Variable length, &gt;7 day difference in cycle length</td>
<td>Interval of amenorrhea &gt;60 days</td>
<td>Amenorrhea</td>
</tr>
<tr>
<td>FSH (cycle day 2-5)</td>
<td>variable</td>
<td>Variable</td>
<td>↑ &gt;25 IU/L</td>
<td>Variable</td>
</tr>
<tr>
<td>AMH</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>Vasomotor Symptoms (VMS)</td>
<td>VMS likely</td>
<td>VMS most likely</td>
<td>Increasing sx of urogenital atrophy</td>
<td></td>
</tr>
</tbody>
</table>

**Women’s Health Initiative (WHI)**

**Does “Hormone Replacement Therapy (HRT)” Prevent Disease?**

**E+P vs. PBO**
- 16,000+ mostly asymptomatic PM women age 50-79 (mean age 63) randomized to continuous, combined estrogen-progesterone (CEE 0.625 mg + medroxy-progesterone acetate 2.5 mg vs. placebo)
- Discontinued July 2002 – average follow up 5.2 years due to increased breast cancer, CHD, stroke, VTE

**E vs. PBO**
- 11,000 PM mostly asymptomatic women
- Unopposed estrogen (CEE 0.625 mg) vs. placebo
- Discontinued Feb. 2004 – average follow up 6.8 years due to increased risk of stroke
Absolute Risks by 10 yr Age Groups in WHI During Intervention Phase: E+P vs PBO

Conclusions from WHI Extension

- 81.1% of surviving participants of WHI followed through 9/30/10 (8.2 yrs for EPT and 13.2 yrs for ET)
- Post intervention, most risks and benefits were attenuated but persisted in the estrogen plus progestin group
- Most risks and benefits were more neutral in the estrogen alone group
- Neither regimen affected all-cause mortality during intervention, post intervention and during cumulative follow up
Updated Summary of the Effects of CEE Alone or CEE+P in Women 50-59 yrs During Intervention Phase of WHI
Stuenkel et al JCEM 2015:100(11):3975

Recommendation for Hormone Therapy (HT) for Menopausal Symptoms
Endocrine Society Clinical Practice Guideline

“For postmenopausal women <60 yrs of age or <10 yrs past menopause with bothersome VMS who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take MHT, we suggest initiating ET for those without a uterus and EPT for those with a uterus”
Stuenkel et al JCEM 2015;100(11):3975

Specific Cautions to Use of Systemic MHT or SERMs for Treatment of Menopausal Symptoms
Stuenkel et al JCEM 2015;100(11):3975

ET should not be used in women with:
- Undiagnosed abnormal genital bleeding
- Breast cancer
- Estrogen dependent neoplasia
- VTE
- Active arterial thromboembolic disease (OCA, MI) or a hr or these conditions
- Liver impairment or disease
- Known protein c, protein s, or antithrombin deficiency or other thrombophilic disorders
- Known pregnancy

Caution should be exercised with:
- Gallbladder disease (oral ET)
- Hypertriglyceridemia (>400 mg/dl; oral ET)
- Diabetes
- Hypoparathyroidism (risk of hypocalcemia)
- Intermediate or high risk of breast cancer
- High risk of heart disease
- Migraine with aura (oral ET)

Benefits of MHT

- Vasomotor symptoms—ET is the most effective treatment for VMS and improving QOL in symptomatic women
- Genitourinary Syndrome of Menopause (GSM )
- Vulvovaginal atrophy and urinary tract dysfunction
- Sleep disruption
- Anxiety and depressive symptoms
- Arthralgia
- Reduction of menopause-related bone loss and fragility fx risk in older women
- Reduction of diabetes risk

Risks of MHT: Breast Cancer and Estrogen Therapy


- In WHI, women 50-59 or < 10 yrs after menopause, risk not increased by ET (CEE). 2% reduction of invasive breast cancer in 13-year cumulative follow up was of similar magnitude in each age group. (Manson L, JAMA, 2013)

- et events per 1000 women per 5 yrs use with E alone: -2.5 cases

The risk of breast cancer from estrogen alone, taken for five years, appears to be small

Stuenkel et al JCEM 2015:100(11):3975

Risks of MHT: Breast Cancer and Combined EPT

- Studies with combined EPT consistently show increased breast cancer risk. (Endo Soc Sci Statement, JCEM 2010; Chlebowski, A, JAMA 2010)

- Risk of invasive breast cancer was significantly increased with EPT in WHI at avg f/u of 5.6 yrs (HR 1.2) vs PBO events per 1000 women per 5 yrs use with E +P: -3 cases

- In women ages 50-59 in WHI; excess risk of breast cancer during intervention phase persisted for 7 yrs after cessation of EPT with 4.5 excess cases per 1000 over 5 yrs (HR 1.34 (1.03–1.75) (Manson, J, JAMA, 2013)

- Observational studies report greater risk when EPT is started close to menopause (Chlebowski JNC, 2013; Prentice, Am J Epidemi, 2009; Fournier, J Clin Oncal 2009)

Santen et al JCEM 2010;95:v1
The Study of Women’s Health Across the Nation

1/16/2017
Risk of MHT: CHD and Timing of Exposure

- WHI: no increased risk of CHD in women 50-59 or < 10 yrs postmenopause (2007) with CEE and CEE+MPA
- WHI coronary calcification study (Manson, NEJM, 2007)
- Salpeter meta analysis of clinical trials- reduction in CHD and mortality (2006, 2009) with ET younger PM women
- DOPS: Danish Osteoporosis Prevention Study (2012)
  E2 + progestin vs no treatment
  women <50 yr at study onset, 10 yrs of MHT
  Secondary analysis, reduced risk of composite outcome of mortality, heart failure or MI
  No placebo grp, unusual composite outcome
  Schierbeck BMJ 2012

TIMING HYPOTHESIS
Differential effect on atherosclerosis risk and clinical events according to when HT is initiated

KEEPS: KRONOS Early Estrogen Prevention Study
- 727 women within 36 months of FMP
- Age 42-58 (menopause >age 40)
- Baseline low CAC, CIMT and exclusions for CVD, CHD
- CEE 0.45 mg vs. transdermal E2 50 mcg vs. placebo (cyclic micronized P 200 mg x 12 days/month)
- Treatment duration 4 years
- 466 (64%) completed trial and 118 (16%) discontinued study med but were followed through duration of trial
- Endpoints: carotid IMT, coronary artery calcium score--(Women too young and healthy and study too small to look at MI risk – surrogate markers used)

KEEPS: KRONOS Early Estrogen Prevention Study
CIMT

Table 3. Changes in CAC Score, by Treatment

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants With</th>
<th>Risk Difference vs.</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CAC Change*</td>
<td>Placido (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>217 (21.3)</td>
<td>0</td>
<td>0.36</td>
</tr>
<tr>
<td>E2</td>
<td>181 (17.4)</td>
<td>-3.6 (-11.4 to 4.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>n-CES</td>
<td>172 (18.3)</td>
<td>-2.1 (-10.0 to 5.7)</td>
<td></td>
</tr>
</tbody>
</table>
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**KEEPS: KRONOS Early Estrogen Prevention Study**
*Harman et al Ann Int Med 2014;161;249-260*
- Favorable effects on VMS, mood and anxiety, sexual function, and bone density
- Coronary artery calcium and carotid IMT: no different with HT vs placebo
- No statistically significant differences in rates of breast cancer, endometrial cancer, myocardial infarction, TIA, stroke, or venous thromboembolic disease between the three groups

**ELITE: Early vs Late Intervention Trial with Estradiol**
- 643 women with LMP <6 or >10 yrs prior to enrollment
- Oral estradiol 1 mg/ day vs. placebo (vaginal progesterone gel 4% 10 days/month if uterus)
- Treatment duration 6 yrs
- Primary outcome: Carotid IMT progression
  - >10 yrs from menopause: no difference from placebo
  - <6 yr slower progression of atherosclerosis
- Data supports timing hypothesis

**Endocrine Society Clinical Practice Guideline 2015**
- Individualize therapy based on clinical factors and patient preference
- Before initiating MHT, estimate patient’s : 10-year cardiovascular risk (ACC/AHA)
  - use transdermal ET if moderate 5-10% risk
  - avoid ET if high risk >10%
- 5-year breast cancer risk (NCI or IBIS)
  - http://www.cancer.gov/bcrisktoolmobile
    - <1.67% MHT ok, 1.67-5% caution, >5% avoid

**Effective Low Dose Estrogen Equivalents for Hot Flashes**
- 0.5 oral mg micronized 17 beta estradiol
- 25 mcg/day transdermal 17 beta estradiol
- 0.3 mg oral conjugated equine estrogen
- 2.5 mcg oral ethinyl estradiol (most OCPs contain 20-30 mcg EE)

**HT: What route of estrogen?**
- Transdermal 17β estradiol
  - Avoids first-pass hepatic metabolism (TG, T)
  - Lower risk of stroke in older women (if dose <50 mcg) Renoux BMJ 2010
  - Lower risk of VTE (Canonico et al, BMJ 2007)
  - Meta analysis of all observational studies and RCT oral and transdermal estrogen
  - Oral E2 : 2-3 x increase in VTE, higher in 1st yr
  - Baseline risk 1/1000 woman yrs, additional 1.5 events per 1000 women each year
  - No significant increase in VTE with transdermal E2
Risks of MHT: Endometrial Cancer

• Unopposed ET increases the risk of endometrial hyperplasia and cancer
• Concurrent progestogen therapy for at least 12 days per month reduces this risk and is recommended for all women with a uterus
  – Continuous combined CEE + MPA associated with reduced risk of endometrial cancer over 13 yrs cumulative f/u
  – After 6-10 yrs, sequential regimens may be associated with a 2-fold increased risk of endometrial cancer

Santen et al JCEM 2010;94:s1
Manson et al JAMA 2013;310:1353

Progestogen Options

• Medroxy progesterone acetate 2.5 mg daily, 5 mg cyclic
• Micronized progesterone 100 mg daily or 200 mg cyclic
• Appropriate progestin doses for lower E doses unclear

Tolerability issues (vaginal bleeding, mood effects, breast tenderness, breast density)

Women who cannot tolerate them?
• Progestin IUD (levonorgestrel) - (Sombanporn Menopause 2011) NOT FDA APPROVED but used in Europe to prevent endometrial hyperplasia
• Bazedoxifene, SERM

Bazedoxifene Effects

• Prevents bone loss in women with low BMD
• Reduces nonvertebral fractures in women with osteoporosis
• Reduces nonvertebral fractures in high risk women
• Favorable endometrial, ovarian, and breast safety profile in women with osteoporosis


TSEC: Tissue Selective Estrogen Complex

• Bazedoxifene (BZA) paired with conjugated estrogens (CE) has been evaluated in multiple phase III trials in > 6000 women SMART trials
  • Selective estrogens
  • Menopause
  • And Response to Therapy

Bazedoxifene plus Conjugated Estrogen Effect on Daily Number of Hot Flashes

Pinkerton, J V Menopause 2009;17:1116

Bazedoxifene plus Conjugated Estrogen Effect on Daily Severity Score of Hot Flashes

Pinkerton, J V Menopause 2009;17:1116
### TSEC: Tissue Selective Estrogen Complex

Bazedoxifene (20 mg) with CE (0.625 or 0.45 mg)
- Relieves vasomotor symptoms
- Improves vaginal symptoms
- Improves sleep and quality of life
- Decreases bone turnover and bone loss
- Effects breast tenderness, vaginal bleeding, and rates of endometrial hyperplasia similar to placebo therapy
- No changes in mammographic breast density


### Conjugated Estrogen and Bazedoxifene (Duavee)

- Conjugated estrogen 0.45 mg and bazedoxifene 20 mg tablets (Duavee)
- FDA approved 10/1/13 for treatment of moderate to severe vasomotor symptoms in women with a uterus and prevention of postmenopausal osteoporosis
- First therapy to pair conjugated estrogen with an estrogen agonist/antagonist (TSEC) - uses bazedoxifene instead of progestin to prevent endometrial hyperplasia
- Phase III clinical trials in Selective Estrogens, Menopause, And Response to Therapy program (SMART):
  - 74% reduction in frequency of hot flashes at 12 wks vs 47% with placebo
  - 39% reduction in VMS severity vs 13% with placebo
  - Increases in BMD at years one and two at total hip and lumbar spine
- Side effects: muscle spasms, nausea, diarrhea, upset stomach, abd pain, throat pain, dizziness, neck pain

### Stopping Hormone Therapy

- Abrupt withdrawal may result in return of VMS in approximately 55% if MHT based on WHI *(Ockene JAMA 2005;294:183)*
- Data re: tapering MHT vs. abrupt cessation are conflicting
- For recurrent sx, monitor, try non-hormone alternative Rx, resume MHT and gradually taper

### Selective Serotonin Reuptake Inhibitors and Selective Serotonin Norepinephrine Reuptake Inhibitors (SSRIs & SNRIs)

- Randomized, placebo controlled trials show significant reduction in hot flashes with
  - **venlafaxine**
  - **desvenlafaxine**
  - **paroxetine**
  - **citalopram**
  - **escitalopram**
- Less support with sertraline and fluoxetine

### Importance of Placebo Effect

- Efficacy of various agents studies in reducing VMS in clinical trials is confounded by placebo effect
- Placebo effect can reduce VMS by 20-50%
- Women with higher anxiety scores may be more likely to respond to placebo
  - van Die Menopause 2009
Hot flash frequency and composite score with nonhormonal prescription therapies for relief of VMS

**Low Dose Paroxetine (Brisdelle)**

- Paroxetine (Paxil) first and only non hormone therapy for VMS approved by FDA 7/2013
- Simon et al Menopause 2013;20:1027 – two randomized controlled trials of paroxetine vs placebo
- Marketed as “Brisdelle” 7.5 mg qhs
- Side effects: headache, fatigue, N/V
- Avoid paroxetine in women taking tamoxifen
  - Cytochrome P-450 2D6 involved in metabolism of tamoxifen and SSRIs. Tamoxifen metabolites decreased by 24-64% at 4 wks with paroxetine Rx.
  - Breast Ca recurrence 2x higher in one study with 2 yrs tamoxifen plus CYP2D6 Rx
  - Paroxetine > fluoxetine >>> venlafaxine

**Gabapentin**

- Reduces frequency of hot flashes in randomized, placebo controlled trials
- Side effects: headache, dizziness, drowsiness—improves within 2-4 wks. May be associated with weight gain
- Gabapentin 300-900 mg at bedtime may be helpful relieving night sweats and minimizes side effects if given daytime combination with SSRI (venlafaxine) is no more effective than gabapentin alone
- Rejected by FDA May 2013 for vasomotor symptom indication

**Clonidine**

- Shown to relieve hot flashes in some clinical trials—consistent efficacy
- Consider in a woman with hypertension
- 0.1 mg/d –transdermal patch or oral option dosed two-three times daily.
- Side effects: dry mouth, dizziness, constipation, sedation.

**Complementary Therapies**

- Lack of consistent evidence for benefit for botanicals, black cohosh, red clover, Vitamin E, mind/body alternatives including anxiety control, acupuncture, paced breathing, hypnosis
  - No evidence better than placebo, but considerable heterogeneity (red clover, soy supplements)
- Black Cohosh (Cimicifuga):
  - HALT trial- Black cohosh alone no more effective than placebo. CEE effective. (Newton, Ann Intern Med 2006)
  - Cochrane 2012- no evidence that better than placebo but heterogeneity

**Treatment of Genitourinary Syndrome of Menopause (GSM)**

- Low Dose Vaginal Estrogen Therapy
  - Effectively treats vaginal dryness and dyspareunia
  - Estradiol tablet (Vagifem) 10 mcg daily x 1 week, then twice weekly
  - Estrogen ring (Estring) q 3 months
  - Estrogen cream 0.50 gm vaginally 2 times weekly
  - Progestin not required
  - Vaginal estrogen
    - Increases blood flow to vagina
    - Increases elasticity of vulvovaginal tissue
    - Decreases vaginal pH
Treatment of Genitourinary Syndrome of Menopause

OSPEMIFENE

- Ospemifene (Osphena) 60 mg po daily
- First SERM FDA approved (2/26/13) for moderate-severe dyspareunia
- 1889 women age 40 to 80 randomized to ospemifene 60 mg vs placebo
- Two 12 wk trials showing efficacy (vaginal maturation index, vaginal pH, symptoms—dryness/dyspareunia
- One long-term (1 year) safety study
- No studies in women with breast cancer
- Similar contraindications to estrogen


Patient Resources

- Endocrine Society's Menopause Map (www.hormone.org)
- North American Menopause Society (www.menopause.org)
- Free mobile app: MenoPro (algorithm and mobile app for menopausal sx mgmt and hormonal/non-hormonal therapy decision making (clinical decision-support tool from NAMS)
  2 modes: for health care provider and for patient

Summary

- HT is indicated for treatment of VMS in women with moderate to severe symptoms
- 5 yrs of E+P is considered safe in women less than 60 or less than 10 yrs postmenopause without contraindications to ET and without increased risk for CVD and breast cancer
- Consider transdermal vs oral route especially when more than 5 yrs or moderate risk

Summary

- Taper and stop after 4 to 5 years (breast cancer risk)
- After stopping, try SSRIs/SNRIs or gabapentin if recurrent flashes
- Continued use of HT beyond age 60 should be individualized
- Vaginal estrogen should be discussed with all women, particularly when systemic estrogen is stopped