Treatment of Menopausal Vasomotor Symptoms with Hormone Therapy

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- None

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Disclaimers

- Will use “female”/”women” to describe individuals born with ovaries and a uterus at birth. I understand that those individuals may not identify as “female” or “woman” and this is not indicating that they should.
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52-year-old G1P2 Postmenopausal Honduran woman

- CC: Hot flashes and accompanying sweats
- Wakes her up from her sleep nightly and stop her from going to social events

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Past Medical History

- LMP was 3 years ago.
- She denies any postmenopausal bleeding or Hx of Hysterectomy.
- Prior to 45 yo her periods were regular.
- Menarche was at 10 yo.
- She had her twins at 36 yrs old.
- 10-yr ASCVD risk from her most recent annual physical was 4.5%.
- She denies personal of Family hx of cancer.
- Colonoscopy and Mammogram are normal..
- BMI is 26.
- No Hypertension
- No Diabetes
- She is a never smoker.

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Objectives

1. REVIEW EPIDEMIOLOGY, CLINICAL PRESENTATION AND DIAGNOSIS OF MENOPAUSAL VASOMOTOR SYMPTOMS

2. REVIEW THERAPIES FOR MENOPAUSAL VASOMOTOR SYMPTOMS

3. DISCUSS SYSTEMIC APPROACH TO HORMONAL MENOPAUSAL TREATMENT

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Almost all females experience menopausal symptoms & Vasomotor Symptoms are the most common

- 85% report ≥1 symptom such as:
  - Vasomotor symptoms (79%): hot flashes, sweats (including night sweats)
  - Sleep disruption (43%)
  - Depressed Mood (34%)Have a life expectancy of at least 10 years,
  - Other: sexual dysfunction, cognitive symptoms, vaginal dryness, urinary incontinence, and somatic or bodily pain symptoms
- Symptoms are not specific to menopause

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Diagnosis of Menopause is defined as 12 months of Amenorrhea

- 95% have final menstrual period between ages 45 - 55 years
- Excluded:
  - underlying anovulatory cycles
  - taking oral contraceptives
  - s/p Hysterectomy
  - s/p endometrial ablation
  - Age < 40 yo (Primary Ovarian Failure)

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Vasomotor Symptoms are most common in the the first 5 years pre- and post-menopause

Portsmouth Regional Hospital

The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in females

Menarche — FMP (0)

Stage	−5	−4	−3b	−3a	−2	−1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	Variable				Variable	1-3 years	2 years (1+1)		3-6 years	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ strength	Variable length: Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			 Low Low	 Variable* Low Low	 ↑ Variable* Low Low	 ↑ >25 international units/L¶ Low Low	 ↑ Variable Low Low		 Stabilizes Very low Very low	
Antral follicle count			Low	Low	Low	**Low**	Very low		Very low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms likely	Vasomotor symptoms most likely			Increasing symptoms of urogenital atrophy

FMP: final menstrual period; FSH: follicle-stimulating hormone; AMH: anti-müllerian hormone;
Arrow: elevated.

* Blood draw on cycle days 2 to 5.

¶ Approximate expected level based on assays using current interna

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Providers and Patients are uncomfortable with medical management of menopausal symptoms

- 10% of Women seek out Healthcare Provider
  - Medical Students and Residents receive little or no training in the management of menopausal women
    - 50-60% of of residents in their final year of training could not identify optimal therapy for a 52-year-old menopausal woman with severe symptoms (and no contraindications to estrogen) or recommend appropriate treatment for an otherwise healthy, 39-year-old woman with primary ovarian insufficiency
  - Women's Health Initiative (WHI) study-induced hesitancy
    - 80% reduction in MHT prescriptions since the initial publication of the WHI results in 2002
  - The North American Menopause Society has also changed recommendations

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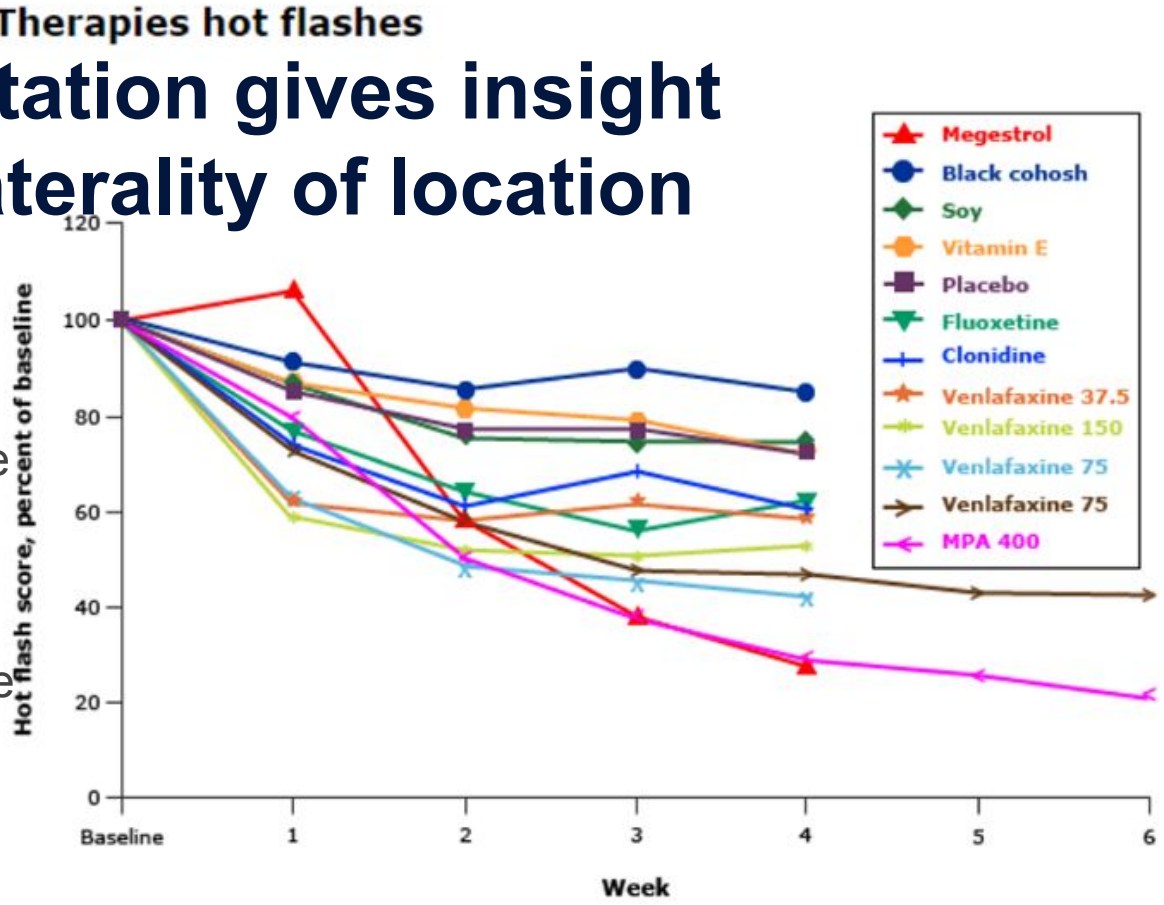
Clinical presentation gives insight into possible laterality of location

- Hormonal therapy is the most effective intervention
- SSRIs/SNRIs are a safe alternative in those with contraindications
- Placebo effect is significant, found to be correlated with anxiety



Hot flash score changes from baseline for a series of eight randomized, placebo-controlled trials, plus a trial in which women were randomized to venlafaxine (75 mg/day) versus a single dose (400 mg) of intramuscular medroxyprogesterone acetate. Six week data shown for the latter trial.

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Estrogen is the “active ingredient” in treating menopausal vasomotor symptoms

- All estrogens are effective in treating vasomotor symptoms
  - Resolution of symptoms in 80%
  - Reduced severity and frequency in 20%
- 17-beta estradiol is most structurally similar to endogenous estradiol
- There is no standard dose: start at the lowest dose and titrate up as needed to get desired effect

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Some estrogen products

Drug and United States brand name	Available strengths
Estrogen preparations and doses for the management of vasomotor symptoms	
Oral estradiol*	
Estrace¶	0.5, 1, 2 mg
Oral esterified estrogen*	
Menest	0.3, 0.625, 1.25 mg
Oral CEE*	
Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg
Oral estrogen-progestin combinations	
Prempro^Δ	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg
Prefest	1 mg estradiol/0.09 mg norgestimate (cyclic)
Activella, Amabelz, Mimvey¶	0.5 mg estradiol/0.1 mg norethindrone acetate, 1 mg/0.5 mg
FemHRT, Jevantique Lo	2.5 mcg ethinyl estradiol/0.5 mg norethindrone acetate
Jinteli	5 mcg ethinyl estradiol/1 mg norethindrone acetate
Angeliq	0.5 mg estradiol/0.25 mg drospirenone, 1 mg/0.5 mg
Oral CEEs and bazedoxifene	
Duavee	0.45 mg CEE/20 mg bazedoxifene
Estradiol patches*	
Alora (twice weekly)	0.025, 0.05, 0.075, 0.1 mg per day
Generic (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Minivelle (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Vivelle-Dot (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Climara¶ (weekly)	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg per day
Menostar (weekly)	0.014 mg per day
Estrogen-progestin patches	
Combi-Patch (twice weekly)	0.05 mg estradiol/0.14 mg norethindrone, 0.05 mg/0.25 mg per day
Climara Pro (weekly)	0.045 mg estradiol/0.015 mg levonorgestrel per day
Topical gel*	
EstroGel 0.06%	0.75 mg estradiol per pump
Elestrin 0.06%	0.52 mg estradiol per pump
Divigel 0.1%	0.25, 0.5, 1 mg estradiol per pouch
Topical spray*	
EvaMist	1.53 mg estradiol per spray
Depot options (oil, intramuscular)	
Estradiol cypionate	
Depo-Estradiol	5 mg/mL (5 mL)
Estradiol valerate	
Delestrogen	10, 20, or 40 mg/mL (all 5 mL)

Some esterified estrogen-methyl testosterone (EEMT) combinations remain available in United States. These are considered unapproved products by US Food and Drug Administration (FDA) and are not recommended; refer to section on androgens in UpToDate topic review of treatment of menopausal symptoms with hormone therapy.

CEE: conjugated equine estrogens.

* For women with an intact uterus, a progestin must be added to estrogen therapy.

¶ Also available as a generic product in United States and some other countries.

Δ Also available as Prempbase, which contains both combination tablets and estrogen alone.

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Progestins are used to prevent endometrial hyperplasia

- Cyclic Dosing (mimics luteal phase of premenopausal women):
    - 200 mg/day for 12 days/month
- Continuous Regimen
    - 100 mg daily
- Some of its metabolites are associated with somnolence which may help with sleep disturbances of menopause (take at bedtime)
- Avoid MPA as it has increased risk of Coronary Heart Disease

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Clinical Indications for MHT

1. Moderate-Severe Symptoms
   - negative impact on sleep
   - negative impact on quality of life
   - negative impact on ability to function at home and/or work
2. Final Menstrual Period < 10yrs ago
3. Age < 60 years old
4. Low (<1.67%) 5-yr risk of Breast Cancer
5. No contraindication to treatment

The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in females

	Menarche						FMP (0)			
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* Blood draw on cycle days 2 to 5.

¶ Approximate expected level based on assays using current international pituitary standard.

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Contraindications to MHT: Significant risk/Hx of ASCVD

- Previous venous thromboembolic (VTE)
- Chronic Heart Disease
- History of Stroke
- History of Transient ischemic attack
- 10-yr ASCVD Risk > 10%:
  - NOTE: For women at moderate risk of cardiovascular disease (CVD; 5 -10% 10-year risk), transdermal rather than oral estrogen is recommended

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Contraindications to MHT: Hypercoagulable States

- Active liver disease
- Unexplained vaginal bleeding
- High-risk endometrial cancer
- History of breast cancer
- Moderate - High 5-yr risk of Breast Cancer
- Smoker

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Calculation of 5-year Risk of Breast Cancer

- **Breast Cancer Risk Tool from NIH**
- https://bcrisktool.cancer.gov

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Your Answers

These results are based upon how you answered the following questions:

Questions:	Answers:
1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) or has she received previous radiation therapy to the chest for treatment of Hodgkin lymphoma?	**No**
2. Does the woman have a mutation in either the *BRCA1* or *BRCA2* gene, or a diagnosis of a genetic syndrome that may be associated with elevated risk of breast cancer?	**No**
3. What is the patient's age?	**52**
4. What is the patient's race/ethnicity? Assessments for Hispanas/Latinas are subject to greater uncertainty than those for white and African American/black women. Researchers are conducting additional studies, including studies with minority populations, to gather more data and to increase the accuracy of the tool for women in these populations.	**Hispana/ Latina**
a. What is the sub race/ethnicity or place of birth?	**Born outside the US**
5. Has the patient ever had a breast biopsy with a benign (not cancer) diagnosis?	**No**
a. How many breast biopsies with a benign diagnosis has the patient had?	**n/a**
b. Has the patient ever had a breast biopsy with atypical hyperplasia?	**n/a**
6. What was the woman's age at the time of her first menstrual period?	**7 to 11**
7. What was the woman's age when she gave birth to her first child?	**30 or older**
8. How many of the woman's first-degree relatives (mother, sisters, daughters) have had breast cancer?	**None**

5–Year Risk of Developing Breast Cancer	
Patient Risk	Average Risk
1.5%	0.8%

Lifetime Risk of Developing Breast Cancer	
Patient Risk	Average Risk
12.7%	6.8%

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Calculation of 5-year Risk of Breast Cancer

- **Breast Cancer Risk Tool from NIH**
- https://bcrisktool.cancer.gov
- High Risk: > 3% 5-yr Risk of Breast Cancer, >30% lifetime risk of Breast Cancer
- Moderate risk: [>1.67 5-yr risk of Breast cancer], >17% lifetime risk of breast cancer
- **NOTE: May 9 2023 USPSTF Draft Recommendation (B) switching breast cancer screening to every other year starting at age 40. Needs more data on if dense breast tissue will require increased frequency of screening.**

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Take Home Points

- Screen patients for menopausal symptoms
- Symptom severity matters
- Know the contraindications for estrogen
- Estrogen is most effective
- Progesterone for people with a uterus
- SSRI also effective
- Assess breast cancer risk (note
- Follow up in office in 3 months
- Treat for as long as patient has no contraindications
- Talk to the patient about the transition out of MHT
- Discontinuation Side effects should be limited with taper

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