Menopausal Vasomotor Symptoms

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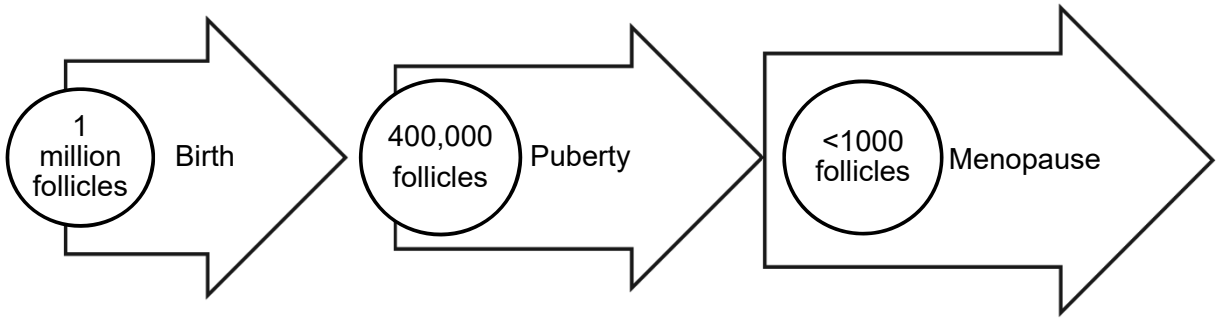
Menopause

- The menopause transition is a natural event
- Postmenopause is defined by the final menstrual period (FMP) and confirmed after 1 year of no menstrual bleeding
  - Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually because of aging
- Median age in US women: 51-52 years



Menopause Matters

- U.S. populations are projected to age over the coming decades with the number of women aged 50+ expected to grow significantly

- Overall life expectancy of US females is 80.2 years
  - Women may spend 40% of their lives postmenopausal
- 2013 survey of OB/GYN residents found <20% received formal training in menopause and 80% felt “barely comfortable” discussing or treating menopause
  - In a 2023 survey of OB/GYN residency programs, only 31% reported having a menopause curriculum

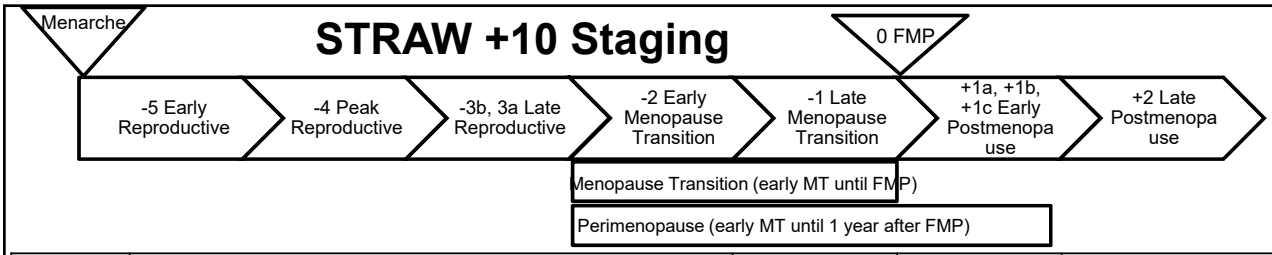
Objectives

Understand	Review	Discuss
Understand menopause terminology and staging	Review symptoms of the menopause transition • Vasomotor symptoms (VMS)	Discuss management of VMS • Menopausal hormone therapy (MHT) • Nonhormonal agents

Terminology

- Premenopause- Reproductive stage between menarche and onset of perimenopause
- Premature menopause- FMP before age 40 years– also termed primary ovarian insufficiency
- Menopause transition (MT)- Stage in menopause transition characterized by irregular menstrual cycles (early perimenopause) or 2-12 months of amenorrhea (late perimenopause) <u>until the FMP</u>
- Perimenopause- Stage in menopause transition characterized by irregular menstrual cycles (early perimenopause) or 2-12 months of amenorrhea (late perimenopause) <u>until 1 year after FMP</u>
- Early menopause- FMP before age 45 years
- Late menopause- FMP after age 54 years
- Natural menopause- Permanent cessation of menses because of loss of follicular activity
- Induced menopause- Surgical or iatrogenic loss of ovarian function
- Postmenopause- Defined as 12 months of amenorrhea due to loss of ovarian follicular function

STRAW +10 Staging



Duration	Variable					**1-3 years**	+1a, +1b: 2 years +1c: 3-6 years	Remaining lifespan
Menstrual Cycle	Variable to regular	Regular		-3a: Subtle changes in flow & length	**Variable length, persistent ≥7-day difference in length of consecutive cycles**	**Interval of amenorrhea of ≥60 days**		
Endocrine Markers			-3b: FSH low AMH low	FSH variable AMH low Inhibin B low	FSH ↑/variable AMH low Inhibin B low	**FSH ↑/variable *>25 IU/L** AMH low Inhibin B low	FSH ↑/variable (stabilizes +1c) AMH very low Inhibin B very low	
Antral Follicle Count			Low				Very low	
Symptoms						**VMS likely**	**VMS most likely (+1a, +1b)**	**Increasing symptoms of urogenital atrophy (GSM)**

The Early Menopause Transition

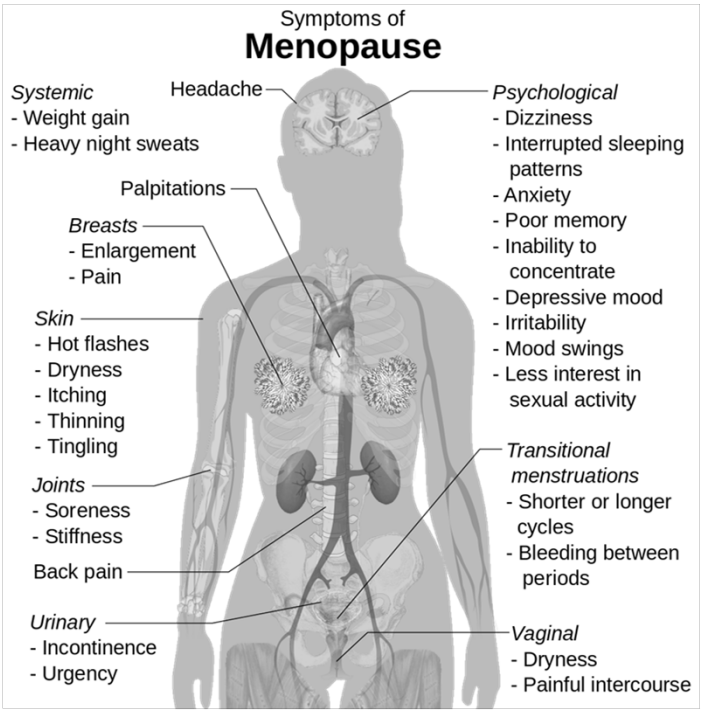
- Decreasing ovarian reserve and reduced cohort of follicles; inhibin B and AMH drop
- Loss of inhibin restraint of FSH leads to
  - Monotropic rise in FSH
  - Faster growth of remaining follicles (short follicular phase)
  - Increase in atresia
  - Occasional LOOP cycles
- Common symptoms
  - **Cycle irregularity by ≥7 days**
  - Skipped menstrual cycles (because of ovulatory failure)
  - Pronounced premenstrual syndrome symptoms (because of longer luteal phase)

Perimenopause Elevations in Estrogen: The LOOP Phenomenon

- **LOOP: Luteal-Out-Of-Phase event**
  - Luteal phase FSH elevation recruits follicles for the subsequent cycle before the current cycle is over (second follicle during luteal phase of ongoing cycle)
  - **Excess luteal estradiol production** as new follicles start growing
  - Very short follicular phase
- LOOP cycles may explain common early perimenopause symptoms:
  - Menorrhagia
  - Mastalgia
  - Worsening migraines
  - Growing fibroids
  - Risk of endometrial hyperplasia

The Late Menopause Transition

- Number of remaining oocytes drops below a critical level, with sporadic follicular development
- Ovulation is more sporadic
- Rare follicular development results in poor rate of ovulation with low progesterone levels
- Eventually follicular development drops, resulting in estradiol deficiency
- Common symptoms
  - **Amenorrhea ≥60 days**
  - Estrogen deficiency symptoms such as VMS and vaginal dryness



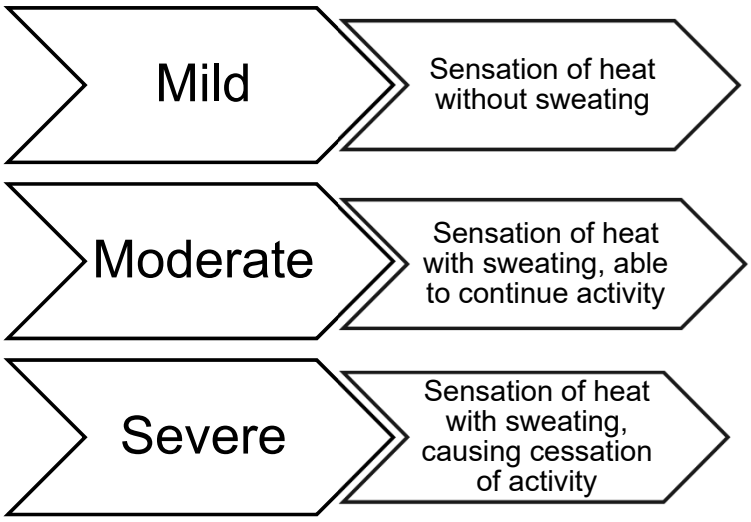
Study of Women Across the Nation (SWAN)

	The Menopause Transition	Midlife Aging (40-65 years old)
Transient	○ ↑ Vasomotor symptoms ○ ↑ Cognitive difficulties ○ ↓ Physical function performance	○ ↑ Depression and anxiety
Chronic	○ ↑ Sleep complaints ○ ↑ Vaginal dryness ○ ↑ Sexual pain ○ ↑ Lipids ○ ↑ Vascular remodeling ○ ↑ Metabolic syndrome ○ ↑ Fat mass ○ ↓ Lean mass ○ ↓ Bone mineral density ○ ↓ Sexual desire	○ ↑ Urinary incontinence ○ ↑ Body mass index ○ ↑ Blood pressure ○ ↓ Cognitive performance (after menopause)

Vasomotor Symptoms (VMS)

- Frequently termed *hot flushes (or flashes)* when occur during the day and *night sweats* when occur at night
- Characterized by sudden intense sensation of heat in the upper body, particularly the face, neck, and chest, that *lasts 1-5 minutes*
  - Can be accompanied by perspiration, chills, anxiety, and occasionally, heart palpitations
- Number of episodes per day varies
- *VMS last for a median of 7-10 years (4-5 years after FMP)*
  - Last longer when they start earlier
  - 9% persist after age 70 (“super flashers”)

Intensity of VMS



- Characterized as mild, moderate or severe
- "Moderate to severe" frequency: ≥7-8/d or 50-60/wk
- Most intense and frequent in perimenopause and for first 1-2 years after the last menstrual period

Prevalence of VMS

- **Most reported symptom of the menopause transition**
  - 60% seek care
- Varies by menopause phase
  - 21% reported VMS in premenopause
  - 41% reported VMS in perimenopause
  - 42% reported VMS in postmenopause
- Varies by racial/ethnic group
  - Native American > Black > Hispanic > White > Asian

Up to 80% of women will experience VMS due to menopause

Risk Factors for VMS

- Low socioeconomic position
- Low educational attainment
- Obesity
- Tobacco/Nicotine use
- Hysterectomy/Oophorectomy

Predictors of VMS Duration

Shorter	Longer	Median Years
Postmenopausal onset	Pre/perimenopausal onset	4.4 vs 11.8
Japanese/Chinese	AA race	4.8/5.4 vs 10.1
Non-Hispanic	Hispanic	6.5 vs. 8.9
Education ≥ college	Education < college	7.7 vs 9.9
Stress never/almost never	Stress at least sometimes	8.9 vs 10.8
No depression	Depression	7.7 vs 11.0
No anxiety	Anxiety (mild-severe)	5.0 vs 7.4

*Other factors predictive of longer VMS duration: financial strain, single, smoker, poor social group, BMI ≥30

Impact of VMS

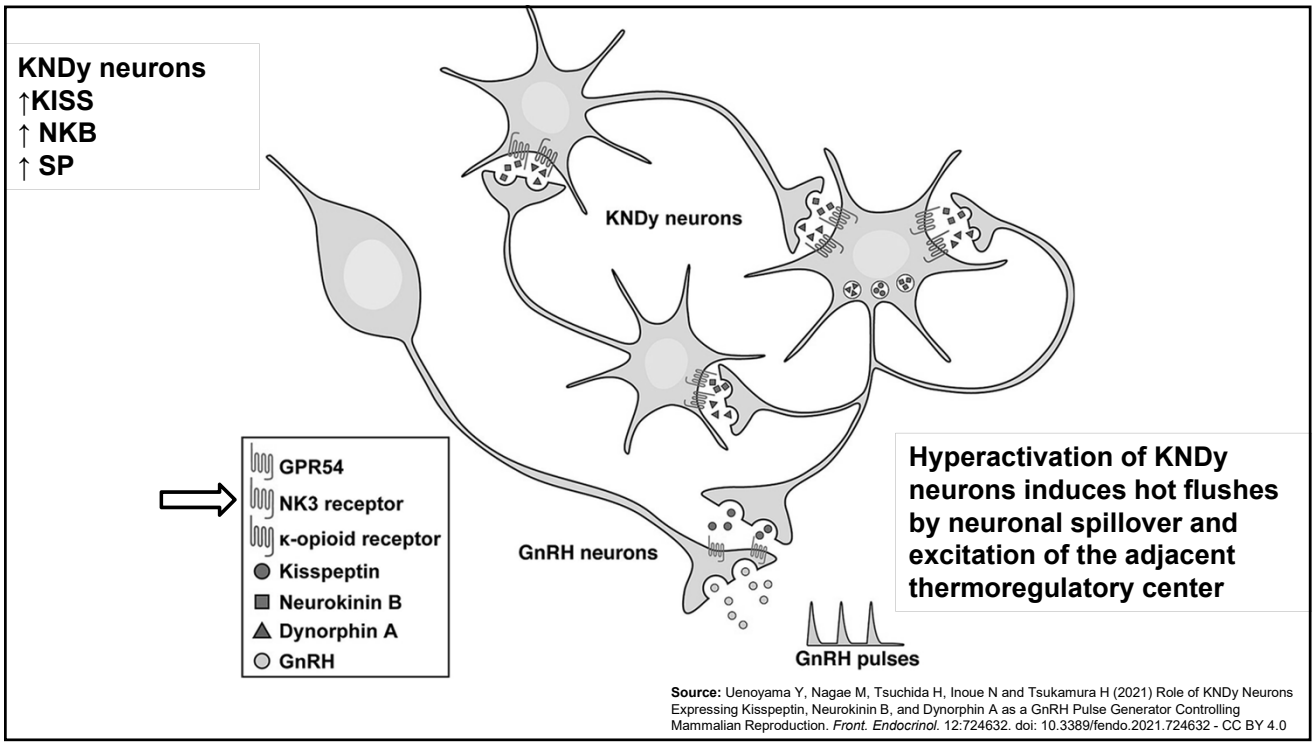
- VMS are associated with
  - Sleep disturbance
  - Depressive symptoms
  - Cognitive function

Estimated annual loss
$1.8 billion

- Evidence of link between VMS and CVD and poor bone health
- Negative impact in the workplace
  - A 2023 survey of employed 45 to 60-year-old women found that 13% reported at least one adverse work outcome due to menopause symptoms
    - 11% reported missing work in the preceding 12 months due to menopause symptoms
  - These impacts on ability to work are associated with an estimated annual loss of $1.8 billion

Physiology of VMS

- Complex interplay between central nervous system and peripheral physiologic processes
- Loss of estrogen leads to dysregulation, disinhibition, and hypertrophy of kisspeptin-neurokinin B-dynorphin (KNDy) neurons
- Thermoregulatory center is altered by the increase in KNDy neurons
  - Activation of the neurokinin-3 receptor (NK3R) causes hot flushes
  - Blockade of the NK3R reduces/eliminates hot flushes
- May also be affected by serotonin, epinephrine, and norepinephrine, as well as sympathetic and parasympathetic nerve activity



Source: Uenoyama Y, Nagae M, Tsuchida H, Inoue N and Tsukamura H (2021) Role of KNDy Neurons Expressing Kisspeptin, Neurokinin B, and Dynorphin A as a GnRH Pulse Generator Controlling Mammalian Reproduction. *Front. Endocrinol.* 12:724632. doi: 10.3389/fendo.2021.724632 - CC BY 4.0

Prescription Therapies for VMS

- Treatment is based on the person's tolerance of symptoms, health history, risk factors, and personal preferences

FDA-approved prescription treatments

- Menopausal hormone therapy (MHT)
- Paroxetine
- Fezolinetant (May 2023)

Off-label prescription therapies

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Gabapentin
- Oxybutynin

FDA-Approved Indications for MHT

First-line therapy for relief of moderate to severe **vasomotor symptoms** in appropriate candidates

To **prevent bone loss and reduce fractures** in postmenopausal women at elevated risk of osteoporosis or fractures

For women with **hypogonadism, primary ovarian insufficiency, or premature surgical menopause** without contraindication, HT is recommended for health benefits until the average age of menopause

Low-dose vaginal estrogen therapy is recommended first line for isolated **genitourinary syndrome of menopause** to treat symptoms of vulvovaginal atrophy

No role for menopausal hormone therapy to "balance hormones"

prevention of CVD or cognitive function decline/dementia

Contraindications to Systemic MHT Use

More than 10 years from menopause onset or age older than 60 years (new start)

Unexplained vaginal bleeding

Liver disease

Prior estrogen-sensitive cancer (including breast cancer)

Prior coronary heart disease (CHD), stroke, MI, or VTE

Personal history or inherited high risk of thromboembolic disease

Caution in patients with DM, hypoparathyroidism, benign meningioma, increased risk of breast cancer (avoid if >20% lifetime risk)

- Increased risk of heart disease (.ASCVD)→ contraindicated if high risk (>10%)
- Migraines with aura, hypertriglyceridemia, gallbladder disease (avoid oral HT)

Key Points for Safe Prescribing

- Estrogen alone is recommended for patients without a uterus, while addition of a progestogen (or bazedoxifene) is recommended for patients with a uterus for the purpose of endometrial protection (against development of hyperplasia/cancer)
- **Dosing matters for endometrial protection**
- Approximate equivalent estrogen doses for postmenopausal use (standard estrogen doses)
  - 0.625 mg conjugated estrogens (CE) oral
  - 1 mg 17β-estradiol (E2) oral
  - 0.005-0.015 mg ethinyl estradiol (EE) oral
  - 0.05 mg transdermal estradiol (TDE2) patch
  - 0.5 mg 17β-estradiol vaginal ring

Minimum Progestogen Dosing Requirements for Endometrial Protection with Standard Estrogen Dosing

	Continuous-cyclic EPT (daily, 12-14d/mo)	Continuous-combined EPT (daily)
Oral Tablets		
Medroxyprogesterone acetate	5 mg	2.5 mg
Norethindrone	0.35 mg-0.7 mg	0.35 mg
Norethindrone acetate	2.5 mg	0.5-1 mg
Micronized progesterone	200 mg	100 mg
Intrauterine System		
Levonorgestrel*	N/A	6-20 mcg/d
Vaginal		
Progesterone gel*	45 mg	45 mg

*Not FDA-approved for endometrial protection with ET

Initiation Estrogen Doses

Depending on severity of symptoms:

- 0.025-0.05 mg TDE2
- 0.3-0.625 mg CE oral
- 0.5-1 mg E2 oral

Premature and early menopause:

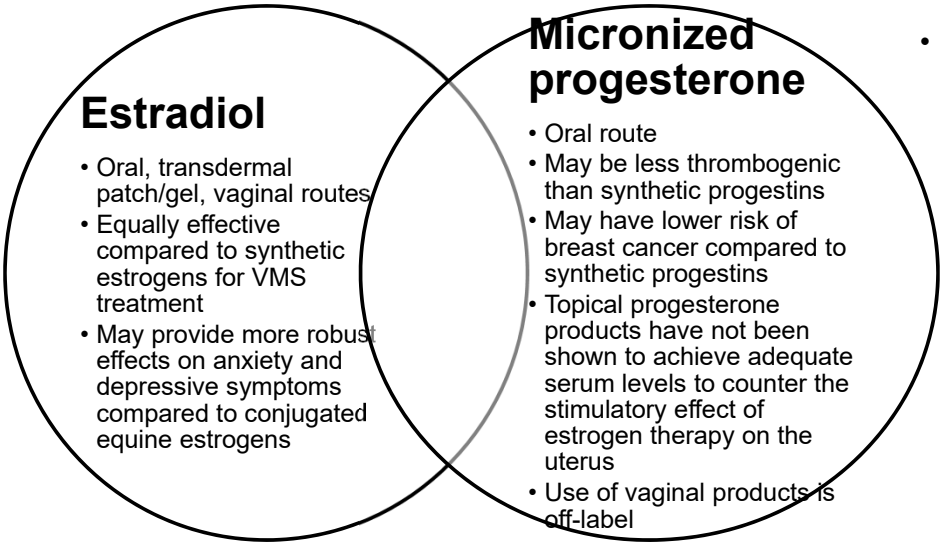
- 0.1 mg TDE2
- 1.25 mg CE oral
- 2 mg (1 mg BID) E2 oral (half-life 16 hours)
- Hormonal contraception doses

See patient back in ~3 months and adjust dose as needed until stable symptoms

Monitoring MHT

- Annual return visits
  - More frequent visits for new starts or those with adverse events
- Annual mammogram
- Endometrial sampling is not required unless postmenopausal bleeding develops
- Clinical goal
  - Use the appropriate HT dose, duration, regimen, and route of administration
  - Therapeutic goal should be to use the most appropriate, often lowest, effective dose of systemic MHT consistent with treatment goals
- When to stop?
  - Decision should be individualized based on severity of symptoms and risk-benefit ratio considerations
  - *No general rule for stopping at age 65*

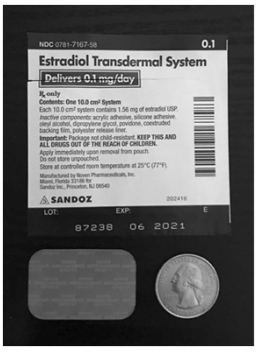
FDA-Approved Bioidentical Hormones



- **Compounded bioidentical hormone therapy (cBHT) is NOT recommended** due to minimal government regulation and monitoring, overdosing and underdosing, presence of impurities, lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks

Potential Benefits of Nonoral Estrogen

- Less impact on
  - Cholesterol (triglycerides)
  - Coagulation factors (possible lower blood clot risk)
  - Inflammatory makers
  - Gallbladder disease
  - Sexual functioning (SHBG)
- More stable serum levels
- Various formulations:
  - Patch (estradiol alone or combination with progestin)
  - Gels
  - Vaginal ring (systemic and low-dose formulations)



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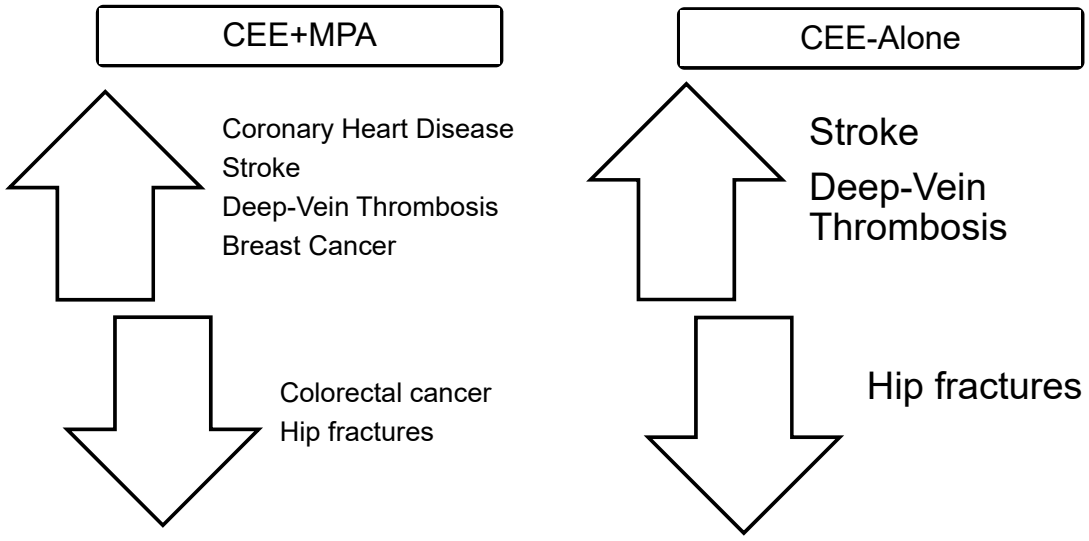
Potential Adverse Events of MHT

- Uterine bleeding (starting or returning)
  - Breakthrough bleeding occurs in 40% of women on a continuous-combined regimen during the first 3-6 months
  - ~80% of women who start with continuous-combined therapy become amenorrheic within 12 months
- Breast tenderness (sometimes enlargement)
- Nausea
- Abdominal bloating
- Fluid retention in extremities
- Changes to the shape of the cornea (sometimes leading to contact lens intolerance)
- Headache (sometimes migraine)
  - Consider transdermal for better hormone stabilization
- Dizziness
- Mood changes with EPT, particularly with progestin
- Angioedema
- Gallstones, pancreatitis

Women's Health Initiative (WHI) Findings



CEE- conjugated equine estrogen, MPA- medroxyprogesterone acetate

Risks By 10 Year Age Group

Outcome	Age (years)			Years Since Menopause		
	50-59	60-69	70-79	<10	10-19	≥20
CHD	-2	-1	+19	-6	+4	+17
Total mortality	-10	-4	+16	-7	-1	+14
Global index*	-4	+15	+43	+5	+20	+23

Cases per 10,000 person/years by age and years since menopause in combined WHI Trials (E+P and E-alone)

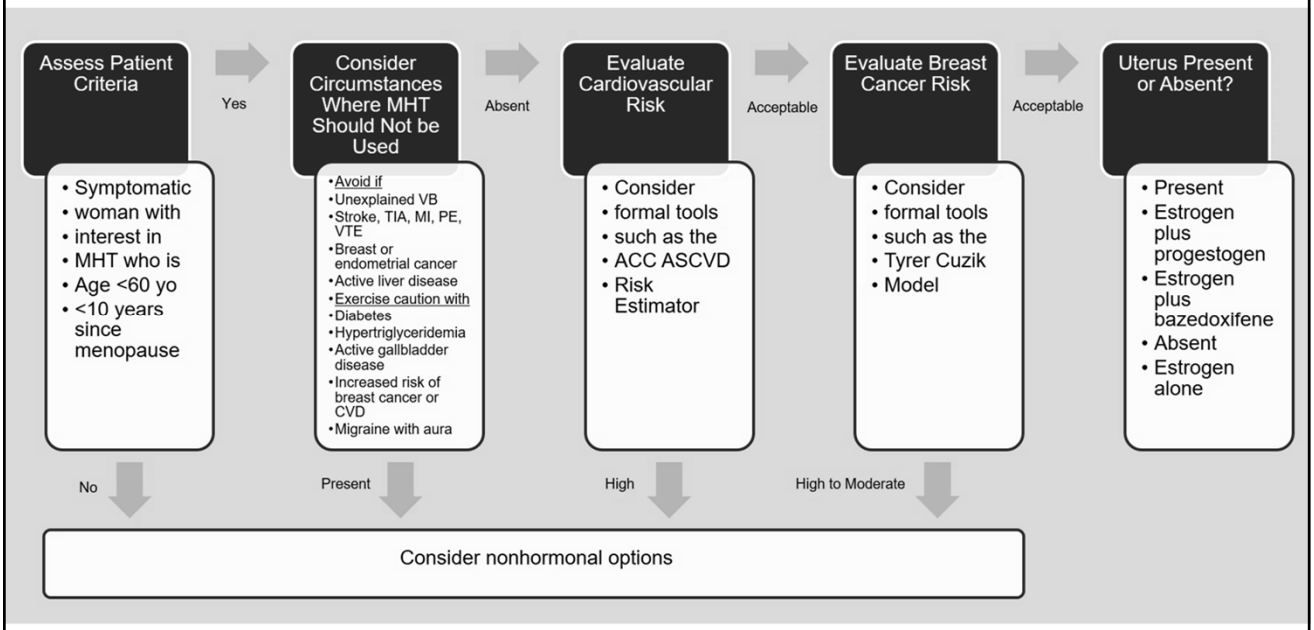
*Global index is a composite outcome of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and mortality

MHT and Breast Cancer Risk

- MHT (combined estrogen and progestogen) might slightly increase risk of breast cancer if used for more than 3 to 5 years
  - +1 case per 1000 women per year of HT use
  - Comparable to 2 alcoholic drinks/day, obesity, or low physical activity
- Using estrogen alone (for women without a uterus) does not increase breast cancer risk at 7 years but may increase risk if used for a longer time
- For women experiencing an early menopause (<45 years) the benefits of using HT until the average age of natural menopause are believed to outweigh the risks
  - No evidence that HT increases the risk of breast cancer in this age group

Risk Factor	Relative Risk of Breast Cancer
First degree family member	1.4-1.5
Early puberty (<12)	1.2
Late menopause (>55 y)	2
Nulliparity	2
Late first pregnancy (>30 y)	1.5
Obesity	1.5
Diet (high fat)	1.2
Alcohol (≥2/d)	1.2
Hormone therapy (E+P)	1.2 (E only RR 0.8)
Increase breast density	Heterogeneously 1.2 Extremely 2.1
Atypical hyperplasia	4
LCIS or DCIS	5.8
BRCA1 or BRCA2	10

Approach to Patient with VMS Contemplating MHT



NAMS Position Statement

The 2023 nonhormone therapy position statement of The North American Menopause Society

"Hormone therapy remains the most effective treatment for vasomotor symptoms and should be considered in menopausal women within 10 years of their final menstrual periods. For women who are not good candidates for hormone therapy because of contraindications (eg, estrogen-dependent cancers or cardiovascular disease) or personal preference, it is important for healthcare professionals to be well informed about nonhormone treatment options for reducing vasomotor symptoms that are supported by the evidence."

Recommended Nonhormonal Treatments for VMS

- Cognitive-behavioral therapy (Level I)
- Clinical hypnosis (Level I)
- SSRIs/SNRIs (Level I)
- Gabapentin (Level I)
- Fezolinetant (Level I)
- Oxybutynin (Levels I-II)
- Weight loss (Levels II-III)
- Stellate ganglion block (Levels II-III)

Level I: good and consistent scientific evidence
Level II: limited or inconsistent scientific evidence
Level III: consensus and expert opinion

Not Recommended for VMS

Paced respiration (Level I)	Supplements/Herbal remedies (Levels I-II)	Cooling techniques, avoiding triggers (Level II)	Exercise, yoga, mindfulness-based intervention, relaxation (Level II)	Soy foods and soy extracts, soy metabolite equol (Level II)
Suvorexxant (Level II)	Cannabinoids (Level II)	Acupuncture (Level II)	Calibration of neural oscillations (Level II)	Chiropractic interventions (Levels I-III)
	Clonidine (Levels I-III)	Dietary modification (Level III)	**Pregabalin** (Leve III)	

Suggested Dosing Ranges for Nonhormone Prescription Therapies

Agent	Dose	Titration
SSRIs		
Paroxetine salt	7.5 mg/d	Single dose, no titration needed
Paroxetine	10-25 mg/d	Start with 10 mg/d
Citalopram	10-20 mg/d	Start with 10 mg/d
Escitalopram	10-20 mg/d	Start with 10 mg/d (for sensitive or older women, start with 5 mg/d for titration, but this dose has not been evaluated for efficacy)
SNRIs		
Desvenlafaxine	100-150 mg/d	Start with 25-50 mg/d and titrate up by that amount each day
Venlafaxine	37.5-150 mg/d	Start with 37.5 mg/d
Gabapentinoids		
Gabapentin	900-2400 mg/d	Start with 100-300 mg at night, then add 300 mg at night, then add a separate dose of 300 mg in the morning (start at 100 mg if concerned about sensitivity)
Neurokinin B antagonists		
Fezolinetant	45 mg/d	Single dose, no nitration needed
Anticholinergic/antimuscarinic		
Oxybutynin	2.5-5 mg BID	Start with 2.5 mg or 5 mg twice daily, titrate up to 15 mg extended-release daily

Fezolinetant

- Selective NK3R antagonist
  - Oral daily (45 mg) tablet
- Indication: treatment of moderate to severe vasomotor symptoms due to menopause
- Contraindications: cirrhosis, severe renal impairment or end-stage renal disease, concomitant use with CYP1A2 inhibitors
- Monitoring: bloodwork prior to initiation to evaluate for hepatic function and injury
  - AST, ALT, serum bilirubin (total and direct)
- Follow-up evaluations of hepatic transaminase concentration
  - 1, 2, 3, 6, and 9 months
  - Or if symptoms suggest liver injury (eg, nausea, vomiting, jaundice)

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYPA12	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, vemurafenib	Acyclovir, allopurinol, cimetidine, peginterferon, alpha-2a, piperine, zileuton

Future

- Elinzanetant oral daily (120 mg) tablet
  - Selective NK1, NK3 receptor antagonist
- Data from phase 3 clinical trials (double-blind, randomized, placebo-controlled): OASIS 1 and 2
  - Statistically significant reductions in both frequency and severity of VMS at weeks 4 and 12 compared to blinded placebo over 12 weeks compared to placebo
  - Sleep disturbances and menopause-related quality of life were significantly improved compared to placebo
  - Favorable safety profile
    - Headache and fatigue were the most frequent treatment-related adverse events
    - No significant abnormal laboratory findings, including liver tests
- OASIS 3: 52-week study on efficacy and safety demonstrated consistent long-term results
- OASIS 4 (ongoing): participants have either breast cancer or are at high risk for breast cancer, taking tamoxifen or aromatase inhibitors
- New drug application was submitted and accepted by the FDA (fall 2024)

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