Menopause: Diagnosis and Treatment
...and the HEAT GOES ON!

(20+ Years After the Publication of the Principal Results from the WHI)*

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*Women's Health Initiative
Writing Group for the Women's Health Initiative. JAMA. 2002;288:321-333.

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Disclosure

I have no financial interests or relationships to disclose.

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Learning Objectives

1. Analyze the WHI data through a modern lens, specifically the safety profile of initiating HT in healthy women under 60 or within 10 years of menopause onset.
2. Select appropriate HT regimens based on the presence or absence of a uterus, including the role of micronized progesterone and transdermal estradiol.
3. Prescribe non-hormonal therapies, including SSRIs/SNRIs and the new NK3 receptor antagonist (Fezolinetant), for vasomotor symptoms.

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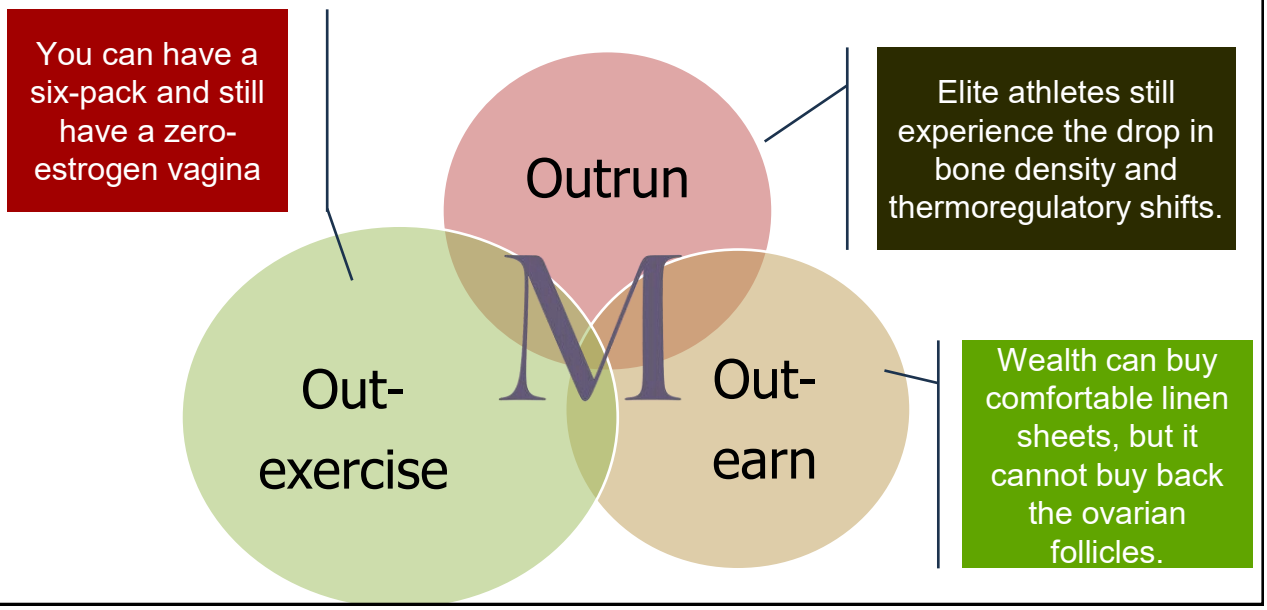
The Equality of Biology



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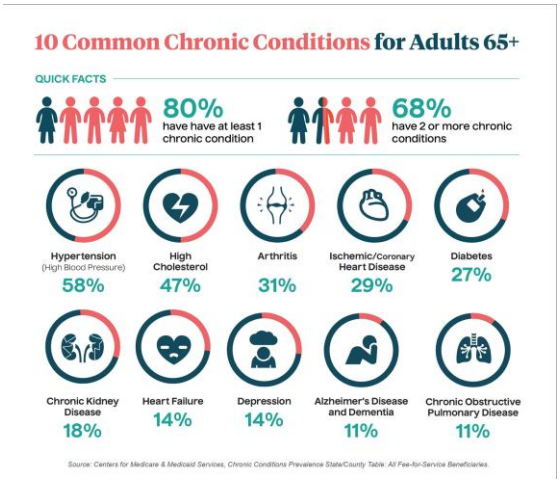
Chronic Disease and Aging

- Prevalence and incidence of most chronic conditions increase with age
- Excess risk for these conditions that can be attributed to menopause ALONE is uncertain



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The Three Faces of Menopause

Case 1 - 52-year-old

- healthy, having severe night sweats and mood swings.

Case 2 - 48-year-old

- had a total hysterectomy (ovaries remained) 3 years ago for fibroids. Now experiencing "brain fog" and intense hot flashes.

Case 55-year-old

- with a history of Stage II Breast Cancer (ER/PR positive) currently on Tamoxifen. She is "miserable" with 15 hot flashes a day.

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The Big M Is Universal

The Stat

100%

Who live past middle age will experience menopause

The Volume

In U.S. -
- 6000 reach M daily
- 46 million estimated to be > 55
- Another 30 years to live after menopause

Worldwide 2030

1.2 billion postmenopausal women

The Clinical Gap

Despite being a universal biological certainty

Yale U study of insurance claims revealed that although 60% of women suffering from significant symptoms of menopause seek medical attention, **three-quarters of them are NOT being treated**

2021 Survey – 73% of respondents experiencing menopause symptoms were NOT treating them.
(Bonafide Health "State of Menopause Study," 2021)

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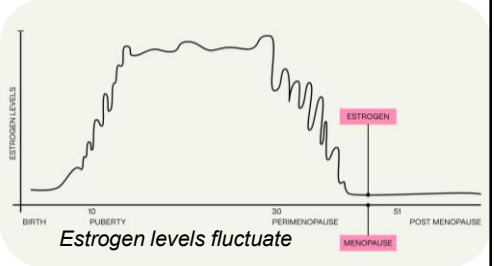
Defined and Diagnosed

- **Menopause –**
  - The time that marks the end of menstrual cycles
  - Confirmed after 1 year of **no** periods
  - Median age **51.3** (Range 45-55)
- **Three stages -**
  I. Perimenopause (Climacteric; **Menopausal Transition**)
     - Hormonal changes and clinical symptoms occur over a period leading up to and immediately following menopause. Ovaries begin to atrophy leading to a decline in E/P
  II. Menopause
  III. Postmenopause



Estrogen levels fluctuate

https://www.joinmidi.com/post/normal-estradiol-levels-by-age

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Do Not Routinely Test **FSH** Levels to Establish Menopausal Status

Clinical Diagnosis

- ✓ **Conditions which can be diagnosed without testing serum FSH in otherwise healthy women > 45 years of age with menopause symptoms.**
  - Perimenopause based on vasomotor symptoms and irregular periods
  - Menopause in women who have not had a period for greater than 12 months and are not using hormonal contraception
  - Menopause based on symptoms in women without a uterus
- ✓ **Do not use these laboratory tests and imaging to diagnose perimenopause in women > 45 years.**
  - Anti Mullerian hormone
  - Inhibin A & B
  - Estradiol
  - Antral follicle count
  - Ovarian volume
- ✓ **Do not use FSH if a woman is on the combined estrogen or progestogen contraception or using high dose progestogen.**

Choosing Wisely — An initiative of the ABIM Foundation | ConsumerReportsHealth | American Academy of Ophthalmology | ABIM Foundation

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Choosing Wisely
American Society for Reproductive Medicine

- Don't obtain follicle-stimulating hormone (FSH) levels in women in their 40s to identify the menopausal transition as a cause of irregular or abnormal menstrual bleeding.

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http://www.choosingwisely.org/clinician-lists/

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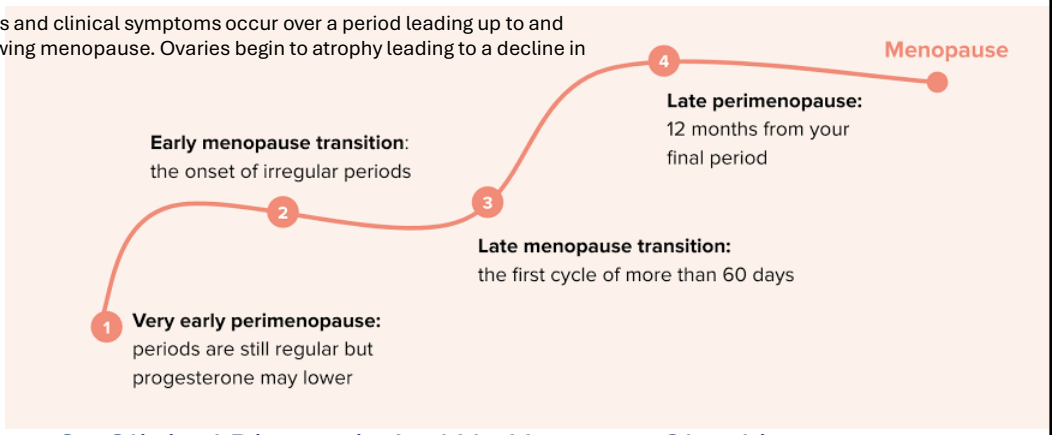
Perimenopause (Climacteric; **Menopausal Transition**)

- Hormonal changes and clinical symptoms occur over a period leading up to and immediately following menopause. Ovaries begin to atrophy leading to a decline in E/P



So Clinical Diagnosis And No Hormone Checking –

(Gold) Standard for Reproductive Aging

Clinical "GPS" for Menopause

Moving Away from Chronological Age and Focusing Instead on Bleeding Patterns and Hormonal Markers

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STRAW+10

Stages of Reproductive Aging Workshop + 10

STAGES	-2 (Early Transition)	-1 (Late Transition)	0 (The Event)	+1 (Early Postmenopause)	+2 (Late Postmenopause)
Terminology	Perimenopause	Perimenopause	Menopause	Postmenopause	Postmenopause
Cycle Length	Variable; length differs by ≥7 days.	Intervals of ≥60 days of amenorrhea.	The Final Period.	12 months of amenorrhea.	N/A
FSH Level	Variable.	Elevated (>25-30 IU/L).	Elevated.	Elevated.	Elevated/Stable
Symptoms	Vasomotor (Hot flashes) begin.	VMS are most intense.	VMS likely.	VMS Peak/GSM starts.	GSM (Atrophy) progresses.

Zone of chaos

Harlow, S. D., et al. (2012). *Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. The Journal of Clinical Endocrinology & Metabolism, 97(4), 1159–1168. doi:10.1210/jc.2011-2162.*

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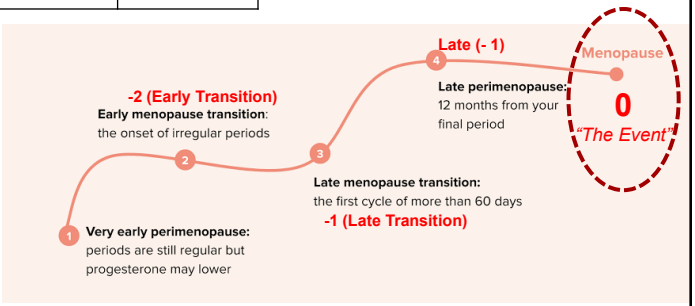

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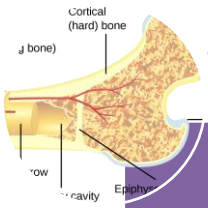
Ideal Starting Point for MHT

Zone of Chaos

Stage -1 (Late Transition)

CV Risk

Profile begins to shift



Bone Loss

Accelerates most rapidly

Use STRAW+10 to manage expectations. When a patient is in Stage -1 (Late Transition), tell them: 'You are in the stormiest part of the transition. It won't be like this forever, but we need to support your hormones now to protect your bones and heart for the next 30 years.'

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Consider Using an FSH Test to Diagnose Menopause ONLY in the Following Situations:

- ☑ **Women 40 – 45 years** with menopause symptoms including a change in their menstrual cycle
- ☑ **Women < 40 years** where a premature menopause is suspected

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So HOW Is the STRAW+10 Used

48 yo presents to the office – she keeps a calendar of her menses – if her cycle length has varied by more than 7 days

- 21 days one month
- 35 days the next month

✓ She is in **Stage -2**

✓ *Diagnose perimenopause and discuss treatment.*

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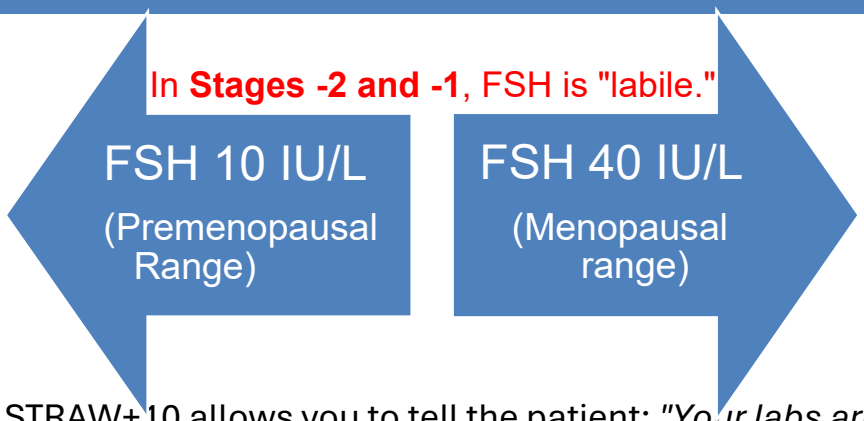
Some of You Are Going to Get into the FSH TRAP!



- Using STRAW+10 allows you to tell the patient: *"Your labs are normal today, but your cycle history tells me you are in Stage -1, which explains your insomnia."*

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WHEN Is It Used: 3 Critical Decision Points

Decision Point	When/Why
Initiating Hormone Therapy	**When:** Stages -2 through +1. **Why:** This is the "Window of Opportunity." Starting HT in these stages provides the best cardiovascular protection and prevents the rapid bone loss that occurs in the one year preceding and following the Final Menstrual Period (FMP).
Contraception vs. HRT	**When:** Stage -2 and -1. **Why:** Patients in these stages can still ovulate "rogue" eggs. STRAW+10 helps you decide to stay on a low-dose birth control pill (which manages symptoms and prevents pregnancy) versus switching to HRT (which manages symptoms but does not prevent pregnancy).
Managing GSM (The "Silent" Shift)	**When:** Stage +1 and +2. **Why:** Once a patient moves into **Stage +1 (Early Postmenopause)**, the focus shifts from managing hot flashes to monitoring for **Genitourinary Syndrome of Menopause**. This is when you proactively ask about vaginal dryness before it becomes a crisis in **Stage +2**.

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ARS Question 1

A 49-year-old cisgender woman presents to your family medicine office with concerns about changes in her health. The third-year medical student working with you is alarmed when he exits the exam room and explains that there are positive symptoms in every system reviewed.

Which One of the Following Is Considered an Uncommon Symptom of Perimenopause or Menopause that Warrants Further Evaluation?

A. Heart palpitations
B. Joint pain
C. Difficulty sleeping
D. Hot flashes

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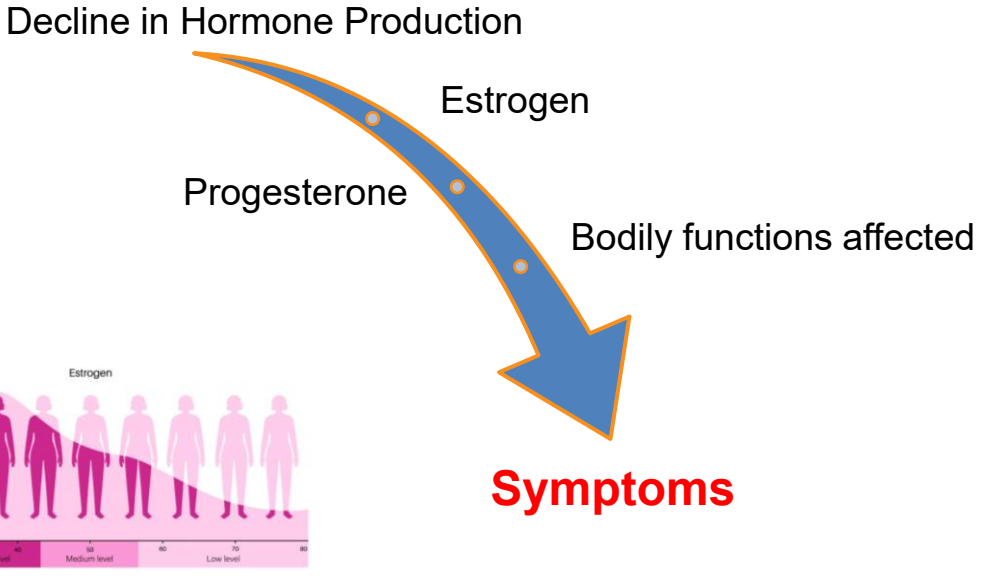
What Happens?



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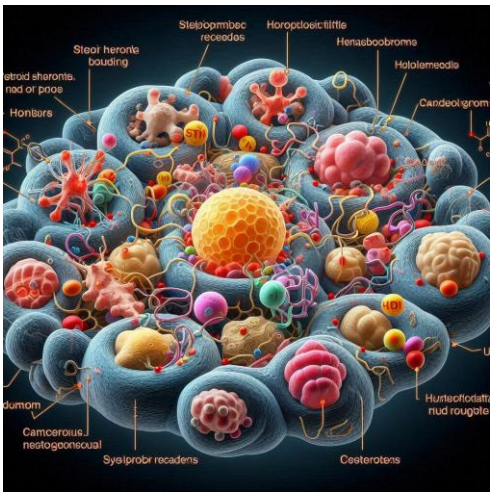

David Glenn Weismiller, MD, ScM, FAAFP

Image of steroid hormones binding to cytoplasmic receptors, forming activated complexes that are translocated to the nucleus where specific genes are activated, leading eventually to protein products as the end point of hormone influence

Steroid Hormones

Influence the transcription of a large number of genes by virtue of their interaction with intracellular receptors, which are modular proteins composed of a ligand binding domain, a DNA binding domain, and several transactivation functions distributed along the molecule.

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Common Indicators

- Irregular periods (frequency and/or flow)
- Hot flashes
- Mood swings
- Sleep disturbances

Common Symptoms

- Hot flashes
- Mood Swings
  - feelings of anxiety, irritability, sadness
  - affect daily life and interactions

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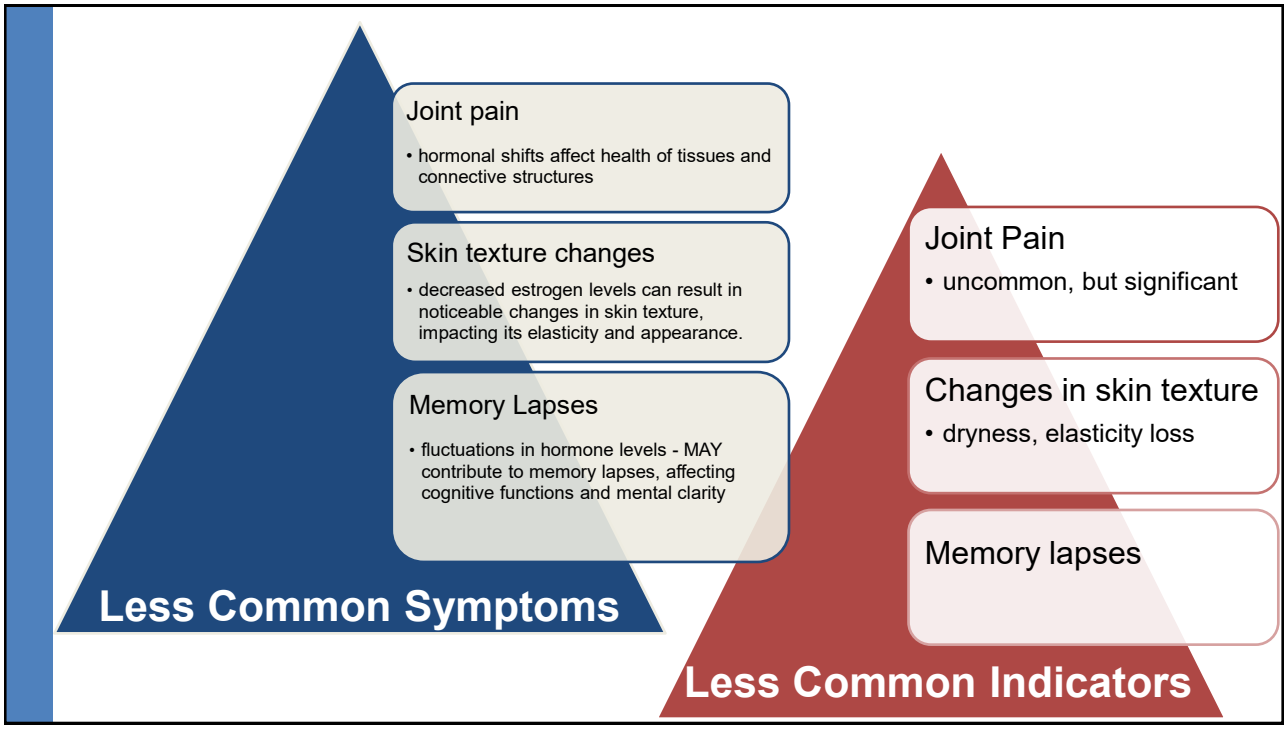
Joint pain
• hormonal shifts affect health of tissues and connective structures
Skin texture changes
• decreased estrogen levels can result in noticeable changes in skin texture, impacting its elasticity and appearance.
Memory Lapses
• fluctuations in hormone levels - MAY contribute to memory lapses, affecting cognitive functions and mental clarity
Less Common Symptoms
Joint Pain
• uncommon, but significant
Changes in skin texture
• dryness, elasticity loss
Memory lapses
Less Common Indicators

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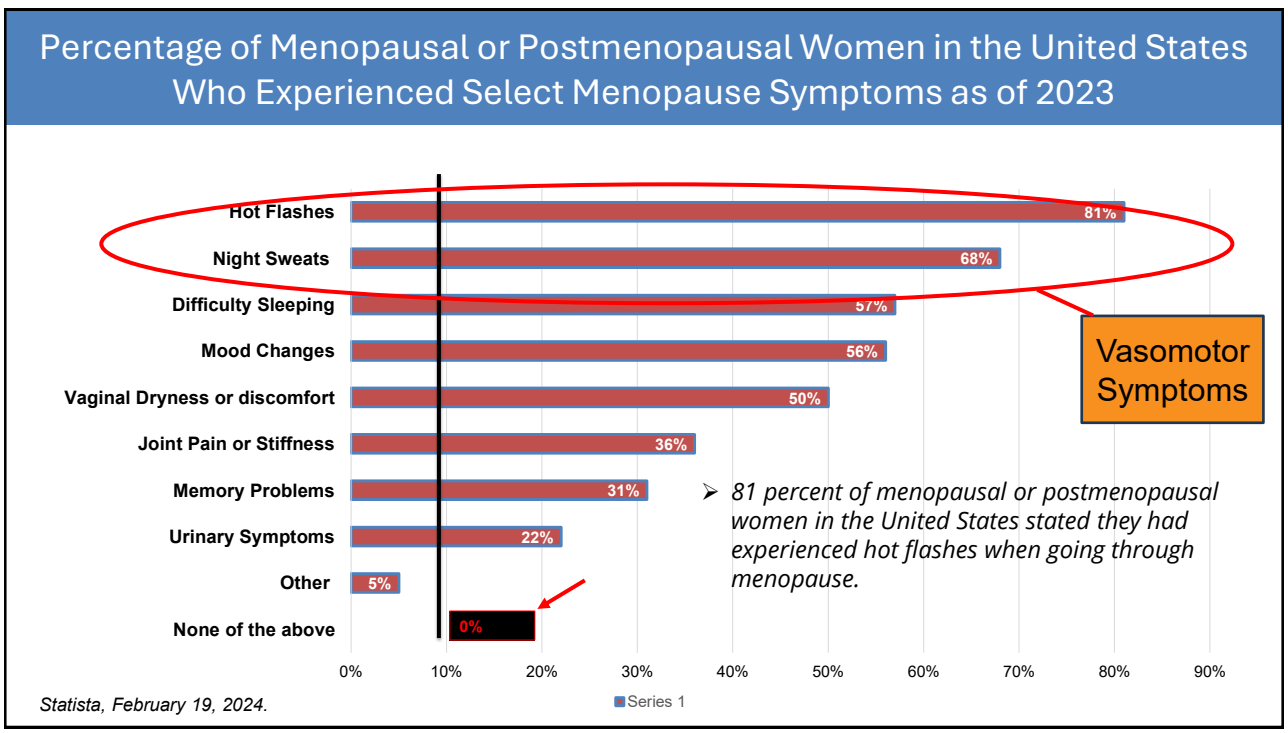
Percentage of Menopausal or Postmenopausal Women in the United States Who Experienced Select Menopause Symptoms as of 2023
Hot Flashes 81%
Night Sweats 68%
Difficulty Sleeping 57%
Mood Changes 56%
Vaginal Dryness or discomfort 50%
Joint Pain or Stiffness 36%
Memory Problems 31%
Urinary Symptoms 22%
Other 5%
None of the above 0%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90%
Series 1
Vasomotor Symptoms
➢ 81 percent of menopausal or postmenopausal women in the United States stated they had experienced hot flashes when going through menopause.
Statista, February 19, 2024.

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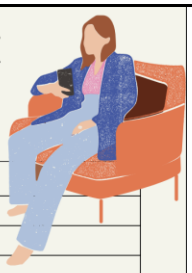
Your Symptoms Checklist



Check off everything you're experiencing so you can explore solutions with a clinician. **Remember: All these symptoms can be improved**

	Hot flashes & night sweats		Dry mouth
	Insomnia		Body odor changes
	Fatigue		Headaches/migraines
	Forgetfulness & cognitive issues (aka "brain fog")		Breast soreness
	Irritability		Unusual itchiness
	Decreased libido		Numbness or pins-and-needles sensation in your extremities
	Anxiety and/or depression		
	Panic attacks		Loss of bone density (osteoporosis)
	Weight gain		Increased tooth sensitivity and/or dental issues (gum disease, decay)
	Vaginal dryness		
	Painful sex		Burning mouth syndrome
	Difficulty achieving orgasm		Bloating
	Joint and/or muscle pain		Digestive issues
	Hair and/or skin changes		Brittle nails
	Incontinence and/or urinary urgency		Irregular heartbeat
	Recurrent urinary tract infections		New onset allergies or asthma

Track your symptoms. You know your body best. Keeping a detailed record of symptoms (including frequency and intensity) can help your healthcare provider tailor your care.

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Vasomotor Symptoms

- Sudden sensation of extreme heat in the upper body, particularly the face, neck, and chest.
- Typically, last 1-5 minutes
  - Perspiration, flushing, chills, clamminess, anxiety, and, on occasion, heart palpitations
- May interfere with sleep and cause chronic sleep disruption.
- Probably hypothalamic in origin
  - *Menopause*
  - Thyroid disease
  - Panic or anxiety disorder
  - Insulinoma
  - Autoimmune disorders
  - Pheochromocytoma
  - Carcinoid Syndrome
  - Tamoxifen and raloxifene

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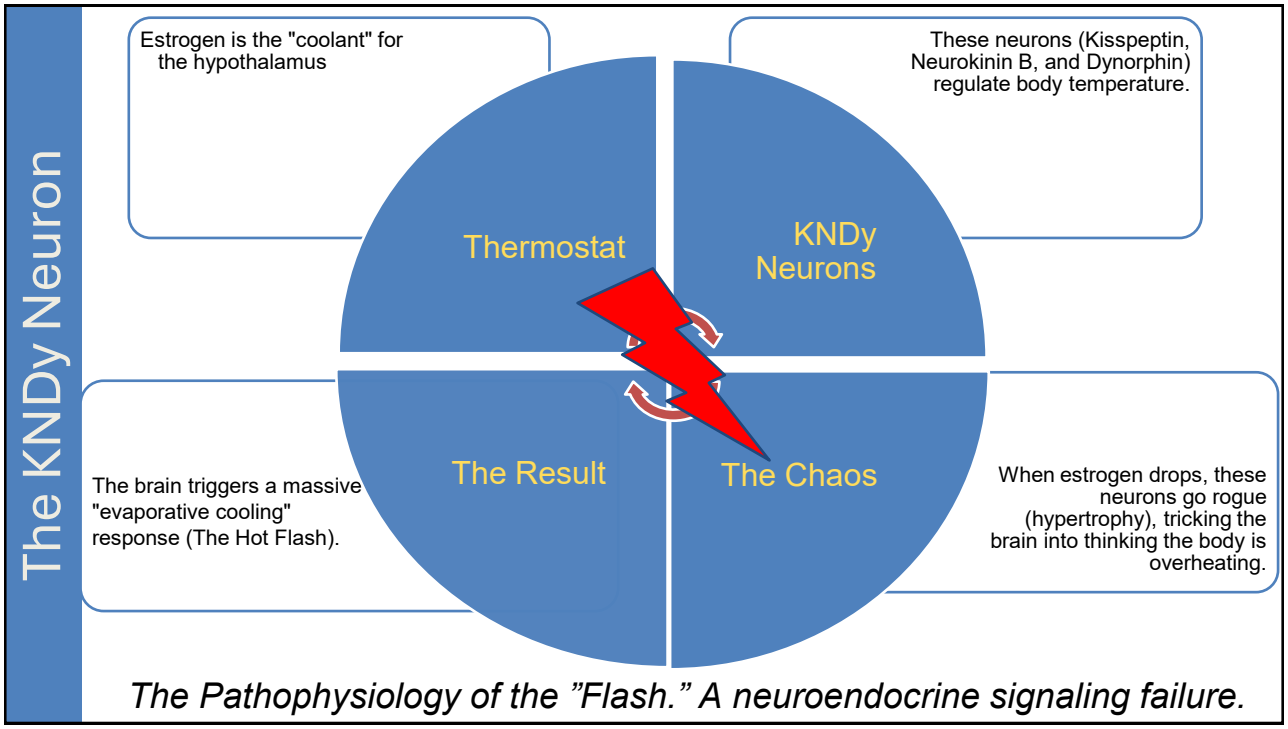

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...and They Last...

- Study of Women's Health Across the Nation (SWAN)
  - Longitudinal observational study of the menopause transition
- 1449 participants
  - Women who were married or partnered, better educated, less financially stressed, and had greater social support had shorter duration of symptoms.
  - Physical activity and alcohol intake did not affect symptom duration

Avis NE et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015 Feb 16; [e-pub].(http://dx.doi.org/10.1001/jamainternmed.2014.8063)

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RESULTS

Group	Mean Duration (years)
1449 with frequent vasomotor symptoms (VMS) (occurring on ≥6 of the preceding 14 days)	7.4
Subset (881) with identifiable final menstrual period (FMP), early onset of symptoms (i.e., during pre- or perimenopause)	
• Longer overall VMS	11.8
• Post FMP persistence	9.4
Post menopausal onset of VMS	3.4
Persistence by race and ethnicity:	
Black	10.1
Hispanic	8.9
Non-Hispanic white	6.5
Chinese	5.4
Japanese	4.8

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What Can We Say?

- Bothersome VMS may persist for more than "a few" years
- New twist to the guidelines for HT "lowest effective dose, shortest duration"
  - Women may need a range of options for a decade or more
    - Hormonal and nonhormonal therapies
    - Behavioral and lifestyle adaptations
  - SWAN results help us individualize counseling as we educate women about the risks and benefits of each treatment strategy

Avis NE et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015 Feb 16; [e-pub].(http://dx.doi.org/10.1001/jamainternmed.2014.8063)

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Influences on Hot Flashes

- **Cultural**
  - More prevalent in African American and Latin American women than in white women
  - Less common in Chinese and Japanese women
- **Other variables associated with increased reporting of hot flashes**
  - Cigarette smoking
  - *Potential risk factors with inconsistent association*
    - *Maternal history*
    - *Early age of menarche and menopause onset*
    - *History of irregular menses*
    - *Higher BMI*
    - *Alcohol use*
    - *Hot/humid weather*

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It's Very Personal

Menopause is not just a physiological experience. It also has deep cultural meaning…

Getting "old." This can trigger many feelings. Some derive meaning and wisdom from menopause, while others may experience depression.

*Cultural values and assumptions about menopause can affect **how a woman feels** about this natural body process.*

The way she reacts to this may affect her relationships and lifestyle. e.g., a woman who believes menopausal weight gain is inevitable might stop exercising.

*Conversely, a woman who takes joy in the wisdom she believes comes with age, **might feel better about herself**. She may, therefore, feel **more adventurous** or sexual than ever before.*

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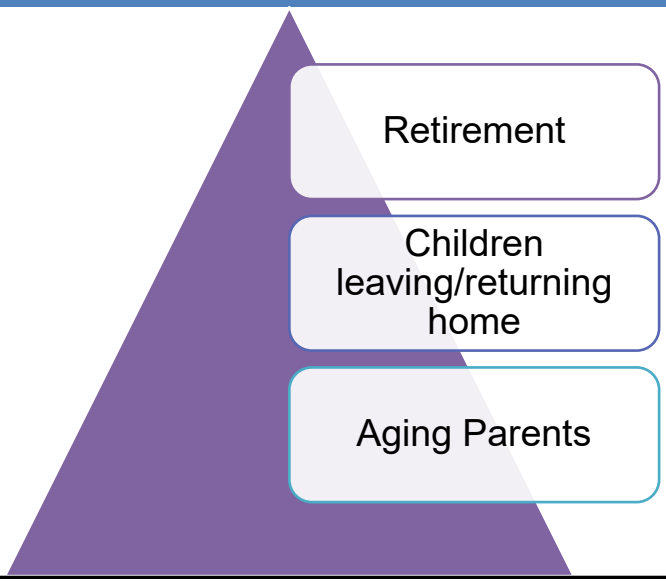
Superimposed Upon All of This…



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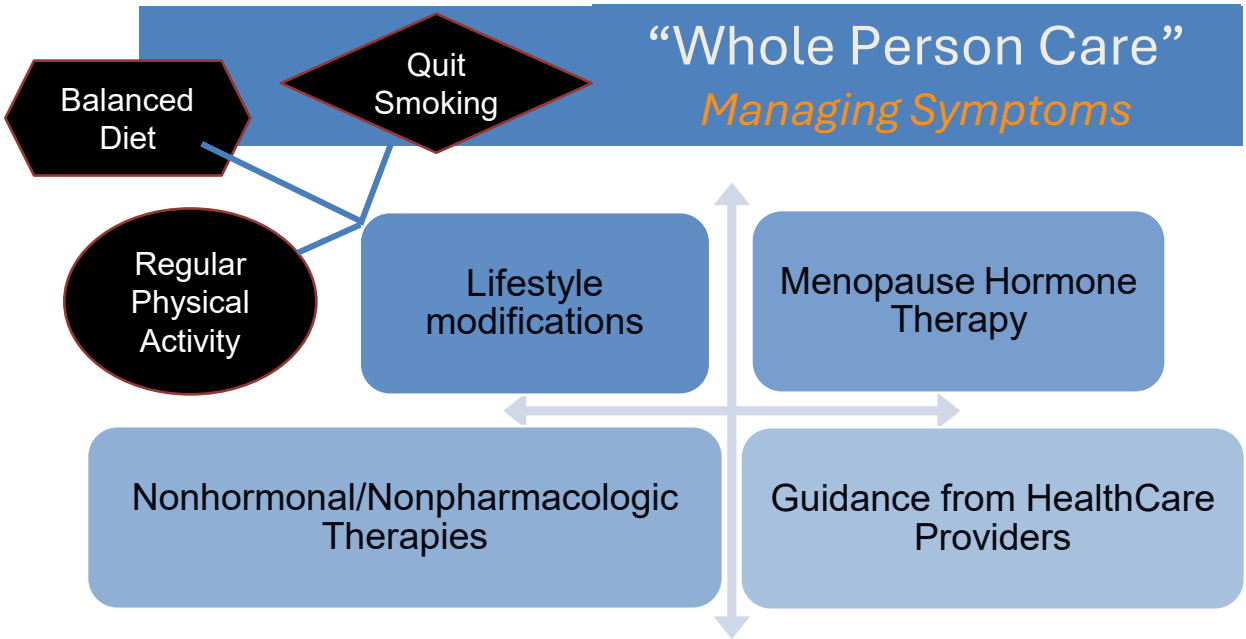
"Whole Person Care"

Managing Symptoms



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ARS Question #2

A 55-year-old postmenopausal woman with bothersome vasomotor symptoms is considering menopausal hormone therapy (MHT). She has a history of hypertension but no cardiovascular disease, thromboembolism, or breast cancer.

Which of the Following Is the Most Appropriate Counseling Point Regarding MHT?

A. MHT should not be initiated in women older than 50 due to cardiovascular risks.
B. Transdermal estrogen may be a preferable option as it has a lower risk of thromboembolism than oral formulations.
C. MHT increases the risk of breast cancer within the first year of use.
D. Women on MHT require routine annual mammograms and pelvic ultrasounds.

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Well, there was a little study called the Women's Health Initiative which turned us upside down in 2002…

TREATMENT

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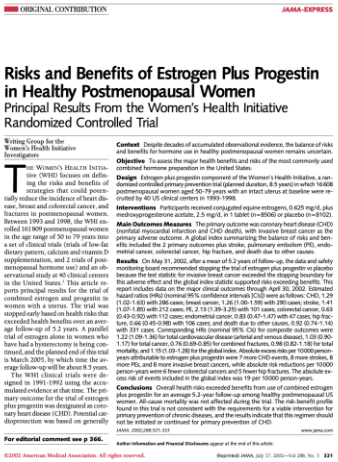

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

THE WOMEN'S HEALTH INITIATIVE (WHI) focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161 809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials (trials of low-fat dietary pattern, calcium and vitamin D supplementation, and 2 trials of postmenopausal hormone use) and an observational study at 40 clinical centers in the United States.[1] This article reports principal results for the trial of combined estrogen and progestin in women with a uterus. The trial was stopped early based on health risks that exceeded health benefits over an average follow-up of 5.2 years. A parallel trial of estrogen alone in women who have had a hysterectomy is being continued, and the planned end of this trial is March 2005, by which time the average follow-up will be about 8.5 years.

The WHI clinical trials were designed in 1991-1992 using the accumulated evidence at that time. The primary outcome for the trial of estrogen plus progestin was designated as coronary heart disease (CHD). Potential contraindications was based on generally

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CI]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CI) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risk per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 person-years.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

For editorial comment see p 366.

Author Information and Financial Disclosures appear at the end of this article.

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- 20+ years of follow-up data

Primary Prevention Study – CVD

- Estrogen Plus Progestin
- >16,000 women
- 8 years (5.3) years

- 24 years since the publication of this primary prevention trial
- *suggest that the results from the observational studies were overstated and the positive findings were a result of confounding biases*

65% of women will not consider using HRTs to treat their menopause symptoms.
(Bonafide Health "State of Menopause Study," 2021)

TREATMENT REGIMEN

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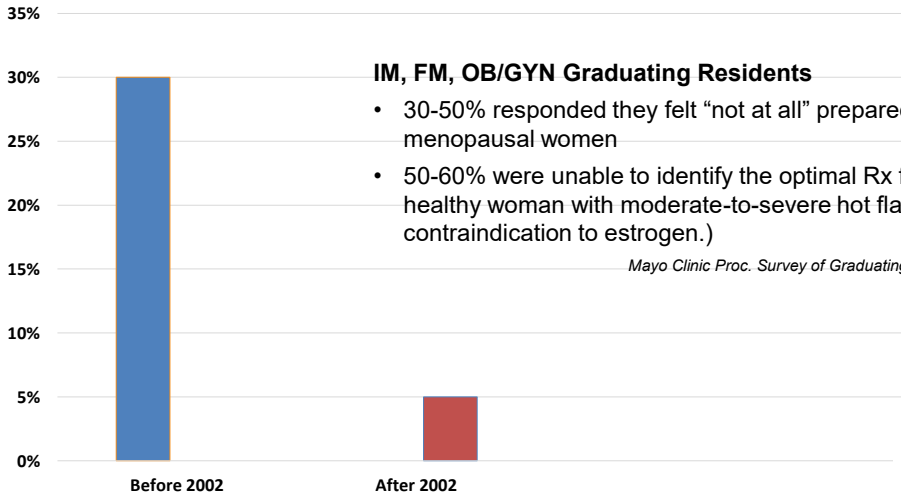
MHT Prescriptions

% of U.S. Menopausal Women Receiving MHT



IM, FM, OB/GYN Graduating Residents

- 30-50% responded they felt "not at all" prepared to manage menopausal women
- 50-60% were unable to identify the optimal Rx for a 52 year old healthy woman with moderate-to-severe hot flashes (and no contraindication to estrogen.)

Mayo Clinic Proc. Survey of Graduating Residents . 2019; 94:242

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The WHI "Right-Sized"

Bridging the Gap Between 2002 and 2026 Reality 2006

The MYTH

HT is dangerous for all women and causes heart disease.

Age and timing matter.

The Reality

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The Three Aspects of Informed Decision Making

Understanding Benefits & Risks

- Clearly weighing the potential benefits against the possible risks of each option.
- Patients must be well-informed about the benefits and risks associated with MHT to make educated choices.

Shared Responsibility

- Clinician and patient work together, sharing the responsibility for the choice.

Patient Preferences

- Honoring the patient's values, goals, and priorities in the final decision.

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What Is MHT?

- Essentially, a medical treatment where a woman takes medications containing female hormones—mainly **estrogen** and sometimes **progestogen**—to replace the hormones the body stops making during and after menopause.

Estrogen [Oral, Transdermal, Gels, Sprays; Vaginal (Femring)]

This is the workhorse hormone. It is what stops the hot flashes, preserves bone density, and keeps vaginal tissues healthy.

Progestogen [Micronized Progesterone]

added solely to protect the uterus; the endometrium thickened abnormally increases the risk of uterine cancer.

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Progestogen

- WHI
  - included only combination hormone therapy with **medroxyprogesterone** used daily orally
- Micronized progesterone
  - May be less thrombogenic than other progestins
  - May be associated with higher risk of endometrial cancer
- Current Guidelines:
  - Micronized progesterone
    - 200 mg PO daily 12-14 days/month or
    - 100 mg PO Daily
  - Observational studies
    - Have suggested risk of breast CA may be less with use of micronized progesterone compared with synthetic progestogens,
    - Adequately dosed for endometrial protection.
    - Improperly formulated/dosed/delivered estrogen plus micronized progesterone combinations have potentially serious health consequences, including increased risk of endometrial neoplasia

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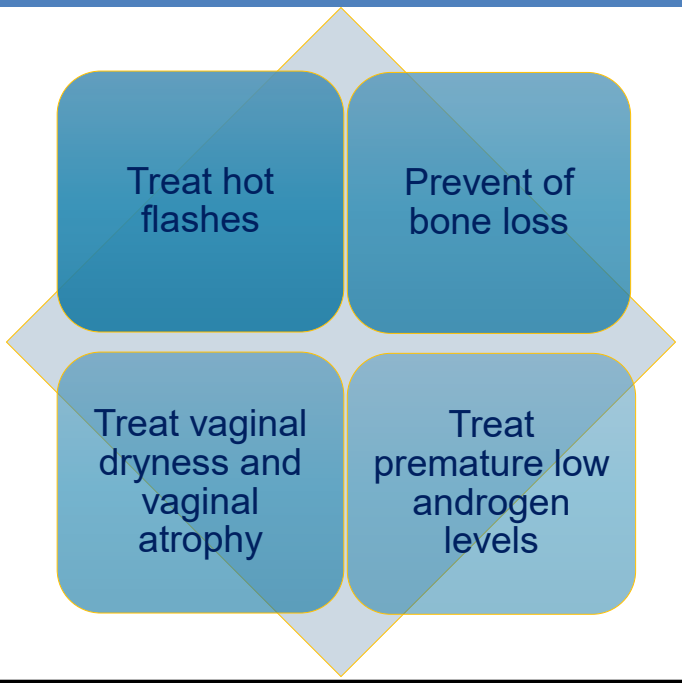
✓ FDA-Approved Indications *for* Menopausal Hormone Therapy

~~WARNING~~



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The Benefits

Solves	What we see
Vasomotor Symptom Relief	Primary indication. Reduces frequency and severity of hot flashes/night sweats by up to 80–90%, improving sleep/quality of life
Bone Density Preservation	Estrogen inhibits bone resorption. MHT prevents postmenopausal bone loss; significantly reduces the risk of osteoporotic fractures.
Cardiovascular Protection (The Timing Window)	When initiated within that 10-year post-menopause "sweet spot," MHT can slow the progression of atherosclerosis; may decrease coronary heart disease and all-cause mortality.
Genitourinary Syndrome of Menopause (GSM)	Systemic therapy helps treat vaginal dryness, dyspareunia (painful sex), and recurrent UTIs.
Metabolic & Mood Stabilization	Can improve insulin sensitivity, mitigate visceral (abdominal) fat accumulation, and help smooth out perimenopausal mood swings and anxiety.

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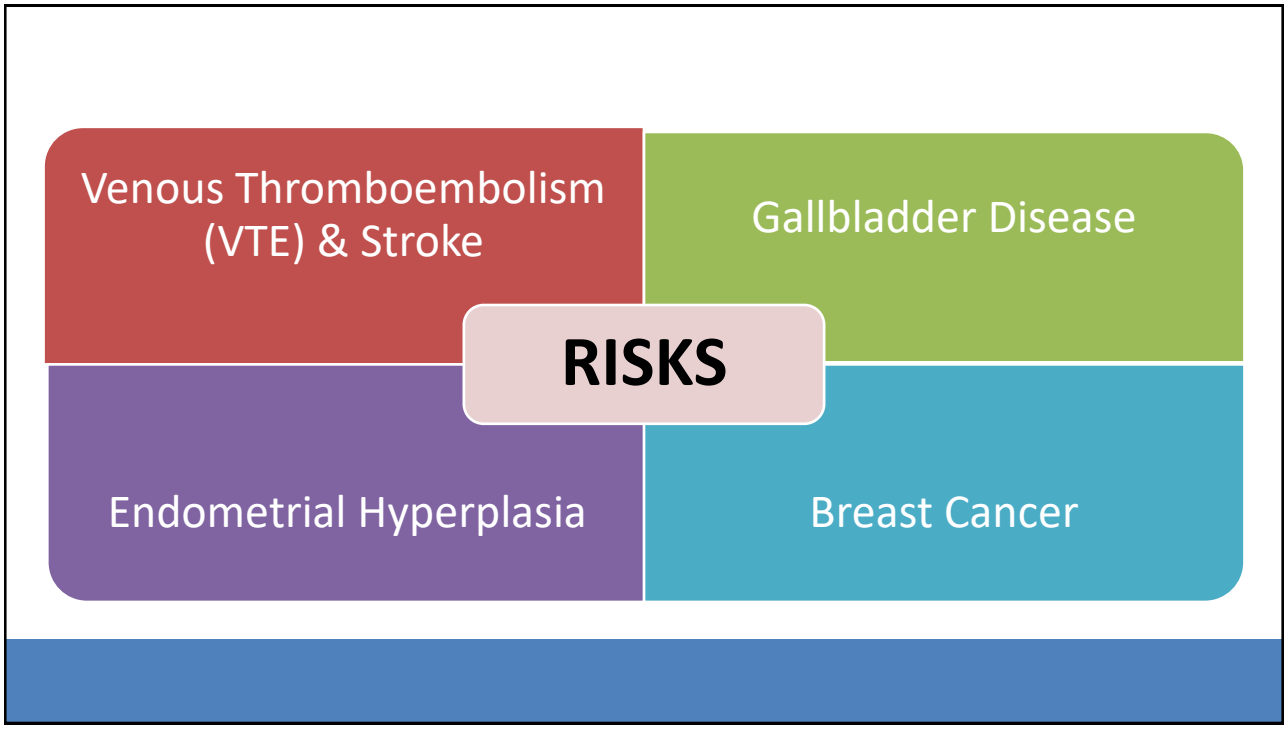

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Venous Thromboembolism (VTE) & Stroke

RISK

Oral estrogen undergoes first-pass liver metabolism, which increases clotting factors and slightly elevates the risk of deep vein thrombosis (DVT), pulmonary embolism, and stroke.

Clinical Pearl: **Using transdermal estrogen (patches or gels) bypasses the liver and does not appear to increase VTE risk, making it an excellent option.**

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RISK

When a patient says, *"I'm afraid hormones will give me breast cancer,"* try this response:

*"I hear that concern, and it's valid based on the old headlines. However, the actual risk is much smaller than most people realize. For every 1,000 women taking combined hormone therapy, there are only about **3 extra cases** of breast cancer over five years. To put that in perspective, the risk from being sedentary or having two glasses of wine a night is actually higher. My goal is to find the lowest dose that protects your heart and bones while making you feel like yourself again."*

Breast Cancer

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Comparing Modern Risks

Combined HT (E+P)
- +3 cases

Alcohol (2+ drinks/night)
- +5 cases

Obesity (BMI> 30)
- +24 cases

Sedentary Life
- +7 cases

Key Counseling Tips

- ✓ **Use Absolute Numbers:** "3 in 1,000" sounds much less scary than "a 26% increase."
- ✓ **Focus on the "Why":** Remind them that untreated menopause increases the risk of **osteoporotic fractures** and **heart disease**, which are statistically much more likely to impact their longevity than HT-related breast cancer.
- ✓ **The "Body-Identical" Benefit:** Mention that **Micronized Progesterone** (Prometrium) appears to have a better breast safety profile in observational studies than the synthetic progestins used in the original 2002 WHI study.

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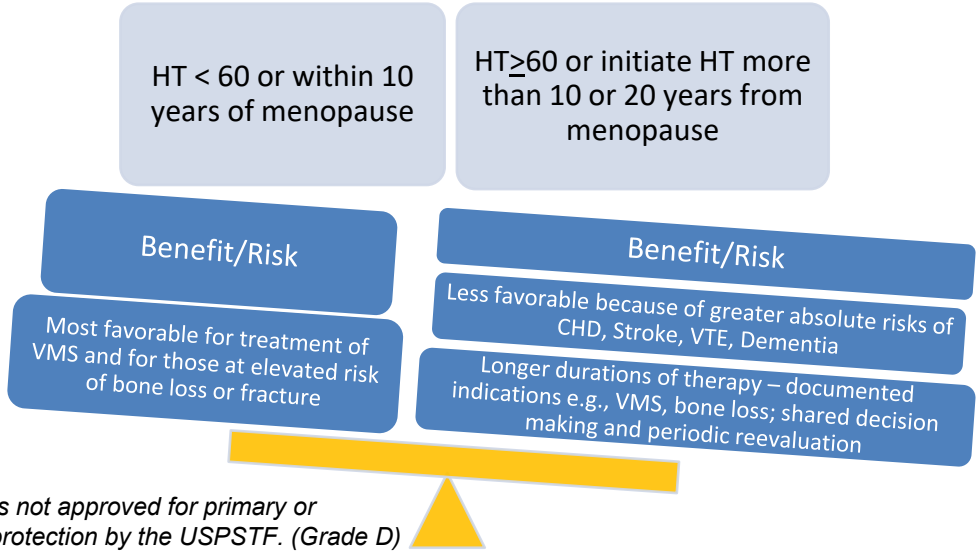
MS Position Statement 2022



Hormone therapy is not approved for primary or secondary cardio protection by the USPSTF. (Grade D)

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The WHI "Right-Sized"

Bridging the Gap Between 2002 and 2026 Reality 2006

The MYTH

HT is dangerous for all women and causes heart disease.

Age and timing matter.

The Reality

The "Window": Women **<60 years old** or **within 10 years of menopause onset** show:
- **Reduced** all-cause mortality.
- **Reduced** risk of bone fractures.
- **Neutral to Positive** effects on cardiovascular health.

Breast Cancer Nuance: Estrogen alone (post-hysterectomy) actually showed a *reduction* in breast cancer incidence in long-term WHI follow-up.

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The "Uterus Rule" and Regimen Selection

Patient Type	Required Hormones	Preferred Delivery
No uterus	Estrogen Only	**Transdermal Patch/Gel:** Lower VTE (clot) risk than oral.
Intact Uterus	Estrogen + Progestogen	**Micronized Progesterone:** "Breast-neutral" and better for sleep.
History of Clots/Migraine	Transdermal Only	Bypasses first-pass hepatic metabolism.

Always include a progestogen if a uterus is present to prevent endometrial hyperplasia. Micronized progesterone (Prometrium) is the gold standard for its safety profile and sedative benefits.

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Effectiveness

- **Compared to placebo**
  - Reduces number and severity of hot flashes
  - Decreases pain with intercourse
  - Reduces vaginal dryness
  - Improvements
    - ✓ Sexual functioning
    - ✓ Menopause-related quality of life
    - ✓ Sleep quality
- Recent 2024-2025 meta-analyses show that **early initiation** significantly reduces the risk of osteoporosis and may have a neutral-to-protective effect on cardiovascular health.

Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/ conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril. 2009;92(3):1025-1038.

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(Relative) Contraindications to Estrogen in MHT


History of Breast Cancer


History of CHD (MI)


History of DVT/PE


History of CVA


Active Liver Disease


Unexplained vaginal bleeding

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Common Side Effects of Systemic HT

- Nausea
- Bloating
- Weight gain
- Fluid retention
- Breast tenderness
- Uterine bleeding
- Mood alterations

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Estradiol Transdermal Equivalency Table

Brand Name	Form	Application Site	"Low" Dose (Approx. 0.025 mg Patch)	"Standard" Dose (Approx. 0.05 mg Patch)	"High" Dose (Approx. 0.1 mg Patch)
Vivelle-Dot / Dotti	Patch	Lower Abdomen	0.025 mg	0.05 mg	0.1 mg
Estrogel (0.06%)	Pump Gel	Entire Arm	1 pump (0.75 mg)	2 pumps (1.55 mg)	4 pumps (3 mg)
Divigel (0.1%)	Packet Gel	Upper thigh	0.25 mg or 0.5 mg	1 mg	1.25 mg (max)
Elestrin (0.06%)	Pump Gel	Upper arm/shoulder	1 pump (0.52 mg)	2 pump (1.04 mg)	3+ pumps
Evamist	Spray	Inner forearm	1 spray	2 spray	3 spray

Clinical Pearls for Switching

- ✓ **The "One-to-One" Myth:** A 1.0 mg packet of **Divigel** does *not* equal a 1.0 mg patch. The "mg" on a gel packet refers to the total estradiol in the gel, while the "mg" on a patch refers to the amount delivered to the blood *per 24 hours*.
- ✓ **The "Standard" Bridge:** If you are moving a patient from a **0.05 mg patch** (standard) to a gel, your safest bet is starting with **2 pumps of Estrogel** or **1.0 mg of Divigel**.
- ✓ **Absorption Surface Area: Estrogel** should be spread thin over the *entire arm* (wrist to shoulder).
  - ➢ **Divigel** is highly concentrated and should only be spread over an area the size of *two palms* on the thigh.
- ✓ **Drying Time:** Remind patients that gels and sprays must dry completely (usually 2–5 minutes) before dressing, and they should avoid showering or swimming for at least 1 hour after application.

Safety Check: The "Transfer" Risk

Unlike patches, gels and sprays carry a small risk of **"skin-to-skin transfer."** ***Advise patients to:***

1. Wash hands immediately after application.
2. Keep the application site covered with clothing once dry if they will be holding children or pets.

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For the 10–20% of women with absolute contraindications (e.g., history of breast cancer), we no longer have to say "just use a fan."

Non-Hormonal "Snipers"

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Nonhormonal Treatments for Vasomotor Symptoms

Medication	Dosage(mg)	Generic (Brand) 1m
Selective serotonin reuptake inhibitors Citalopram	10 to 20 po once daily	$5 (--)
Escitalopram	10 to 20 po once daily	$5 (--)
Paroxetine	10 to 25 po once daily	$5 (--)
Paroxetine mesylate (Brisdelle)†	7.5 po once daily hS	$5 ($230)
Serotonin-norepinephrine reuptake inhibitors Desvenlafxine (Pristiq)	100-150 po once daily	$10 ($415)
Venlafaxine	37.5-150 po once daily	$5 (--)
Alternatives Clonidine	0.1 po once daily	$10 (--)
Gabapentin	300-2400 po daily, in divided doses	$5 (--)
Oxybutynin	2.5-5 po twice daily	$15 (--) for 60 5-mg tablets
Pregabalin(Lyrica)	150-300 po daily, in divided doses	$15 ($600) for 60 150-mg capsules

†—This is the only selective serotonin reuptake inhibitor approved by the U.S. Food and Drug Administration for the treatment of vasomotor symptoms of natural menopause.

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Menopause and Vasomotor Symptoms (NK1 and NK1/3)

It doesn't treat bone loss or vaginal dryness—it is a "sniper" for vasomotor symptoms (moderate–to-severe hot flashes) only.

Generic	Brand	Receptor Target	FDA Approval
Fezolinetant	Veozah	Selective NK_3	May 2023
Elinzanetant	Lynkuet	Dual NK_1/NK_3	October 2025

Fezolinetant (Veozah): The first-in-class NK3 antagonist. It works by blocking the NK3 receptor on KNDy neurons in the hypothalamus to help regulate body temperature.

Elinzanetant (Lynkuet): A dual antagonist. Because it also targets NK1, it has shown additional benefits for sleep disturbances associated with menopause

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Neurokinin Inhibitors for Menopause

Indication: Moderate to Severe Hot Flashes (does NOT treat atrophic vaginitis)

Common side effects: abdominal pain, diarrhea, insomnia (Veozah), back pain, hot flush and elevated hepatic transaminases

FDA Warning for Liver Injury: LFTs before starting

COST: No Insurance **$484 - $652/month;*** with Insurance **$42/month**
~ 8 out of 10 commercially insured patients have access to VEOZAH

** GOOD RX accessed 13 June 2026*

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Conjugated Estrogens/Bazedoxifene (Duavee)

Dosage: 0.45mg/20mg Tablet PO Daily

- Combines conjugated estrogen with bazedoxifene, a selective estrogen receptor modulator
- Bazedoxifene stimulates estrogen receptors in bone and has antagonistic effects in the breast and uterus
  - improves bone mineral density (lumbar spine and hip; effect on fractures not known
  - lowers the risk of uterine cancer due to SERM's varying mechanism of action in tissues
- Labeled for the treatment of **moderate to severe vasomotor symptoms** associated with menopause **and prevention of postmenopausal osteoporosis**.
  - Will maintain bone mineral density in the lumbar spine and hip, but its **effect on fractures is not known.**
- May be better tolerated than conjugated estrogens/medroxyprogesterone
- Precludes the need for endometrial protection with progesterone
- **Cost $210/month**

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Bioidentical Synthetic Hormones

- Plant derived, chemically similar or structurally identical to those produced by the body
  - FDA Approved – but **NO** evidence to suggest greater effectiveness over standard estrogens
    - Estradiol
    - Estrone
    - Micronized progesterone
  - Non-FDA regulated
    - Compounded preparations; purity, potency, and quality are concern
    - Overdosage and underdosage possible because of variable bioactivity and bioavailability

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MS Position Statement 2022

- **Compounded bioidentical** HT presents **safety concerns** such as minimal government regulation and monitoring, overdosing or underdosing, presence of impurities or lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks.
- Salivary hormone testing to determine dosing is **unreliable**.
- **Prescribers of compounded bioidentical HT** should document the medical indication for compounded HT over government-approved therapies, such as allergy or the need for dosing or a formulation not available in FDA-approved products

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Testosterone?

- In **combination** with HT has been investigated for treatment of menopausal symptoms
  - No benefit
  - Potential adverse effects
    - Detrimental effects on lipid parameters
    - Clitoromegaly
    - Hirsutism
    - Acne
- In **combination** with HT for postmenopausal women
  - Improved sexual function scores
  - Improved number of satisfying sexual episodes
- **Alone**, NOT FDA-approved for use in women

Somboonporn W et al., Testosterone for peri and postmenopausal women. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No. CD004509.

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MS POSITION STATEMENT 2022

No General Rule for Stopping at Age 65

- HT does **not** need to be routinely discontinued in women aged older than 60 or 65 years
  - Considered for continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis/fracture after appropriate evaluation and counseling of benefits/risks.
  - **Ongoing use** of systemic HT by healthy women who initiated therapy **within** 10 years of menopause onset and without new health risks likely has a safety profile **more favorable** than that for women initiating HT when aged older than 65 years, although limited long-duration data are available
- *ACOG recommends AGAINST routine discontinuation of systemic estrogen at age 65 years*
- **Annual reevaluation**, including reviewing comorbidities and periodic trials of lowering or discontinuing HT or changing to potentially safer low-dose transdermal routes, should be considered

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Assessing Benefit & Risk on MHT

A Yearly, Three-Part Check — Start It the Day You Start Therapy

Before continuing therapy each year, work through three checks:

1. **Medical History Review**
2. **Risk Factor Identification**
3. **Lifestyle Factors**

➢ **Document a shared benefit–risk decision each year — then continue, adjust the dose/route, or taper.**

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The Annual Check: History & Risk Factors

What to Review at Every Visit

Medical History Review

- VMS status — still present? how bothersome?
- Any vaginal bleeding → evaluate before refill
- Breast exam + mammogram up to date
- Blood pressure, weight / BMI
- New diagnoses: VTE, stroke, CHD, breast Ca, liver/gallbladder
- Current dose, route, adherence & side effects

Risk Factor Identification

- VTE / clotting: personal or family history, obesity, immobility → favor transdermal
- Cardiovascular: ASCVD risk, hypertension, diabetes, smoking
- Breast cancer: family history, density, prior biopsies
- Stroke risk factors
- Years since menopause & age (>10 yr out or >60 yr raises risk)
- Bone / fracture risk — DEXA if due

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Optimize & Act on the Assessment

Lifestyle First — Then Tailor the Regimen

Lifestyle Factors

- Smoking cessation — the biggest modifiable VTE/CVD risk
- Weight management & heart-healthy diet
- Weight-bearing & resistance exercise for bone
- Limit alcohol; ensure calcium + vitamin D
- Bone health: DEXA per guidelines
- Sleep, stress, and mood support

Adjust the Regimen

- Use the lowest effective dose for symptom control
- Prefer transdermal estradiol if VTE or CVD risk
- Add progestogen if uterus present (endometrial protection)
- Try periodic dose reduction or a taper trial
- Continue if VMS, QOL, or bone benefit outweighs risk
- Re-document the shared decision each year

Discontinuation –

- HT tapered vs. stopped abruptly – rates of vasomotor symptom recurrence are similar
- Recurrent vasomotor symptoms in approximately 50% of women regardless of age and duration of use

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Transitioning from Hormonal Contraception to HT *(If the Latter Is Needed)*

- ACOG – don't measure an FSH
  - Discontinue contraception when women are in mid-50s; spontaneous conception is rare
  - Checking follicle-stimulating hormone (FSH) levels to determine when OC users have become menopausal is not useful.
    - **This approach is based on the following observations:**
      - ✓ in premenopausal women, FSH levels vary and a single elevated FSH level does not reliably document that contraception is no longer needed
      - ✓ checking of FSH levels on the 5th-7th day of the pill-free interval is not useful, since sex steroids in OCs suppress FSH blood levels for far longer than 7 days; and
      - ✓ about 50% of 52-year-old OC users are not yet menopausal, but by age 55 a great majority of women are menopausal.

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Nonpharmacologic Treatments for Vasomotor Symptoms

- Effective for short-term reduction of VMS and associated sleep disturbances
  - **Cognitive behavior therapy (NNT = 4)**
    - Counseling may help deal with the changes of menopause as well, along with other underlying problems that come to the surface at this time
  - **Clinical hypnosis**
    - Limited research – some studies with promising results

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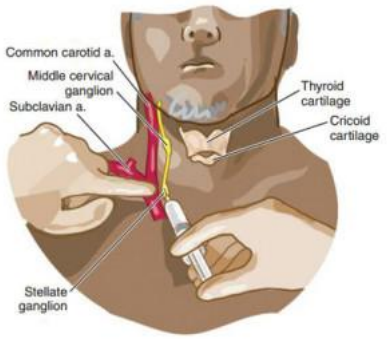
Alternative Techniques



- Local injection of anesthetic (block) into the stellate ganglion (C6-T2 anterior cervical spine)[1]
  - May reduce VMS in women with contraindications to HT
  - More studies needed

[1]Kontos M, et al. Climacteric 2010;13:4-21

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Complementary and Integrative *Effectiveness*


Acupuncture


Reflexology


Soy Isoflavones


Herbs e.g. Balack Cohosh


Yoga

- **Acupuncture and Reflexology** – no benefit to menopausal symptoms.
- **Phytoestrogens**, **herbs**, and other natural products haven't been clearly shown to relieve menopause symptoms. Lack standard formulations.
- **Yoga** has **not** been shown to relieve hot flashes but **may be helpful** for some symptoms associated with menopause.

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Supporting Emotional Aspects of Transition *Expert Opinion*

Emotional Well-Being

Everyday habits that lift mood:

- Balanced, nutritious diet
- Regular physical exercise
- Sufficient, restorative sleep
- Supportive friendships & social connection

Stay Grounded

Ease stress & irritability with mind-body practices:

- Tai chi — gentle, flowing movement
- Meditation & mindful breathing

Diet can also help individuals reduce menopausal mood swings, especially one rich in protein and omega-3 fatty acids

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NIH
National Center for Complementary and Integrative Health

- What do we know about the **safety** of complementary health approaches for menopause symptoms?
  - **Natural products** may have side effects or interact with drugs, and little is known about their long-term safety.
  - **Mind and body practices** such as acupuncture, hypnosis, meditation, and yoga generally have good safety records.
  - Custom-mixed **bioidentical hormones** haven't been shown to be safer than other forms of hormone therapy, and their content may vary from batch to batch.

https://www.nccih.nih.gov/health/menopausal-symptoms-in-depth

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Bottom Line

You don't need to memorize fifty different drugs. Master:
- ❑ one patch
- ❑ one micronized progesterone
- ❑ one vaginal tablet
- ❑ new NK3 antagonist

That's 95% of the care your patients need.

The "Safety Check" Box
- ❑ **Do they have a uterus?** If YES, they **MUST** have Progesterone.
- ❑ **Do they have a history of blood clots or migraines with aura?** If YES, use **Transdermal** only.
- ❑ **Do they have a history of Estrogen-Positive Breast Cancer?** If YES, use **Non-Hormonal** (Veozah/Effexor).

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Modern Menopause Prescribing Cheat Sheet

The Hormonal Regimens

Medication Type	Common Brand	Starting Dose	Primary Benefit	Side effects/Risks
Estradiol Patch	Vivelle-Dot, Dotti	**0.05 mg** (2x weekly)	Gold standard for VMS; lower VTE risk.	Skin irritation; breast tenderness.
Micronized Progesterone	Prometrium	**0.05 mg** (2x weekly)	Endometrial protection; aids sleep.	Drowsiness; vivid dreams.
Oral Estradiol	Estrace	**1 mg** (Daily	Effective, low cost.	Higher VTE risk than transdermal.
Combined Patch	Climara Pro	**0.045/0.015 mg**	Convenience (1 patch for E+P).	Less dose flexibility.

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Modern Menopause Prescribing Cheat Sheet

The Non-Hormonal Regimens

Medication Type	Common Brand	Starting Dose	Primary Benefit	Side effects/Risks
NK3 Antagonist	**Veozah** (Fezolinetant)	**45 mg** (Daily)	Fast hot flash relief without hormones.	Check LFTs (baseline); headache.
SSRI	Brisdelle (Paroxetine)	**7.5 mg** (Daily)	Only FDA-approved SSRI for VMS.	Nausea; sexual dysfunction.
SNRI	Effexor (Venlafaxine)	**37.5 mg** (Daily)	Great for mood + hot flashes.	Dry mouth; BP elevation

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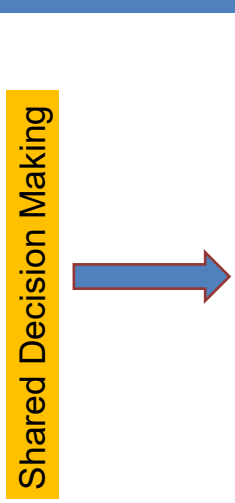
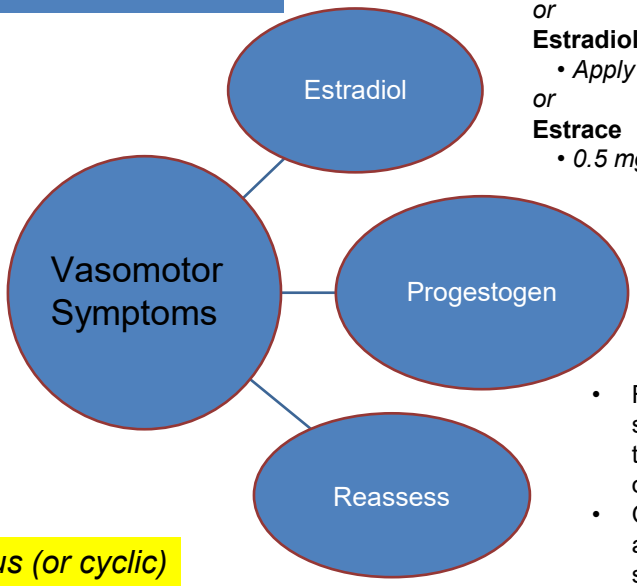
Example





Estradiol gel 0.25mg/pkt
- *Apply one packet to upper thigh daily*

or

Estradiol patch 0.025 mg
- *Apply one patch weekly*

or

Estrace
- *0.5 mg po daily*

Micronized progesterone
- 100-200 mg PO daily

- Reevaluate 6-12 weeks after started. If significant VMS persist titrate up on Estrogen component of therapy.
- Once symptoms are stable, address potential for trial off starting 2-3 years after beginning.

Continuous (or cyclic)

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Troubleshooting Common Issues

Skin Irritation: If a patient has a reaction to the patch adhesive, recommend an **Estradiol Gel** (like Divigel or Estrogel) or **Spray** (Evamist). These offer the same "liver-bypass" safety benefits as the patch.

Drowsiness: If a patient feels "groggy" the next morning from the 100 mg progesterone, ensure they are taking it right before bed on an empty stomach (food can increase absorption and side effects).

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The Three Faces of Menopause

Case 1 - 52-year-old

- healthy, having severe night sweats and mood swings.

Case 2 - 48-year-old

- had a total hysterectomy (ovaries remained) 3 years ago for fibroids. Now experiencing "brain fog" and intense hot flashes.

Case 55-year-old

- with a history of Stage II Breast Cancer (ER/PR positive) currently on Tamoxifen. She is "miserable" with 15 hot flashes a day.

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Case 1

52-year-old, healthy, having severe night sweats and mood swings. Last period was 14 months ago.

The Regimen:

•**Estrogen:** 0.05 mg Estradiol Transdermal Patch (e.g., Vivelle-Dot) changed twice weekly.

•**Progesterone:** 100 mg Micronized Progesterone (e.g., Prometrium) daily at bedtime.

The Rationale:

•**Endometrial Protection:** Unopposed estrogen in a woman with a uterus increases the risk of endometrial cancer by nearly **10-fold**. Progesterone is *non-negotiable* here to keep the lining thin.

•**The "Sedation" Benefit:** Micronized progesterone is metabolically "body-identical" and has a mild sedative effect, helping with the patient's insomnia.

•**Transdermal Safety:** Starting with a patch avoids the "first-pass" through the liver, significantly reducing the risk of blood clots

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Case 2

48-year-old, had a total hysterectomy (ovaries remained) 3 years ago for fibroids. Now experiencing "brain fog" and intense hot flashes.

The Regimen:
•**Estrogen:** 1 mg Oral Estradiol daily OR 0.05 mg Estradiol Patch.
•**Progesterone:** None.
•**The Rationale:**
No Uterus = No Progesterone: Without a uterus, there is no risk of endometrial CA
•**Breast Safety:** The WHI data showed that women on **Estrogen-only** actually had a *lower* risk of breast cancer compared to those on combined E+P. Adding unnecessary progesterone may actually slightly *increase* breast cancer risk.
•**Symptom Sniper:** Since her main complaint is vasomotor and cognitive, estrogen alone is the most efficient way to cross the blood-brain barrier and stabilize the hypothalamus.

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Case 3

55-year-old with a history of Stage II Breast Cancer (ER/PR positive) currently on Tamoxifen. She is "miserable" with 15 hot flashes a day.

The Regimen:
- **First Line:** Fezolinetant (Veozah) 45 mg once daily.
- **Secondary Option:** Venlafaxine (Effexor) 37.5 mg daily.

The Rationale:
- **Safety First:** In ER+ breast cancer survivors, systemic estrogen is generally contraindicated as it could theoretically stimulate dormant cancer cells.
- **NK3 Receptor Blockade:** Fezolinetant acts directly on the KNDy neurons in the brain to "reset" the body's thermostat without touching estrogen receptors. It provides a **60% reduction** in symptoms.
- **The Tamoxifen Factor:** Many SSRIs (like Paroxetine) interfere with Tamoxifen metabolism (CYP2D6 inhibition). Fezolinetant and Venlafaxine do **not** have this interaction, making them the safest choices for oncology patients.

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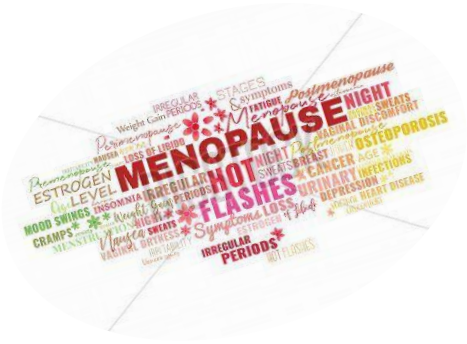

Hot flashes
Night Sweats
Vaginal dryness

Anxiety
Changes in mood
Reduced sex drive

Children leaving the home
Aging parents
Retirement

SUMMARY

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Practice Recommendations

- Systemic HT, with estrogen alone or combined with progestin, is the most effective therapy for vasomotor symptoms related to menopause. (SOR: A)
- Because of potential risks with long-term use of hormone therapy, clinicians should prescribe the lowest effective dose for the shortest duration necessary to improve symptoms. (SOR: C)
- The decision to continue MHT should be individualized based on a woman's symptoms and the risk-benefit ratio, REGARDLESS OF AGE. (SOR: C)
- Combined estrogen/progesterone therapy, but NOT estrogen alone, increases the risk of breast cancer after 5-7 years of use. (SOR: B)
- Nonhormonal medications, including SSRIs, SNRIs, gabapentin, clonidine, and oxybutynin may reduce hot flashes and are reasonable alternatives for patients who cannot or choose not to use hormone therapy. (SOR: B)

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Practice Recommendations

- Cognitive behavior therapy and clinical hypnosis reduce vasomotor symptoms in the short term. Nonpharmacologic treatments, including black cohosh and isoflavones, may be considered for select patients, although low-quality evidence supports their effectiveness. (SOR: B)

The biggest myth of all is that women just have to 'tough it out.' As clinicians, we have the tools in 2026 to ensure the last third of a woman's life is her best third. Let's stop managing symptoms and start optimizing health.

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