Menopause & Hormone Therapy

The most consequential misreading of a trial in modern medicine · and it still denies treatment to women who would benefit

Ask her age first
not how bad the symptoms are

⚠ WHAT WHI ACTUALLY SHOWED

three things were widely missed, and each changes the bedside decision

⚠ THE POPULATION WAS NOT YOUR PATIENT

The 2002 estrogen-plus-progestin arm stopped early (mean 5.6 years) and was read as a verdict on hormone therapy as a whole. But WHI tested whether HT **PREVENTED CHRONIC DISEASE in older women**: **mean age ~63**, many **>10 years past menopause**. **The woman asking about hot flashes is in her early fifties and was barely represented.**

THERE WERE TWO TRIALS, AND THEY DISAGREED

The **ESTROGEN-ALONE arm** (women with prior hysterectomy) showed **NO increase in breast cancer**, and with longer follow-up a **significantly LOWER risk than placebo**. The breast-cancer signal that dominated the headlines came from the **combined** arm, implicating the **progestogen** component rather than estrogen itself.

AGE AT INITIATION CHANGES THE ANSWER

Among women randomized at **50-59**, both arms showed favorable outcomes: **less diabetes, fewer fractures, lower all-cause mortality**. Risk accrues with **later initiation**, especially beyond 65 or more than 10 years out. The plausible mechanism is that estrogen acts differently on **healthy endothelium** than on **established plaque**.

THE TIMING HYPOTHESIS, AND ITS LIMIT

Point	Detail
⚠ **The window**	**Under 60, OR within 10 years of the final menstrual period** = favorable benefit-risk for a symptomatic woman without contraindications. **This is why the first question is "how old is she and how long since her last period," not "are the symptoms bad enough to justify the risk"**
⚠ **What it does NOT license**	**HT is still NOT given to prevent cardiovascular disease or dementia.** It treats **SYMPTOMS**, with bone protection a legitimate secondary benefit. The correction is that **symptomatic women in the window should not be denied treatment** -not that HT is preventive medicine. **Overcorrecting the other way is its own error**
Symptom duration	Vasomotor symptoms last a **median 7-10 years**, far longer than patients are told. **"Wait it out" commits her to a decade of disrupted sleep**
⚠ **Genitourinary syndrome**	Dryness, dyspareunia, urinary urgency, recurrent UTI. **Unlike hot flashes it is PROGRESSIVE and does not remit**, so it needs its own long-term plan -and it is the symptom **patients least often volunteer. Ask directly**

PRESCRIBING

Decision	Approach, and why
⚠ **Uterus intact?**	**Estrogen MUST be combined with a progestogen** -unopposed estrogen drives endometrial hyperplasia and carcinoma. Not optional, not preference. **After hysterectomy: estrogen alone**, which is also the arm with the better breast-cancer data
Route	**TRANSDERMAL preferred where thrombotic risk matters** -it bypasses first-pass hepatic metabolism and so has less effect on clotting factors. Consider for higher VTE risk, obesity, hypertriglyceridemia, migraine with aura
Dose & duration	Lowest effective dose, titrated to symptoms. **NO mandatory stop date** -stopping arbitrarily at 5 years or age 65 is not evidence-based. Reassess periodically. **Warn about breakthrough bleeding early**, the commonest reason women quit
⚠ **Contraindications**	**Breast cancer, coronary heart disease, prior stroke or TIA, VTE or thrombophilia, unexplained vaginal bleeding, active liver disease.** These are hard stops, not cautions
⚠ **Genitourinary syndrome**	**LOW-DOSE VAGINAL estrogen**: minimal systemic absorption, a risk profile separate from systemic HT, **no progestogen needed at usual doses**, continue long term. Treats dryness, dyspareunia and recurrent UTI. Many women whose systemic HT is contraindicated can still use it -**in a breast cancer survivor that call belongs with her oncologist**
⚠ **Any postmenopausal bleeding**	**Requires evaluation for endometrial cancer**, however minor and regardless of HT status. Never attribute it to the transition or to the therapy without investigating

TWO SITUATIONS THAT INVERT THE USUAL RISK CALCULUS

⚠ PREMATURE / EARLY MENOPAUSE & POI

Under 40 (primary ovarian insufficiency) or 40-45 (early menopause) is a DIFFERENT decision entirely. These women are not taking on the risk of added hormones -they are **replacing what an age-matched woman still has**. Untreated, they face **higher cardiovascular risk, accelerated bone loss and earlier osteoporosis**. **Hormone therapy is recommended at least until the average age of natural menopause (~51)**, often at higher doses than for symptom control, and the usual WHI risk framing simply does not apply. **Withholding it here is the error, not prescribing it.**

⚠ SHE IS STILL FERTILE, AND HT IS NOT CONTRACEPTION

Ovulation is erratic but continues, so **pregnancy remains possible until 12 months of amenorrhea** (advised as 12 months over age 50, 24 months under 50). **Menopausal HT does NOT provide contraception** -a widely made and consequential assumption. She needs a contraceptive method alongside, and the **levonorgestrel IUD is useful**: it gives contraception, treats heavy perimenopausal bleeding, **and supplies the endometrial protection estrogen requires.**

DIAGNOSIS & NONHORMONAL OPTIONS

⚠ DO NOT CHECK AN FSH OVER 45

Menopause is a **CLINICAL diagnosis**: 12 months of amenorrhea without another cause. **FSH fluctuates enormously through the transition**, so a normal value in an unmistakably perimenopausal woman is common and an elevated one proves nothing. **Exception: under 40, the question is PRIMARY OVARIAN INSUFFICIENCY** and FSH (repeated) plus a specific workup is required; 40-45 is reasonable. **Always check TSH** -hyperthyroidism reproduces this picture almost exactly. Exclude pregnancy.

NONHORMONAL

SSRIs/SNRIs at lower doses than for depression. ⚠ **NOT paroxetine or fluoxetine with TAMOXIFEN** -potent CYP2D6 inhibitors, and tamoxifen needs CYP2D6 to form its active metabolite, so the combination can undermine cancer treatment. **Use venlafaxine**. **Gabapentin** suits night-predominant symptoms. **Fezolinetant** (NK3 antagonist) blocks the mechanism itself -⚠ **BOXED WARNING for rare serious liver injury added Dec 2024: LFTs at baseline, monthly x3, then 6 and 9 months**. **Elinzanetant** (dual NK1/NK3) approved Oct 2025. **CBT** has evidence. **Lifestyle advice alone in a woman with disabling symptoms is undertreatment.**

PEARLS & PITFALLS

- ⚠ **Compounded "bioidentical" hormones are NOT safer.** Same risks, without purity or dose consistency, and **saliva hormone testing has no validated role**. Approved products already contain bioidentical molecules (17-beta estradiol, micronized progesterone) -so a patient who wants them can have exactly that, from a regulated product.

References: Women's Health Initiative randomized trials of menopausal hormone therapy (estrogen-plus-progestin 2002 and estrogen-alone 2004, with long-term follow-up analyses) · menopause society guidance on hormone therapy and on the genitourinary syndrome of menopause · FDA labeling for fezolinetant (boxed warning for hepatic injury, December 2024) and elinzanetant (approved October 2025).

Educational aid; verify against current guidance, local formulary and patient factors.