Menopause & the Evolving Evidence Behind MHT

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BIG SKY MEDICAL CONFERENCE

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Learning Objectives

1. Understand the physiologic and metabolic changes of the menopausal transition.
2. Review the current evidence on the benefits and risks of menopausal hormone therapy (MHT).
3. Apply evidence-based principles to selecting and timing hormone therapy.

Timeline

Late Reproductive Years:

- VMS can occur in late luteal (near menstruation) or early follicular phases (20%)

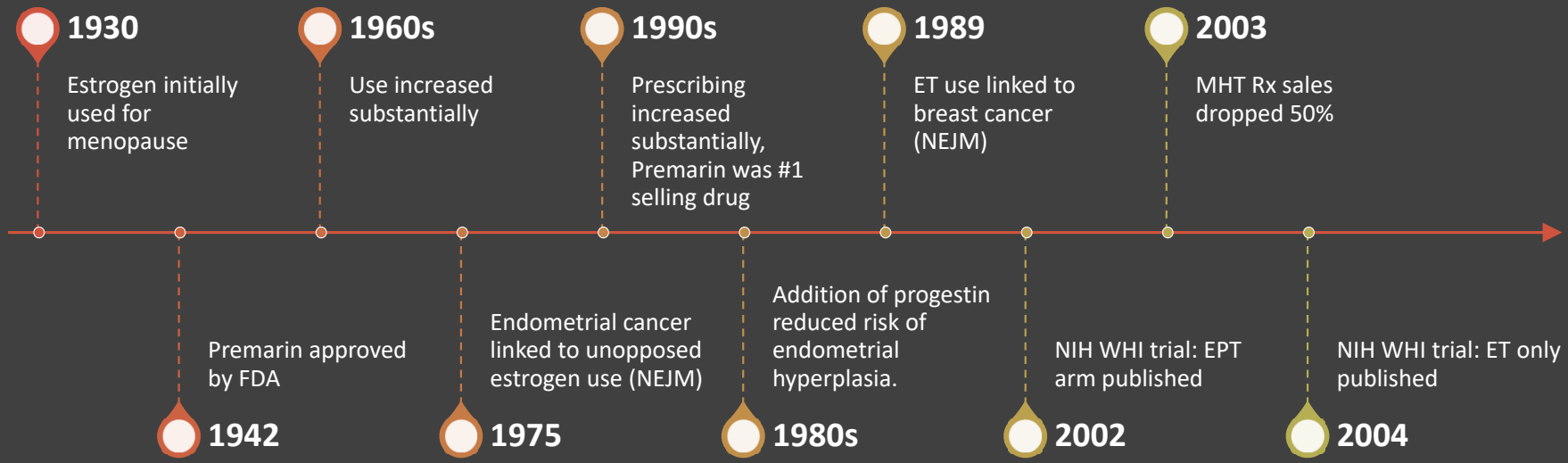
Perimenopause:

- Gradual transition which begins with cycle irregularity approximately 4-8 years prior to onset of menopause
- Two phases: early (DUB) and late (skipped cycles)
- Symptoms of estrogen withdrawal

Postmenopausal:

- Applied when women experience amenorrhea for more than 12 months
- Median age of onset of menopause is 51 years (40-58)
- Increased symptoms of estrogen deficiency (GSM)

History of MHT



WHI 2002

Women's Health Initiative (WHI)

- Largest and longest trial of HT in postmenopausal women

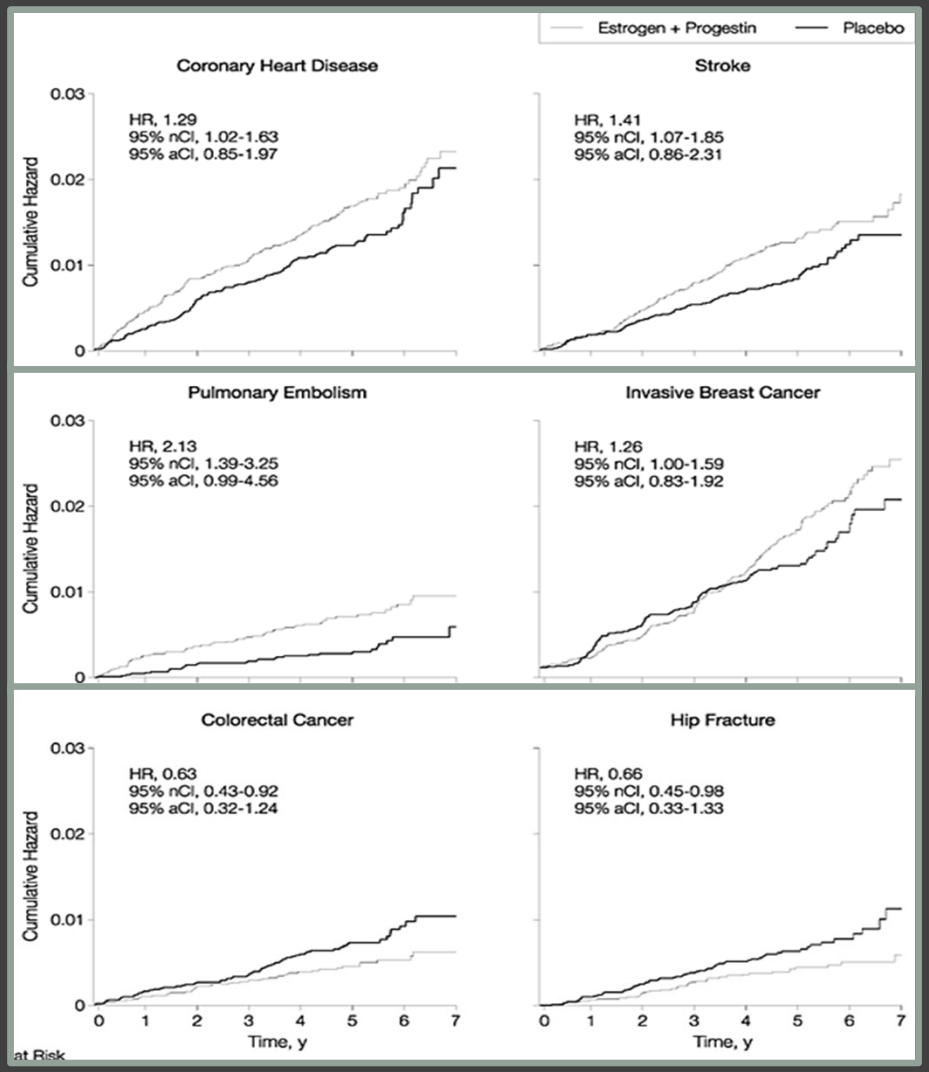
RCT designed to evaluate the benefits and risks of ET and EPT

- CHD, fractures, colorectal cancer
- Breast cancer, stroke, DVT/PE, endometrial cancer

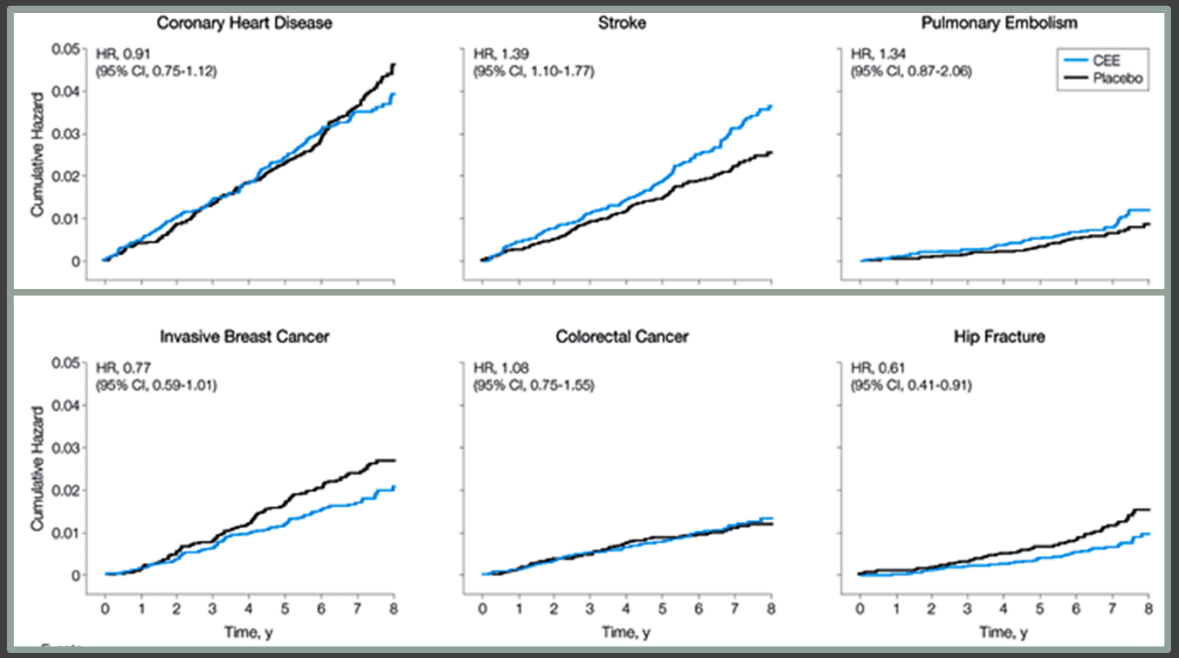
Included nearly 27,000 healthy, post-menopausal women 50-79 (average age 63)

3 Arms:

- EPT (women with uterus): oral conjugated equine estrogen(CEE) 0.625mg plus medroxyprogesterone 2.5mg daily
- ET only (women with hysterectomy): CEE 0.625mg daily
- Placebo



Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes



Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes

Results

EPT arm stopped early after 5.2 years due to increased risk of invasive breast cancer, CAD, stroke and PE

	Relative Risk	Absolute Risk (If 10,000 women took the medication for 1 year)
Coronary heart disease	+29%	+7 cases/10,000/year
Stroke	+37%	+9 cases/10,000/year
Pulmonary embolism	+98%	+9 cases/10,000/year
Invasive breast cancer	+24%	+9 cases/10,000/year
Colon cancer	-37%	-6 cases/10,000/year
Hip fractures	-24%	-5 cases/10,000/year

ET arm stopped after a mean follow-up of 7 years due to increased stroke risk

ET had no effect on CHD risk and was not associated with increased breast cancer risk

Continued Observational Study

Remains largest and longest trial – 18+ years of follow-up data

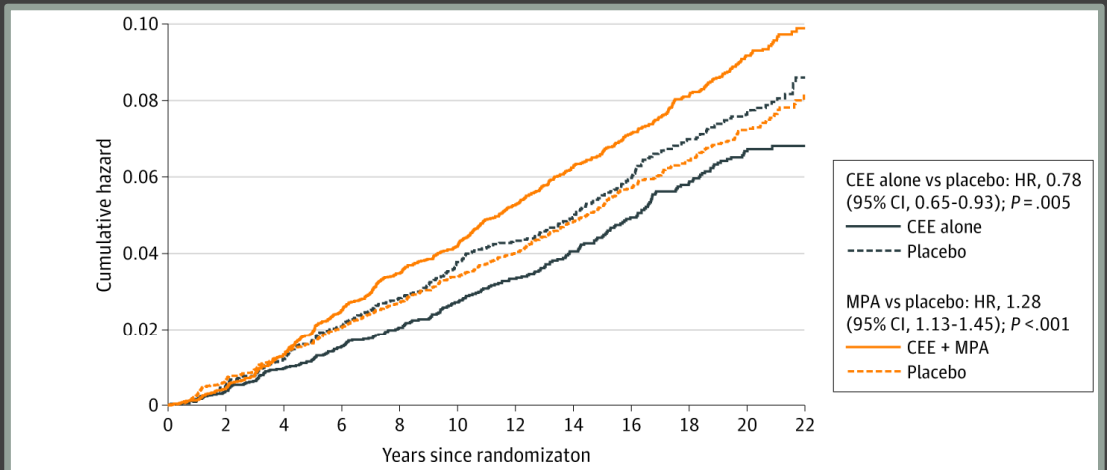
- *Observational follow-up*

Among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.

CEE plus MPA and CEE alone were not associated with increased or decreased risk of all-cause, cardiovascular, or total cancer mortality

Prior randomized use of CEE alone, compared with placebo, among women who had a previous hysterectomy, was significantly associated with lower breast cancer incidence and lower breast cancer mortality

Kaplan-Meier Estimates for the Association of Menopausal Hormone Therapy With Invasive Breast Cancer During Cumulative Follow-up



No. at risk

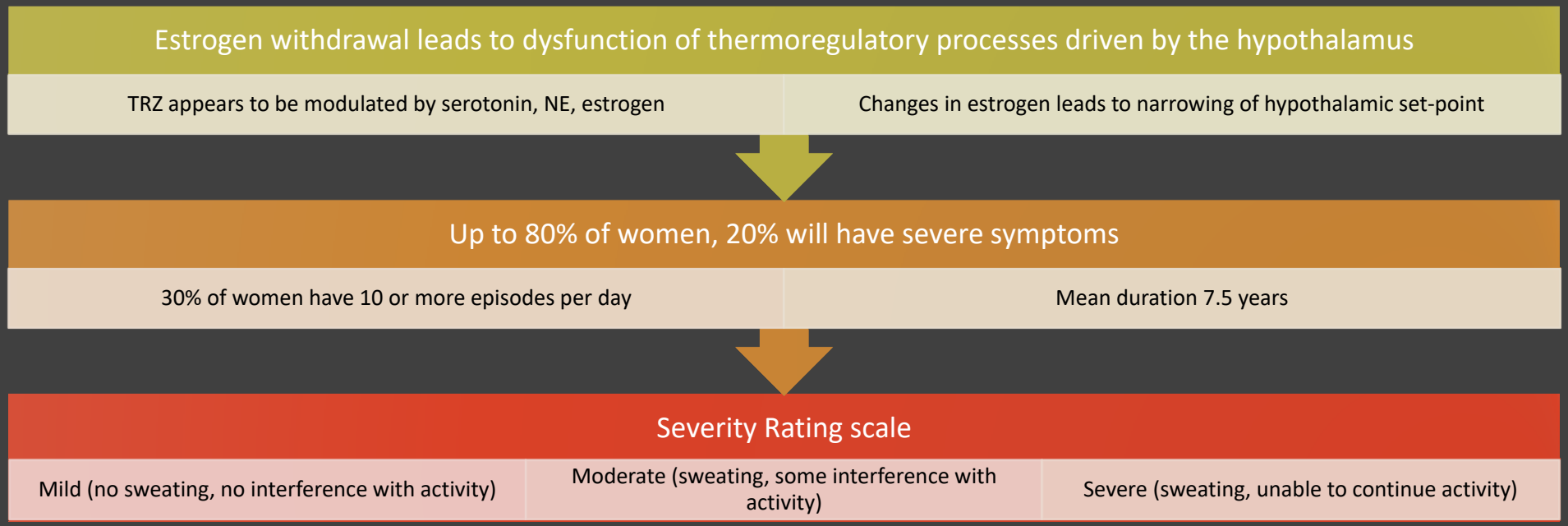
CEE + MPA												
CEE + MPA	8506	8329	8114	7802	7016	6248	5743	5006	4517	4143	3239	881
Placebo	8102	7916	7726	7472	6700	5944	5515	4808	4360	3991	3159	769
CEE alone												
CEE alone	5310	5167	5010	4845	4271	3673	3378	2873	2565	2307	1811	496
Placebo	5429	5280	5105	4915	4307	3717	3387	2892	2567	2307	1807	498

FDA-Approved Indications for HT

- Treatment of moderate-to-severe vasomotor symptoms associated with menopause
- Treatment of genitourinary symptoms of menopause (GSM)
- Prevention of postmenopausal osteoporosis
- Treatment of premature low estrogen levels

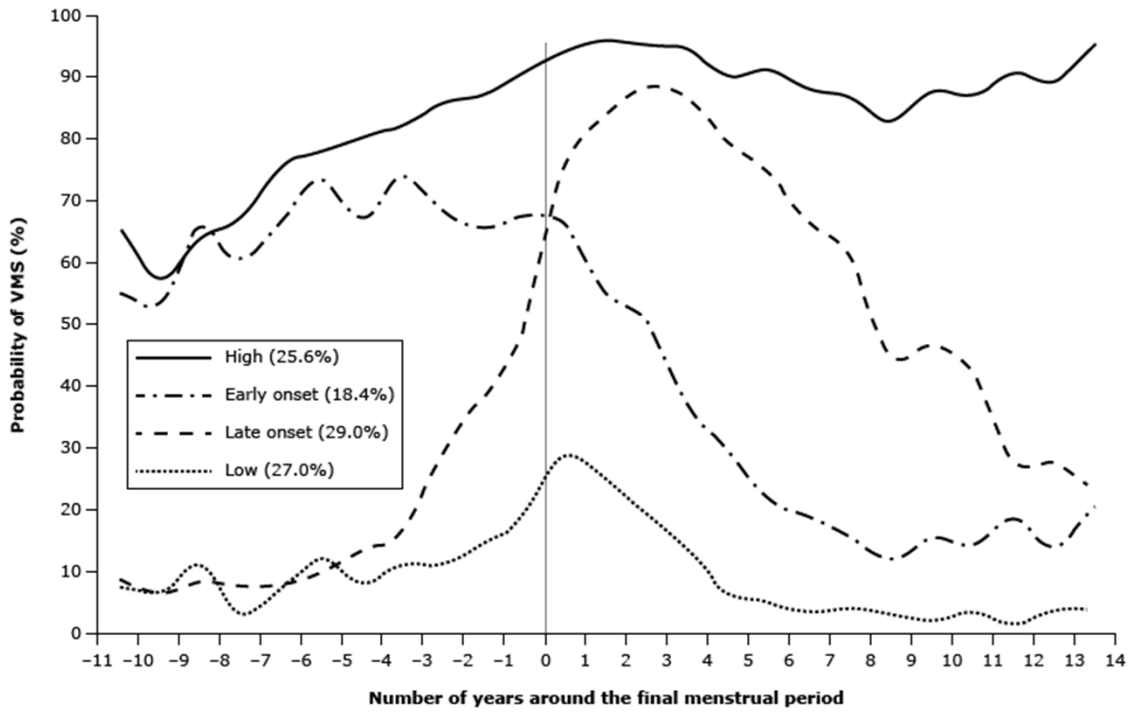
Contraindications to HT

Absolute:	Relative
• Hormone sensitive cancers: breast, endometrial, ovarian • Vaginal bleeding of unknown cause • Thromboembolism (DVT/PE) • Active or recent stroke/TIA, MI • Active liver disease • Thrombophilic disorders	• Family history of hormone sensitive cancers • Uncontrolled sz or HTN • Worsening migraine • Avoid oral: increased TGs, liver disease, gallbladder disease

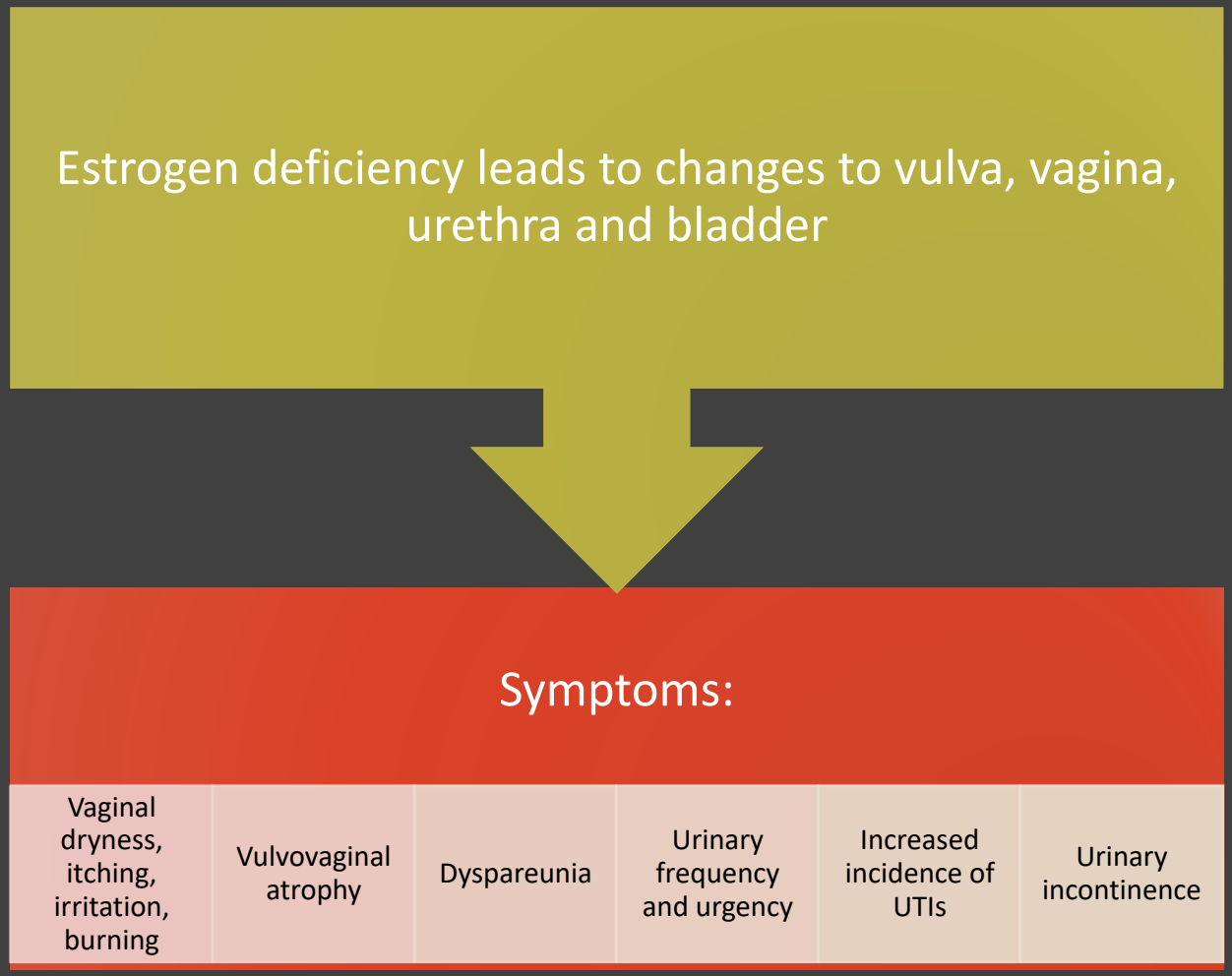


Clinical Presentation: Vasomotor Symptoms

Trajectories of vasomotor symptoms over the menopause transition



Clinical Presentation: Genitourinary Symptoms



Clinical Presentation: Other Symptoms

Menstrual irregularity occurs early

- Varying cycles, DUB

Psychological symptoms

- Anxiety/depression, mood changes
- Sleep disturbances, problems with concentration and memory

Tachycardia and palpitations

Arthralgia

Accelerated loss of BMD

- Begins approximately 2 years before the LMP
- Continues approx 5-10 years following menopause

CVD

- Incr LDL, dec HDL, Inc risk of CAD

Weight gain, skin changes, hair loss, dry eyes

Transdermal vs Oral Estrogen

- Better absorption (bypasses liver/ intestinal variables)
- Better steady state levels (no daily peaks)
- Lower risk of VTE than with oral
- Lower risk of stroke than with oral
- Lower risk of gallbladder disease than with oral
- Less negative impact on triglycerides
- Lower rate of estradiol-to-estrone conversion (lower CA risk to breast & endometrium?)
- All patches contain estradiol (no conjugated equine estrogens)

VVA Symptoms

Mild symptoms

- Water-based products (vaginal moisturizer) plus vaginal lubricant during intercourse

Moderate symptoms

- **1st line**: low-dose vaginal estrogen
  - Low dose cream 0.5gm 1-3 times per week
  - E2 vaginal tablets twice weekly
- Ospemifene (Osphena): oral SERM (EAA)
  - Side effects: hot flashes 7.5%, increased VTE risk
- Prasterone (Intrarosa): DHEA, daily vaginal insert
  - Endometrial safety confirmed at 1 year, less clinical experience compared to vaginal estrogens
  - Avoid use in those with history of breast cancer and undiagnosed AUB

Adequate estrogen therapy leads to restoration of normal vaginal acid pH and microflora, epithelium thickening, increased vaginal secretions, and reduction in UTIs and over-active bladder symptoms.

Progestin: protect the endometrium

- Medroxyprogesterone
- Norethindrone acetate (Aygestin)
  - 0.35mg daily
  - 5mg for cyclic regimens
- Norgestrel/Levonorgestrel
- Micronized progesterone (bioidentical): lowest risks, least side effects
  - 200 mg po qday x 12 days/month
  - 100 mg po qday

Perimenopause

No evidence that checking hormone levels is beneficial because of massive fluctuations in levels. May be beneficial to check other labs:

- TSH (thyroid disorders can mimic perimenopause)
- CBC (r/o infectious causes)
- CMP (ensure no liver disease)
- Lipids (risk stratification)

Cyclic combined regimen (or low-dose OCP's) preferred: 80-90% will have regular monthly withdrawal bleeds, but less unscheduled bleeding

- OCP
- Systemic MHT: patch plus IUD or oral progesterone
- Nonhormonal treatment (SSRI)

REPLENISH Trial

Randomized, double-blind, placebo-controlled, multicenter trial, evaluating single, oral, softgel E2/P4 capsules in postmenopausal women (40-65 y) with a uterus and vasomotor symptoms (VMS)

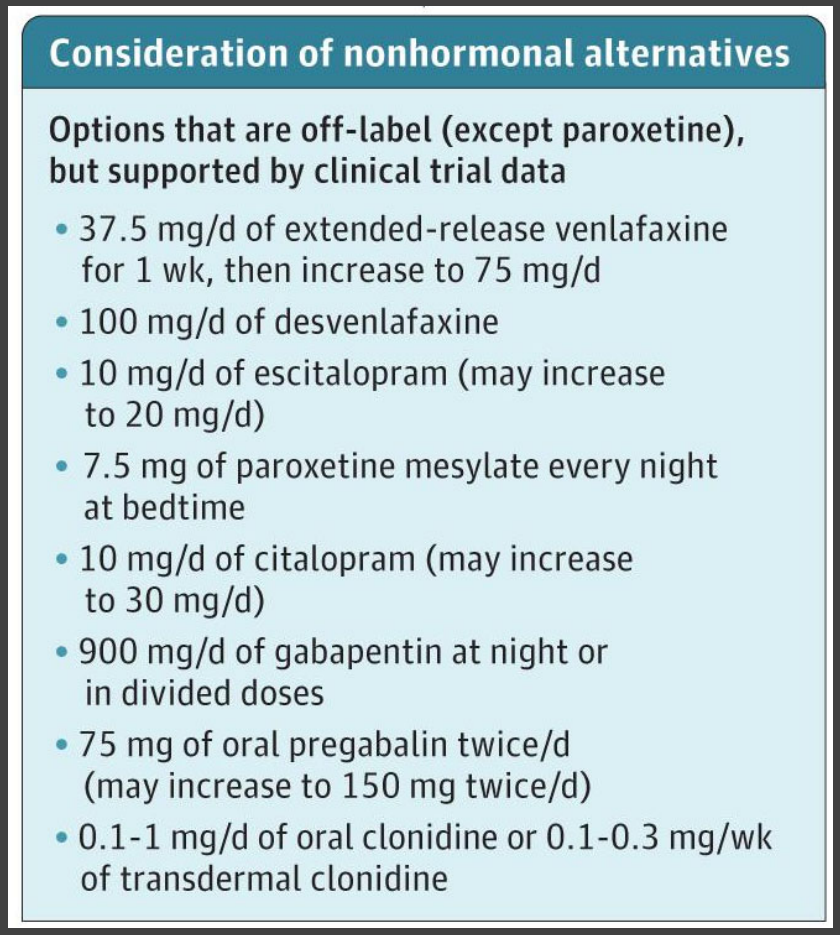
Daily 17β-estradiol (E2) and progesterone (P4) (mg/mg): 1/100, 0.5/100, 0.5/50, 0.25/50, or placebo

VMS frequency and severity decreased significantly with a dose-related response

0 cases of endometrial hyperplasia

ESTHER Study

- Multicenter case–control study of VTE among postmenopausal women aged 45–70 years, between 1999 and 2005, in France.
- Case population consisted of women with a first documented idiopathic VTE.
- 191 hospital cases matched with 416 hospital controls and 62 outpatient cases matched with 181 community controls.
- Oral estrogen use and elevated body mass index (BMI) increase the risk of venous thromboembolism (VTE)
- Transdermal users with increased BMI had similar risk as non-users with increased BMI



Alternatives for VMS

SSRI/SNRIs (10 PRCTs)

- Paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine

Gabapentin (3 PRCTs)

- Especially for nocturnal VMS

Clonidine

Oxybutynin

- Several small studies suggest more effective than placebo, concern for anticholinergic side effects

Neurokinin antagonists

- $$$, modest effect comparable to other non-hormonal options (reduction 2-3/hot flashes/day)

Testosterone

Testosterone declines gradually as women age, is not an abrupt change at menopause

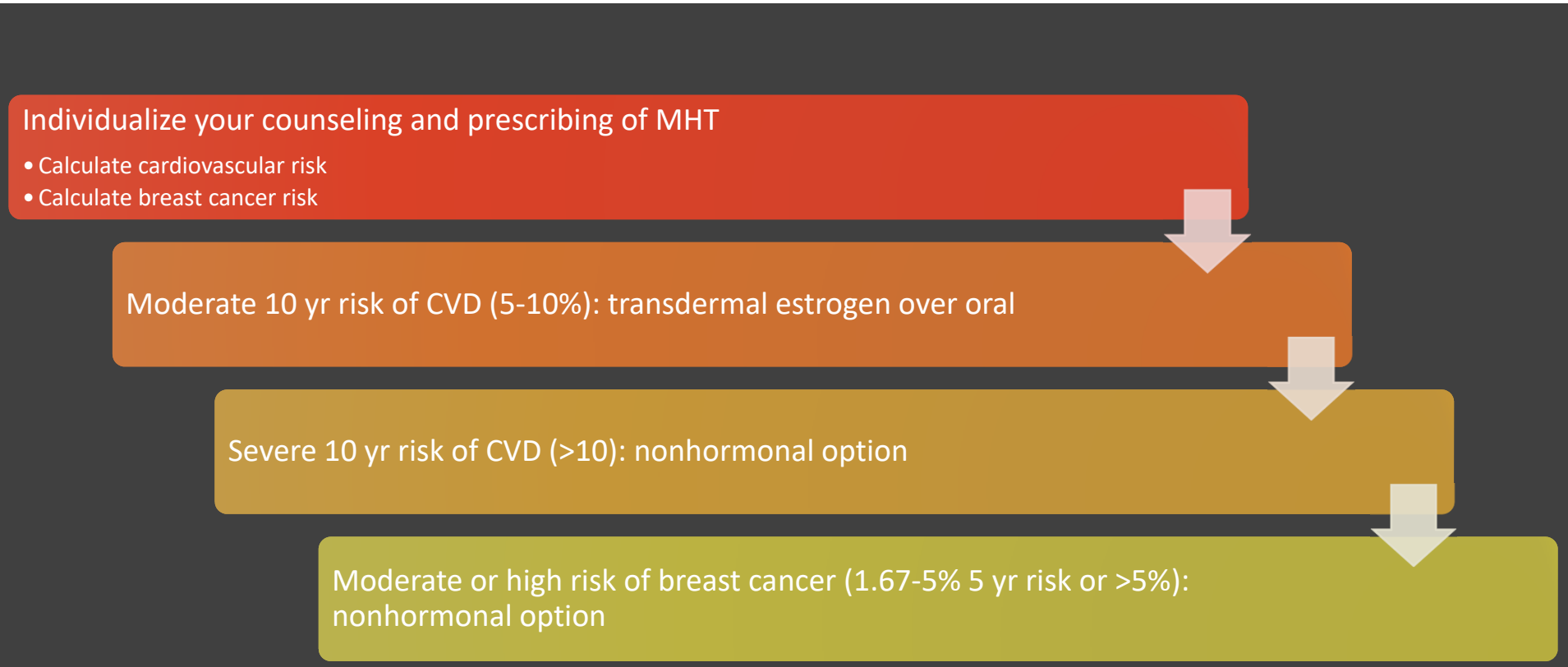
ACOG Review:

- Some evidence for treatment with testosterone for hypoactive sexual desire disorder but **NOT for depression, cognitive changes, muscle mass/strength**
- Eval for contraindications: liver disease, hyperlipidemia, hormone-responsive cancer
- Long-term safety not established
- Supraphysiologic levels can lead to androgenic side effects, although rare when maintained in premenopausal range.

1/10th of FDA approved male T gel (3.5mg/day)

Discontinuation of HT

Women may develop VMS when ET/EPT is abruptly discontinued	• Up to 55% will have some recurrent VMS if abruptly stopped • Symptoms are generally mild and will resolve over 2-3 months
Current data suggest the rates of VMS recurrence are similar when ET/HT is either tapered or abruptly discontinued	• Small trial (n=91), VMS symptoms worse in 1st three months with abrupt discontinuation and worse in tapering group at 6 months, no differences at 9-12 months • Second trial with rapid 2-week taper, no difference compared to abrupt cessation
Tapering dose over a few months is often done in clinical practice	• Reduce by one pill per week over six weeks • Slower taper for those with severe symptoms (6-12 months) • Switch to transdermal patches • Consider nonhormonal treatments as a tool for tapering


Individualize your counseling and prescribing of MHT
• Calculate cardiovascular risk
• Calculate breast cancer risk
Moderate 10 yr risk of CVD (5-10%): transdermal estrogen over oral
Severe 10 yr risk of CVD (>10): nonhormonal option
Moderate or high risk of breast cancer (1.67-5% 5 yr risk or >5%): nonhormonal option

In Practice

Questions?

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