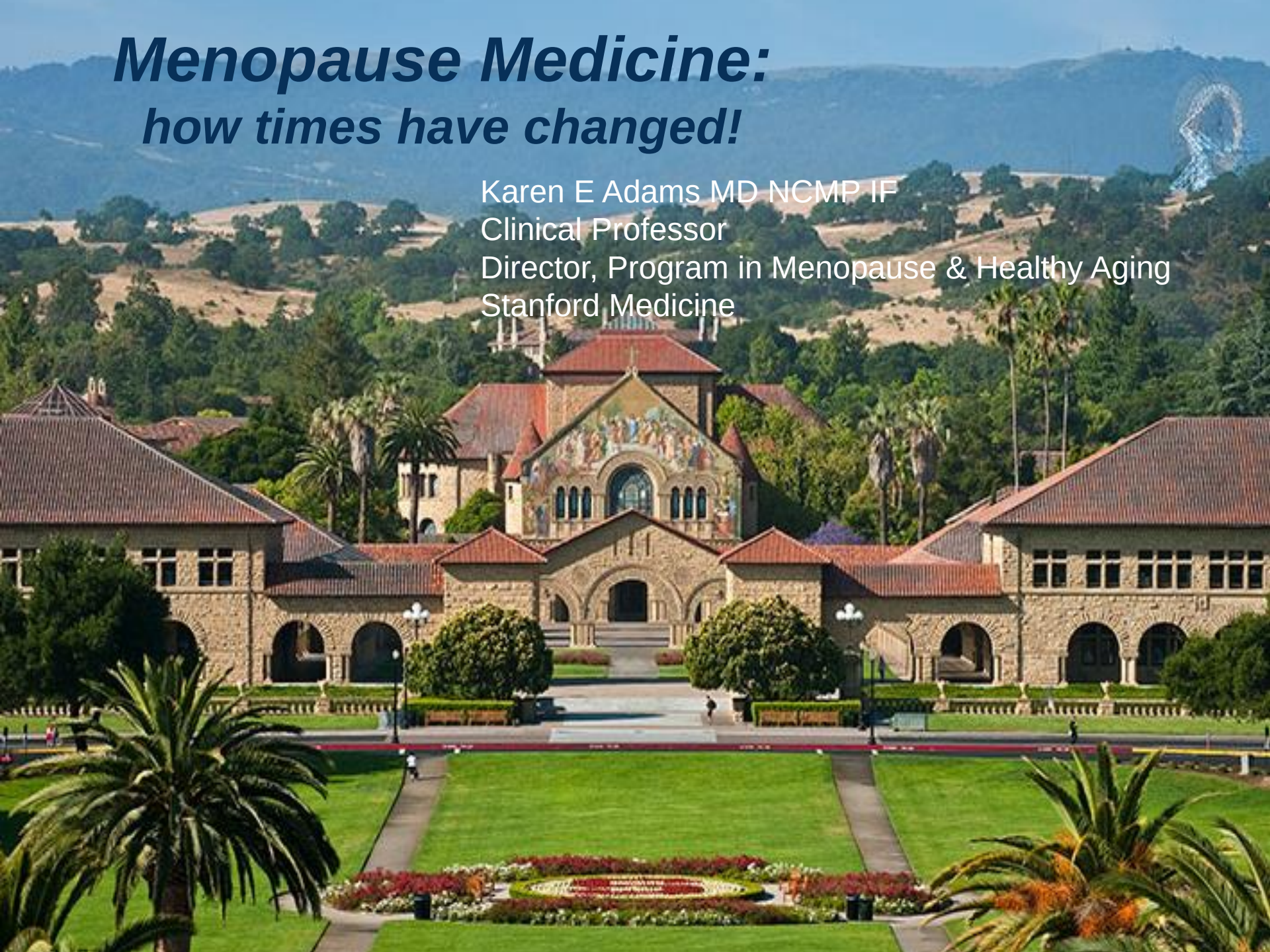
Menopause Medicine:
how times have changed!



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Disclosures/Conflicts

- Today I will discuss both on- and off-label uses of drugs
- No conflicts of interest
- Acknowledgements: North American Menopause Society (now The Menopause Society), ISSWSH, Jan Shifren MD
- When I use the terms “woman” and “female” I am referring to *people who have ovaries* and are experiencing the *cessation of ovarian function* either through normal aging or medical intervention

Objectives:

When this talk is complete you will:

- List the principal indications for systemic hormone therapy (HT)
- Know HT contraindications, risks, and benefits
- Understand how best to optimize and individualize HT options based on patient characteristics

RPH and CPT Question #1

1. What is the principal indication for systemic hormone therapy (HT)?
    a. Management of symptoms
    b. Prevention of heart disease
    c. Treatment of osteoporosis
    d. Prevention of dementia

RPH and CPT Question #2

2. Which of the following is NOT a contraindication to HT?
    a. BRCA1 or 2
    b. History of breast cancer
    c. History of stroke
    d. History of venousthromboembolic event

RPH-only Question #3

3. Which of the following factors should be considered when deciding to begin HT?

a. Patient's weight
b. Patient's age
c. Patient's family history of breast cancer
d. Patient's history of migraine headaches

New York Times January 2023

Women Have Been Misled About Menopause

Hot flashes, sleeplessness, pain during sex: For some of menopause's worst symptoms, there's an established treatment. Why aren't more women offered it?

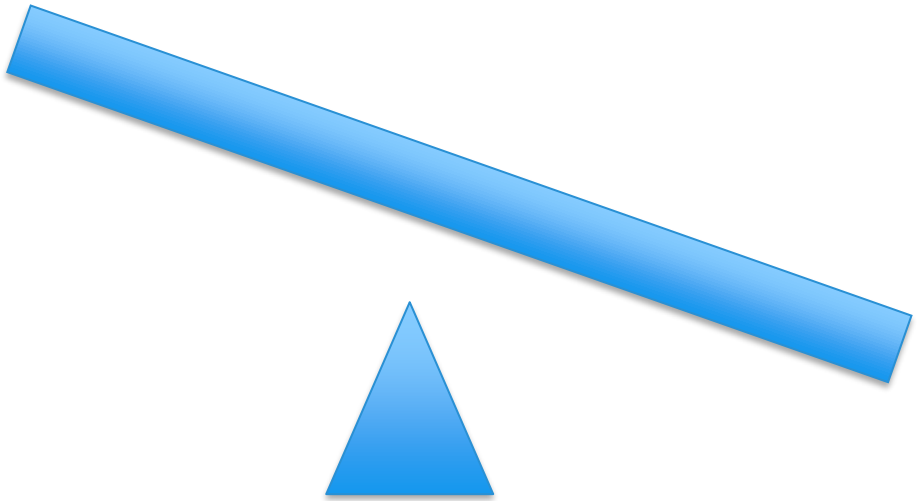
Resident Training in Menopause Management

- 100 US internal medicine residents:
  - 75%+ considered care of menopausal women to be **“very important”**
  - 50% reported a **low comfort level** managing menopausal symptoms
  - 75%+ reported **limited training** opportunities
  - 33%+ reported **no management of menopausal patients** in the past 6 months

Hsieh E et al, J Women’s Health 2013;22:667-72

Balancing Benefits and Risks

The WHI was ***not*** designed to address the **benefits** of hormones for symptomatic women



The WHI is the ***best*** medical evidence we have to date concerning the **risks** of hormone therapy

Individualizing:

- Risks differ for different women depending on
  - Dose
  - Duration
  - Route of administration
  - Timing of initiation
  - Progestin or not?

- Periodic reevaluation

NOT…

Benefits of Hormone Therapy for **Symptoms**

Unequivocal

- Hot flashes and night sweats
- Vaginal dryness

Beneficial for most

- Poor sleep
- Adverse mood
- Joint pain

Conflicting/ Inadequate Data

- Sexual function
- Urinary incontinence
- “Brain fog”
- Changes in body composition
- Skin dryness/wrinkling

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

Essential to know: www.menopause.org

Menopause: The Journal of The North American Menopause Society
Vol. 29, No. 7, pp. 767-794
DOI: 10.1097/GME.0000000000002028

NAMS Position Statement

The 2022 hormone therapy position statement of The North American Menopause Society

Abstract

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" (NAMS) updates "The 2017 Hormone Therapy Position Statement of The North American Menopause Society" and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2017 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Advisory Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. The risks of hormone therapy differ depend-

How We're Going to Think About This Today:

CASES then POSITION STATEMENT

Doris

- 54 yo special ed teacher
- LMP 2 y ago
- Frequent hot flushes and night sweats, poor sleep, fatigue, irritability
- No improvement w black cohosh, soy, yoga, meditation
- Med Hx: hypothyroidism, fibrocystic breasts
- Meds: levothyroxine, Calcium, Vit D

Considerations:

- What are principal indications for systemic hormone therapy (HT)?
- What are HT contraindications, risks, and benefits?
- How best to optimize and individualize HT options?

HT is FDA-approved for **FOUR INDICATIONS**:

- Hot flashes/night sweats
- Genitourinary syndrome of menopause (GSM)
- Premature menopause (surgical/medical/spontaneous)
- Prevention of bone loss and fracture in high risk women

Vasomotor Symptoms

Natural History of Hot Flashes

Transition Stage	% affected*	Age
Premenopause	20-45%	<45
Pre- to-Early Perimenopause	25-55%	45-47
Early-to-Late Perimenopause	50-80%	47-49
Late Peri-to-Postmenopause	35-75%	49-55
Late Postmenopause (>5yr)	16-44%	56+

Barnabei V et al. Obstet Gynecol 2002; 100:1209-18
Gold EB, et al, Am J Pub Health 2006; 96:1226-35
Politi MC, et al. J Gen Intern Med 2008;23:1507–13.

Natural History of Vasomotor Symptoms

- 30-50% of women note spontaneous improvement in 4-5 years
- 85-90% experience resolution within 7-10 years
- Super Flushers: 10-15% of women will continue to have symptoms many years after menopause

Epidemiology of Severe VMS in US women

	Percent affected	Duration in years
Black	46%	10.1
Hispanic	35%	8.9
Caucasian	31%	6.5
Chinese	21%	5.4
Japanese	18%	4.8

Gold EB et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Pub Health* 2006;96(7):1226-35

Other racial disparities in menopause care

- Endometrial stripe thickness is not predictive of endometrial hyperplasia in Black women
- Greater prevalence of fibroids and non-endometrioid histology
- 4 mm stripe cutoff has 47% sensitivity in Black women compared to 88% sensitivity in white women

Doll K et al. US for evaluation of postmenopausal bleeding in a simulated cohort of black and white women in the US. *JAMA Onc* 2021;7(8):1158-1165.

Impact of VMS

- Sleep disruption
- Mood disruption
- Cognitive function
- Social isolation
- Loss of work productivity
- Increased health care costs and utilization
- Future chronic dz risk:
  - CV disease
  - bone health
  - dementia

NAMS Position Statement

- Vasomotor symptoms (VMS) impact quality of life as well as cardiovascular, bone, and brain health

- HT is the gold standard for relief of VMS
  - ET
  - E+PT
  - PT (best alternative to estrogen)

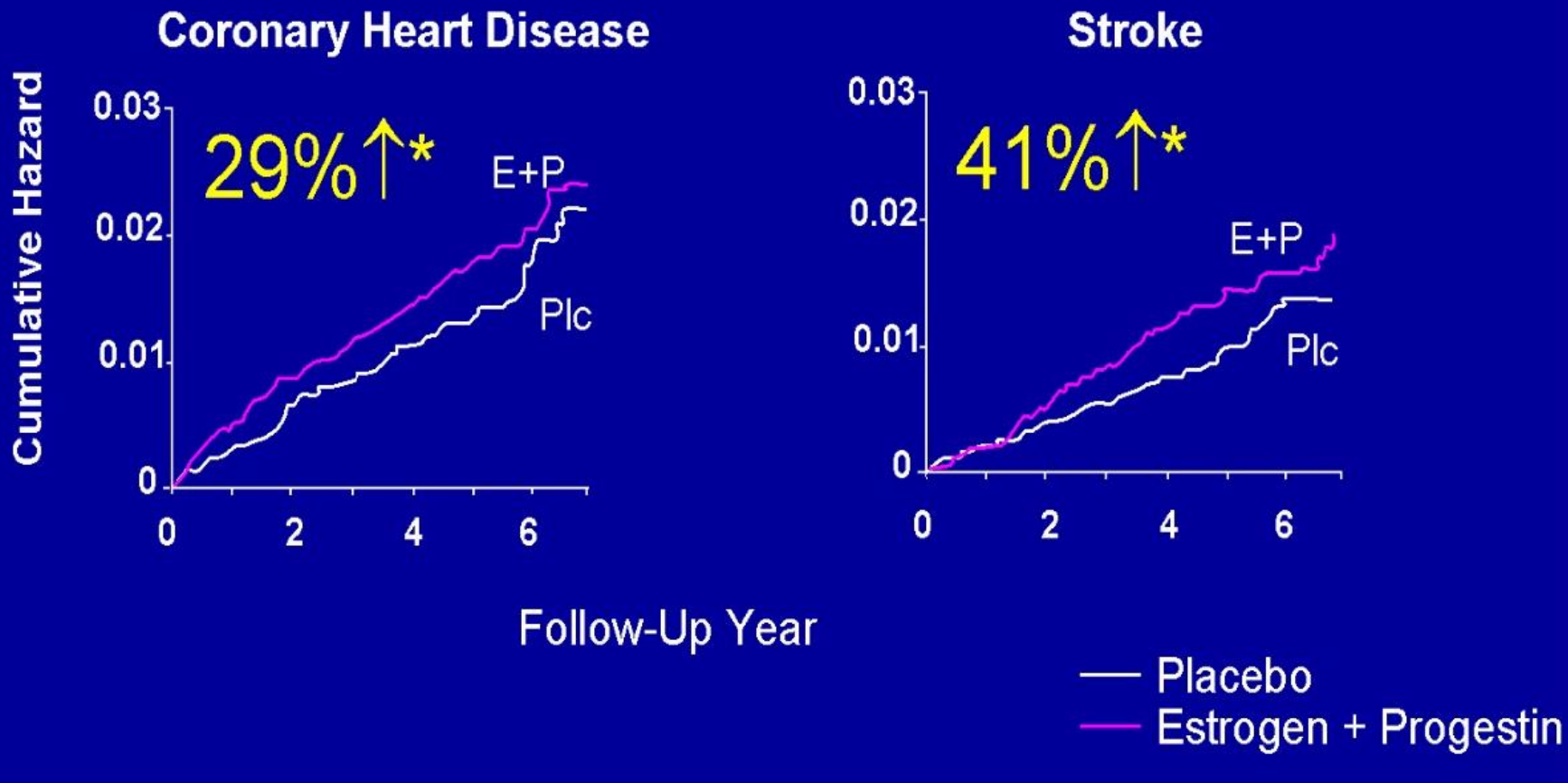
- Use the **lowest dose that gives relief** and periodically reevaluate

It’s not just symptoms, it’s long term health too!


WOMEN'S
HEALTH
INITIATIVE

WHI HRT Study

Kaplan-Meier Estimates of Cumulative Hazards for CHD and Stroke

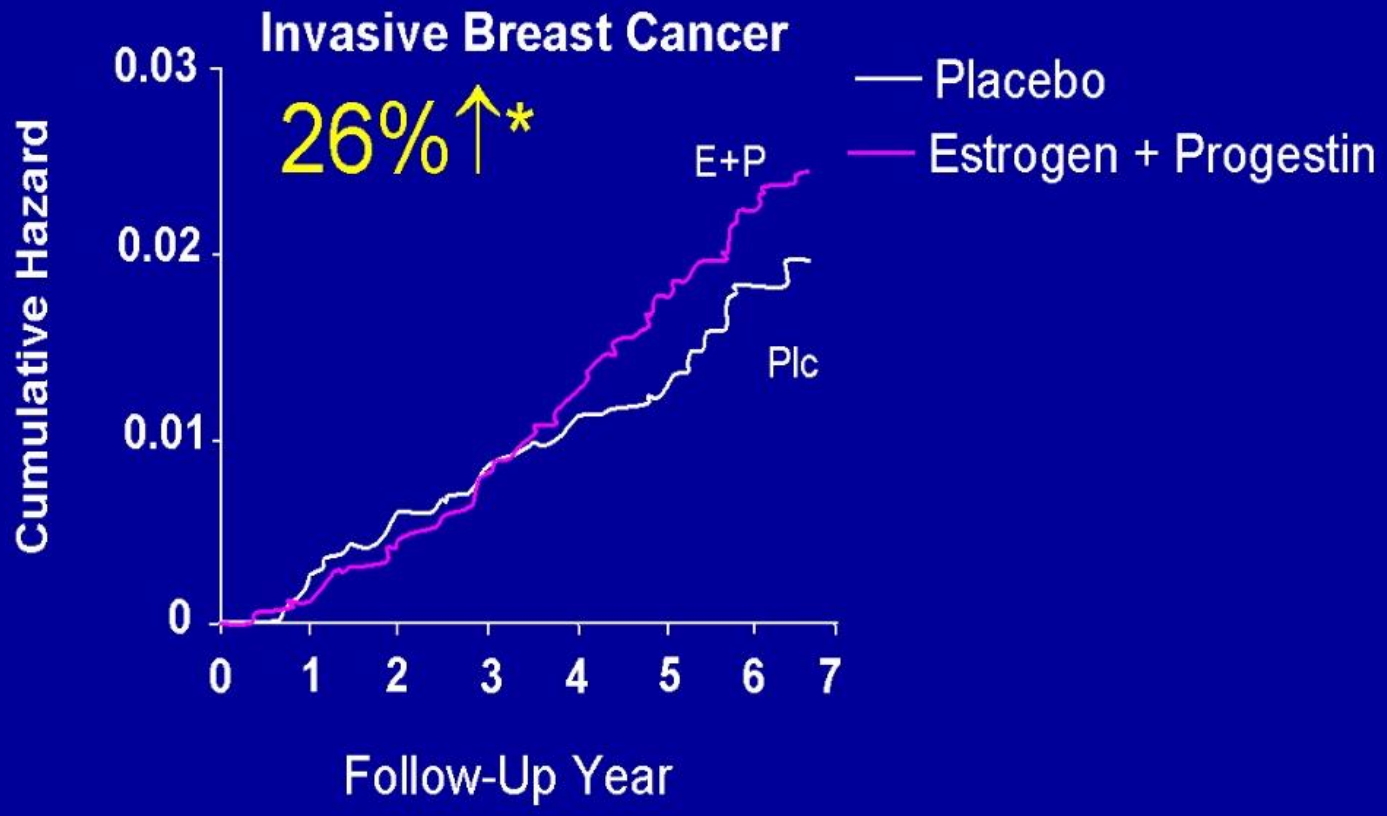


Adapted from: Writing Group for the Women's Health Initiative. *JAMA*. 2002;288:321-333.

*Statistically significant based on 95% nominal CI on Hazard Ratios

WHI HRT Study

Kaplan-Meier Estimates of Cumulative Hazards for Invasive Breast Cancer



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

*95% nominal CI Hazard Ratio = 1.26 (1.00-1.59)

WHI Results

Absolute and Relative Risk or Benefit of combined E/P HT

Health Event	*Relative Risk vs Placebo at 5.2 Years*	*Increased Absolute Risk per 10,000 Women/Yr*	*Increased Absolute Benefit per 10,000 Women/Yr*
Heart attacks	1.29	7	
Strokes	1.41	8	
Breast cancer	1.26	8	
VTEs	2.11	18	
Colorectal cancer	0.63		6
Hip fractures	0.66		5

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.

Absolute Risks and Benefits per 10,000 Women after 5 years

EVENT	E + P	E alone
Heart attack	+7	-3
Stroke	+8	+12
Blood clot	+18	+8
Breast cancer	+8	-6
Hip fracture	-5	-6
Colon cancer	-6	+1

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33

Absolute Excess Risks (cases per 10,000 person/years) by Age and Years Since Menopause in Combined WHI Trials (E+P and E-Alone)

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

* P=0.03 compared with age 50-59 years or <10 years since menopause

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

Roussouw JE, et al. *JAMA* 2007;297:1465

WHI 18+ years later…

CEE + MPA 5.6 years CEE alone 7 years

- NO INCREASE in overall cancer deaths (including breast cancer)
- NO INCREASE in deaths from CV disease
- Statistically significant reduction of all-cause mortality when started at 50-59 years

Manson J *JAMA* Sept 12 2017

Absolute Contraindications to HT

- CV Disease
  - Heart disease
  - Stroke
  - Venous thromboembolic events (DVT and PE)
- Breast Cancer
- Endometrial Cancer (+/- stage)
- Undiagnosed vaginal bleeding

Relative Contraindications to HT

- Risk factors for absolute contraindications

Always a discussion of risk/benefit balance

Patient Factors that Modify CV Risks of HT

- Age *(50-59 vs > 60 years)*
- Years since menopause onset *(<10 vs > 10 years)*
- Lipid status *(LDL <130 vs >130 mg/dl)*
- Metabolic syndrome *(no vs yes)*
- Underlying CHD risk *(low vs high)*

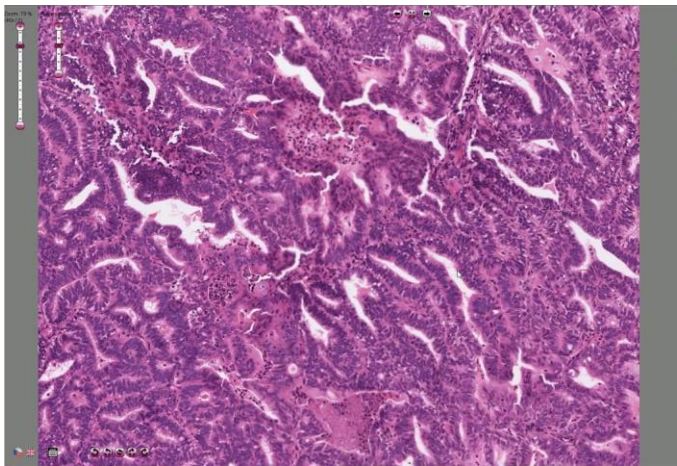
Manson JE *NEJM* 2003, Hsia J *Arch Int Med* 2006, Bray PF, *Am J Cardiol* 2008, Rossouw J, *Circ* 2012, Wild RA *Menopause* 2013

What is “bioidentical” HT?

- Chemical structure identical to reproductive age hormones
- Estradiol, estrone, estriol, testosterone, progesterone
- Plant-based products

Bioidentical ≠ Compounded

- 34% of compounded HT failed FDA quality tests
- Sold without FDA-mandated information re: indications/risks
- Purity, bioavailability, dose-to-dose consistency questionable
- Transdermal P cream ineffective for endometrial protection, inc risk for cancer



Pinkerton J *OBG Mgmt* 2009, Wren B *Menopause* 2003.

Oral vs. transdermal estrogen therapy and thromboembolic complications

Study Publication	Oral Estrogen	Transdermal Estrogen
	Odds Ratios (95% Confidence Intervals)	
Scarabin, et al. Lancet, 2003, 362(9382): p. 428-32.	3.5 (1.8-6.8)	0.9 (0.5-1.6)
Canonico, et al. Circulation, 2007,115: 840-845	4.2 (1.5-11.6)	0.9 (0.4-2.1)

Does the Progestin Matter?

- **Micronized oral progesterone** *(Prometrium)*
  - "bioidentical"
  - Favorable effect on HDL-C (PEPI trial)
  - FDA-approved product available
  - Possible lower VTE and breast ca risk
  - New combination oral HT product available
    - Bijuva 0.5 E2/100 P or 1.0 E2/100 P
- **Reducing progestin exposure**
  - "long cyclic" regimens
  - LNG-containing IUD

Doris

- She is fully menopausal and incredibly symptomatic
- Age 54, no contraindications to HT
- Estradiol 0.05 mg/day patch
  -PLUS-
- Prometrium 100 mg at night or LNG IUD
- Could try a Combipatch
- Give her sleep hygiene recs
  - Get up at same time each day
  - Go to bed only when sleepy
  - No naps
- See her back in 6-8 weeks

Duration?

- Reevaluate risk/benefit balance yearly
- Absolute risks that increase with age
  - CHD
  - Stroke
  - VTE
  - PE
  - Breast cancer
- No recommendation to automatically stop at age 65

Doris

- What if Doris had a hx of VTE?

Treatment of Vasomotor Symptoms—Estrogen Alternatives

- Most effective alternatives are progestins (off-label when used alone)
- Hot flash frequency and severity reduced by 80-90%
  - Micronized P (Prometrium) 300 mg nightly
  - MPA (Provera) 10-30 mg

Doris

- What if Doris had breast cancer?


BREAKING
LIVE
NEWS

May 2023

www.menopause.org

NAMS Position Statement

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

Abstract

Objective: To update the evidence-based Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society.

Methods: An advisory panel of clinicians and research experts in women's health were selected to review and evaluate the literature published since the Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society. Topics were divided into five sections for ease of review: lifestyle; mind-body techniques; prescription therapies; dietary supplements; and acupuncture, other treatments, and technologies. The panel assessed the most current and available literature to determine whether to recommend or not recommend use based on these levels of evidence: Level I, good and consistent scientific evidence; Level II, limited or inconsistent scientific evidence, and Level III, consensus and expert opinion.

Results: Evidence-based review of the literature resulted in several nonhormone options for the treatment of vasomotor symptoms. **Recommended**: Cognitive-behavioral therapy, clinical hypnosis, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, fezolinetant (Level I); oxybutynin (Levels I-II); weight loss, stellate ganglion block (Levels II-III). **Not recommended**: Paced respiration (Level I); supplements/herbal remedies (Levels I-II); cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation, suvorexant, soy foods and soy extracts, soy metabolite equol, cannabinoids, acupuncture, calibration of neural oscillations (Level II); chiropractic interventions, clonidine; (Levels I-III); dietary modification and pregabalin (Level III).

Conclusion: Hormone therapy remains the most effective treatment for vasomotor symptoms and should be consid-

Non hormonal Rx options

- SSRIs (paroxetine 7.5 mg daily FDA-approved)
- SNRIs
  - Effect is rapid, generally in 2 weeks

- Gabapentin
- Oxybutinin/clonidine

Suggested dosing ranges for nonhormonal prescription therapies SSRIs, SNRIs, Gabapentin

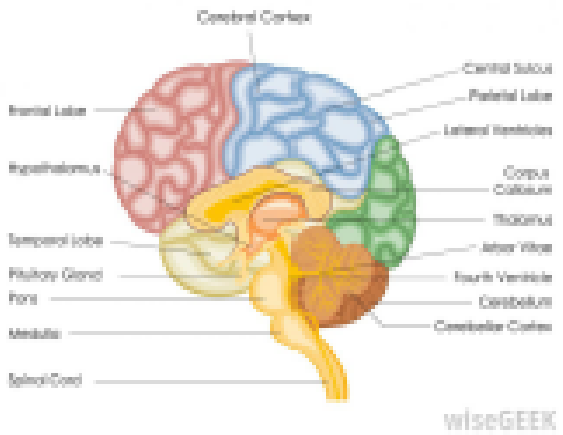
SSRIs		
Paroxetine salt	7.5 mg	Single dose, no titration needed
Paroxetine	10-25 mg/d	Start with 10 mg/d
Citalopram	10-20 mg/d	Start with 10 mg/d
Escitalopram	10-20 mg/d	Start with 10 mg/d (for sensitive or older women, start with 5 mg/d for titration, but this dose has not been evaluated for efficacy)
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	900-2,400 mg/d	Start with 100-300 mg at night, then add 300 mg at night, then a separate dose of 300 mg in the morning (start 100 mg if concerned about sensitivity)

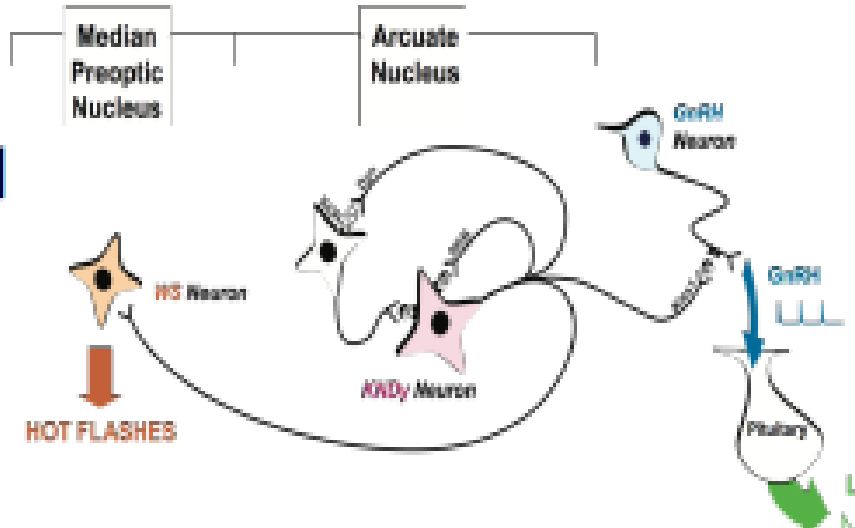
SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.


MORE!!!
BREAKING
LIVE
NEWS

KNDY NEURONS SECRETE NEUROPEPTIDES

- Kisspeptin: G-protein coupled receptor ligand neuropeptide (gene kiss1)
- Neurokinin B: endogenous peptide ligand that belongs to the family of tachykinin peptides (gene TAC) highest affinity NK3R
- Dynorphin: kappa opiod
- KNDy neurons are co-localized with > 95% of ER, PR, AR in arcuate nucleus





VEOZAH (fezolinetant) FDA-approved May 2023

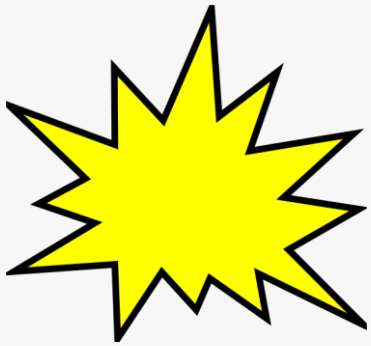
- Blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin/dynorphin (KNDy) neuron
- Modulates neuronal activity in the thermoregulatory center of the hypothalamus
- Efficacy comparable to estradiol
- Daily 45 mg dose
- Contraindications
  - ESRD
  - Active liver dz (check LFTs at baseline, 3, 6, 9 mo)
  - CPY1A2 inhibitors (fluvoxamine, mexiletine, cimetidine)
- Upcoming trials: Phase IV

What about herbs/botanicals?

- Not more effective than placebo:
  - Soy
  - Red clover
  - Dong quai
  - Women's botanical formulas
  - Evening primrose oil

Lifestyle/behavioral interventions

- **YES** (reduces frequency, severity, or bother of VMS)
  - Cognitive behavioral therapy
  - Clinical hypnosis
  - Weight loss
  - Stellate ganglion block
- **NO** (no benefit compared to no treatment)
  - Paced respiration
  - Cooling techniques
  - Avoiding triggers
  - Exercise/yoga
  - Mindfulness training
  - Relaxation
  - Cannabinoids
  - Acupuncture
  - Chiropractic
  - Dietary manipulation or supplements



Vasomotor Symptoms Summary

- 80% of people experience these, SIGNIFICANT impact on QOL, well being, long term health
- Lifestyle changes of limited benefit
- Systemic estrogen is most effective treatment
- Progestin best alternative to estrogen (off label)
- Fezolinetant new option in 2023!
- SSRI/SNRIs, gabapentin effective
- Herbs and botanicals not effective

"lowest effective/most appropriate dose": *typically start with 0.05 mg patch (abdomen) + prometrium 100 mg at night (LNG-IUD option)*

- Treats vasomotor symptoms
  - 30 pg/mL
- Promotes bone health
  - 40 pg/mL
- Cardioprotection
  - 50-80 pg/mL
- POI patients
  - 80-120 pg/mL (may need 2 patches)
  - Goal is to prevent LT effects of premature estrogen deprivation, control symptoms, improve quality of life
- Serum assays are an **advantage** of estradiol over conjugated estrogens or ethinyl estradiol

When to follow estradiol levels?

- NOT routinely
- For a particular therapeutic goal
  - In general, shoot for 40-80 pg/mL
- If patient is not responding clinically
- Progesterone levels not clinically relevant
- *Draw day prior to patch change*
- *Stop biotin-containing vitamins 48 hrs prior*

Barbara

- 40 yo fitness coach
- BRCA1+
- Planning RRBSO

NAMS Position Statement: Family history of breast cancer

- HT does not further increase risk of breast cancer in high-risk women (observational evidence)
  - family history of breast cancer
  - after bilateral salpingo-oophorectomy (BSO) for BRCA 1 or 2

- BRCA+ women who have undergone RRSO can be given HT until at least the age of menopause

- Risk of br ca w HT greater with sedentary lifestyle, alcohol intake, or obesity than estrogen

Barbara

- 0.05 mg patch + LNG IUD or Prometrium 100 mg

- Query re: sexual dysfunction
- Local estradiol if needed

RPH and CPT Question #1

1. What is the principal indication for systemic hormone therapy (HT)?
    a. Management of symptoms
    b. Prevention of heart disease
    c. Treatment of osteoporosis
    d. Prevention of dementia

RPH and CPT Question #1

1. What is the principal indication for systemic hormone therapy (HT)?
    a. **Management of symptoms**
    b. Prevention of heart disease
    c. Treatment of osteoporosis
    d. Prevention of dementia

RPH and CPT Question #2

2. Which of the following is NOT a contraindication to HT?
    a. BRCA1 or 2
    b. History of breast cancer
    c. History of stroke
    d. History of venousthromboembolic event

RPH and CPT Question #2

2. Which of the following is NOT a contraindication to HT?

a. **BRCA1 or 2**
b. History of breast cancer
c. History of stroke
d. History of venousthromboembolic event

RPH-only Question #3

3. Which of the following factors should be considered when deciding to begin HT?

a. Patient's weight
b. Patient's age
c. Patient's family history of breast cancer
d. Patient's history of migraine headaches

RPH-only Question #3

3. Which of the following factors should be considered when deciding to begin HT?

a. Patient's weight
b. **Patient's age**
c. Patient's family history of breast cancer
d. Patient's history of migraine headaches

Wrap Up:

- HT is still first line treatment for bothersome VMS
- Transdermal E and micronized P are preferred
- Use most appropriate dose for most appropriate time, w periodic reevaluation
- Patients <10 y out from menopause are best candidates for HT
- Women w/o a uterus have more favorable risk profile
- Good non hormonal options now available for those with contraindications
- Be aware of (treatable) high levels of sexual dysfunction in patients with early menopause

Questions?

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THANK YOU