2024 Virginia ACP Annual Scientific Meeting
9-27-2024

UVA Health
University Medical Center

Menopause Management: Where Are We Now and Where Are We Going?

JoAnn V. Pinkerton, MD, FACOG, MSCP

Mamie Jessup Professor of Obstetrics and Gynecology

University of Virginia Health

Executive Director Emeritus and Past President, The Menopause Society (formally NAMS)

Disclosures

During this lecture Dr. JoAnn Pinkerton may mention the use of medications for both U.S. Food and Drug Administration (FDA)-approved and non-FDA-approved indications.

Grant Research support: Bayer Oasis 2 Phase 3 Clinical Trial;- Fees to UVA
Consultant- Bayer and Pfizer
Consultant: UpToDate and Merck
Editorial Boards: Menopause, Climacteric, J Women's Health, Contemporary ObGyn

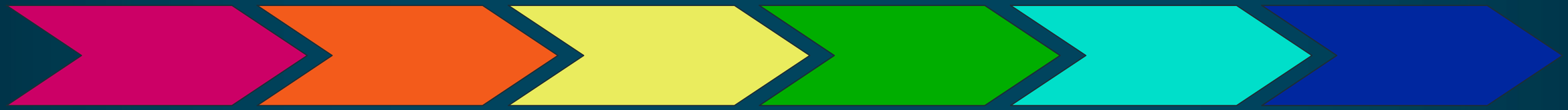
VMS Learning Objectives

- Assess pathophysiological mechanisms that result in VMS due to menopause
- Understand impact of Menopause and VMS on health, work, relationships, and QOL
- Evaluate treatment options for patients with VMS due to menopause – hormonal and nonhormonal
- Review strategies for effective communications on issues and challenges associated with VMS due to menopause

What is the Menopause ?

20s 30s 40s 50s 60s 70s 80s+

Reproductive Menopause transition *Postmenopause*



Menopause

The final menstrual period—diagnosed retrospectively after 12 months amenorrhea

Cynthia Stuenkel CEU 2024

Stuenkel CA; Harlow SD, et al. *Menopause* 2012;19:387-95.

Rowanda Case Study- in her late 40's

- c/o amenorrhea, hot flashes, fatigue, irritability, frequent and severe hot flashes day and night, and weight gain
  - Hot flashes occur 6-8 times per day, moderate to severe intensity
  - Last menstrual period was 6 months ago
- Disrupted Sleep- 3-4 times per night- sometimes just 'covers on and off', sometimes soaking sweats
- Mood swings and irritability that affect her partner, work, and family
- Prior trials: black cohosh, ashwagandha, soy supplements, and magnesium
- She is miserable and comes to you for help
- Her sister had breast cancer at age 60 and she does not want hormone therapy

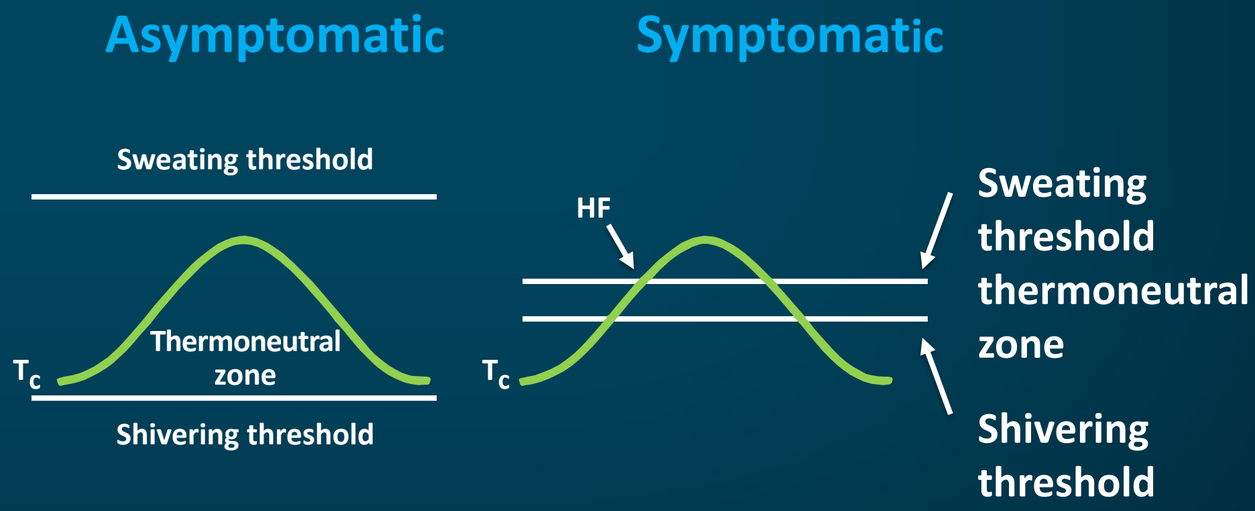
Menopause and Vasomotor Symptoms

- Menopause- defined as 12 months of amenorrhea, due to loss of ovarian follicular activity, median age of 51.3 years in the US.
  - Determined retrospectively
  - Preceded by the menopause transition which on average lasts 4 years
- Nearly 80% of women worldwide suffer from vasomotor symptoms (VMS), ranging in severity and affecting quality of life and overall health; 25% may require treatment
- VMS persist median duration of 7 years; associated with significant comorbidities such as cardiovascular disease, osteoporosis, and cognitive complaints.
- Women who experience VMS during perimenopause may continue to have symptoms for much longer, with a median duration of almost 12 years.
- Race, ethnicity, comorbidities, lifestyle factors, and psychosocial factors affect menopause symptoms

Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. Int J Womens Health. 2023 Feb 14;15:273-287..
Richard-Davis G, Wellons M. Racial and ethnic differences in the physiology and clinical symptoms of menopause. Semin Reprod Med 2013☹31 (5):380-6

Physiologic Mechanisms of VMS

- VMS involve the vasodilation of cutaneous vessels with increased skin temperatures
  - Vasodilation and sweating occur as heat dissipation
- The mechanism is not completely understood; neurokinin receptors are involved
- Related to small fluctuations in core body temperature superimposed on an extremely narrow thermoneutral zone
- Triggered when core body temperature rises above upper (sweating) threshold
- Shivering occurs when core body temperature falls from elevated level to a level below the lower threshold of thermoneutral zonet



Freedman RR, Blacker CM. *Fertil Steril.* 2002;77:487-490. Freedman RR, Subramanian M. *Menopause.* 2005;12:156-159. Freedman RR. *Semin Reproductive Med.* 2005;32:117-125.

Symptoms of VMS

VMS are the most common and bothersome symptoms, hallmark symptoms of hot flashes and night sweats

Hot flashes are described as episodes of sudden intense sensation of heat, often starting in the upper chest area, that may last 1 to 5 minutes

- May be accompanied by chills, sweating, feelings of dread, or palpitations

Night sweats refer to hot flashes occurring in the night, often awakening a person from sleep

- May be just a sensation of warmth to soaking sweats

FDA definition of VMS

Mild: The sensation of heat without sweating

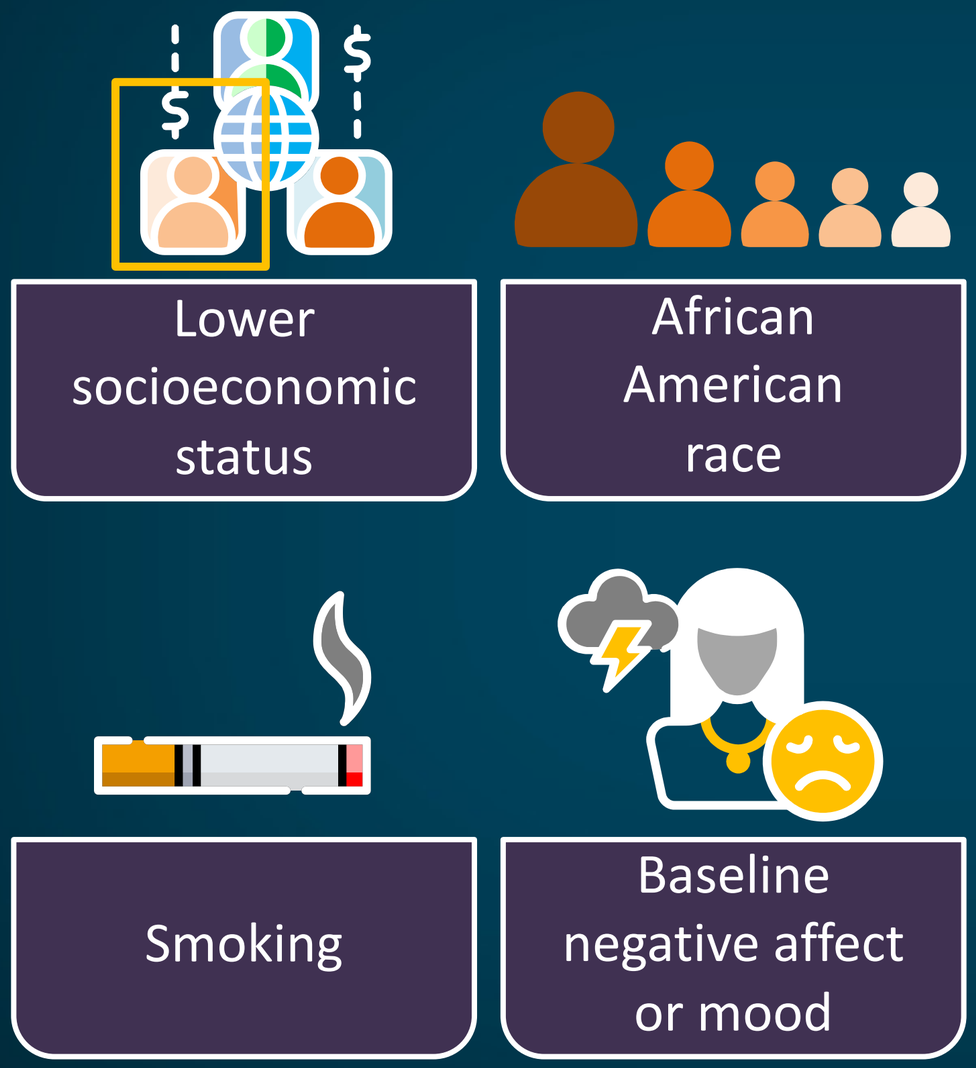
Moderate: The sensation of heat with sweating, able to continue activity

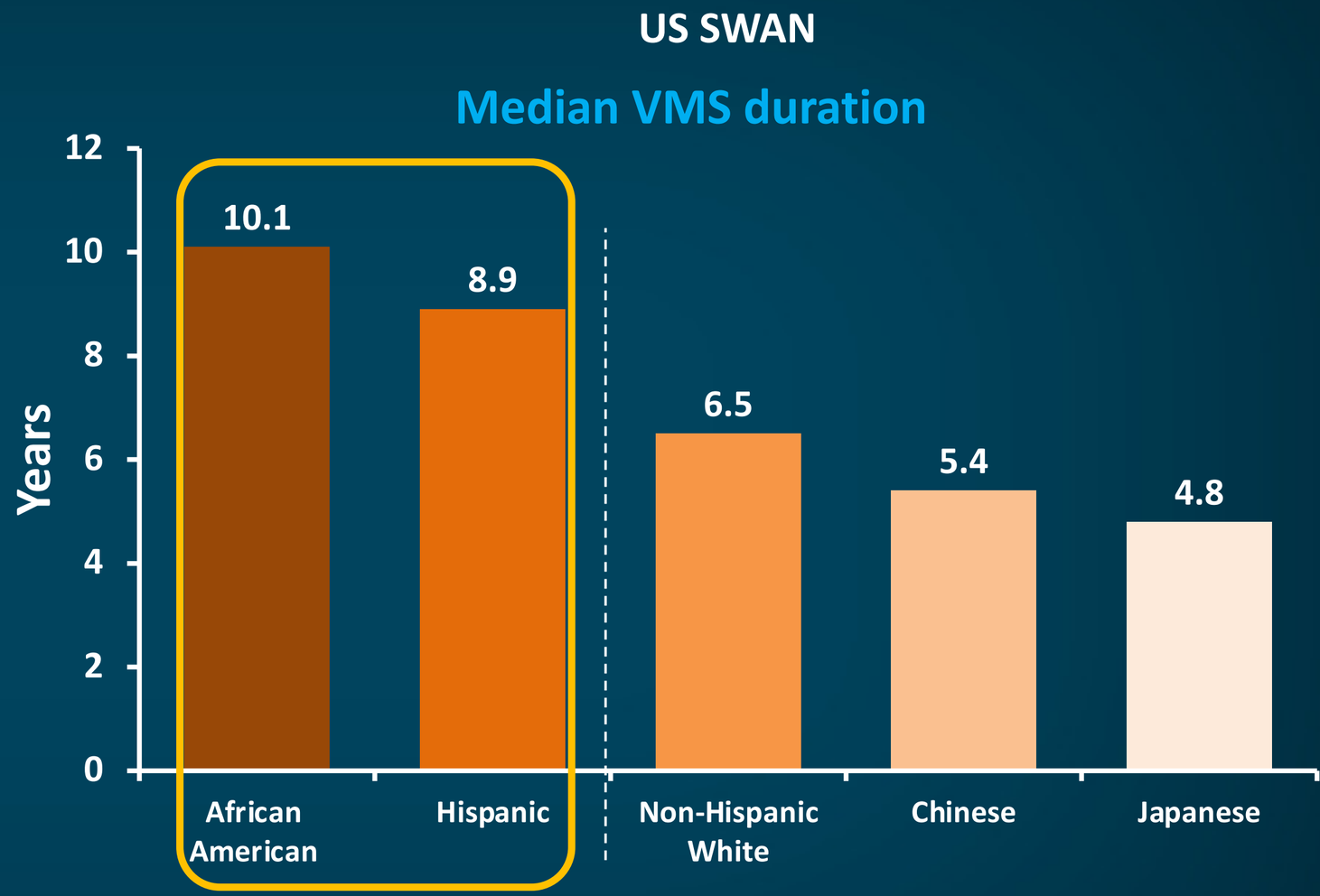
Severe: The sensation of heat with sweating, causing cessation of activity

FDA = US Food and Drug Administration; VMS = vasomotor symptoms.

FDA. Guidance for industry, 2003 (https://www.fda.gov/media/71359/download). Accessed 5/1/2024.

Risk Factors for Developing and Duration of VMS





African American and Hispanic women reported median VMS duration of 10.1 yrs and 8.9 yrs, respectively

Non-Hispanic white, Chinese, and Japanese women reported a median VMS duration of 6.5 yrs, 5.4 yrs, and 4.8 yrs, respectively

SWAN = Study of Women's Health Across the Nation; VMS = vasomotor symptoms.

Khan SJ, et al. *Int J Womens Health*. 2023;15:273-287.

Menopause and Sleep

- Women transitioning into menopause typically complain of
  - Poor sleep quality
  - Insufficient sleep
  - Nocturnal awakenings
  - Apnea
- Sleep deprivation is a known factor for
  - Cardiovascular disease
  - Diabetes
  - Obesity
  - Neurobehavioral dysfunction

Self-reported in 40% to 56% of women compared to premenopausal women

Gava G, et al. *Medicina*. 2019;55(10):688.

Negative Impacts of VMS

VMS can have a significantly negative impact on overall health and well-being

Women who experience frequent VMS (>6 days in the previous 2 weeks) also experience higher rates of anxiety, depression, difficulty sleeping, and overall impaired quality of life

- Almost 3 out of 4 postmenopausal women in a multinational survey suffered from fatigue, and 2 out of 3 had difficulty sleeping

Healthcare utilization and associated costs are higher for women with VMS

73%

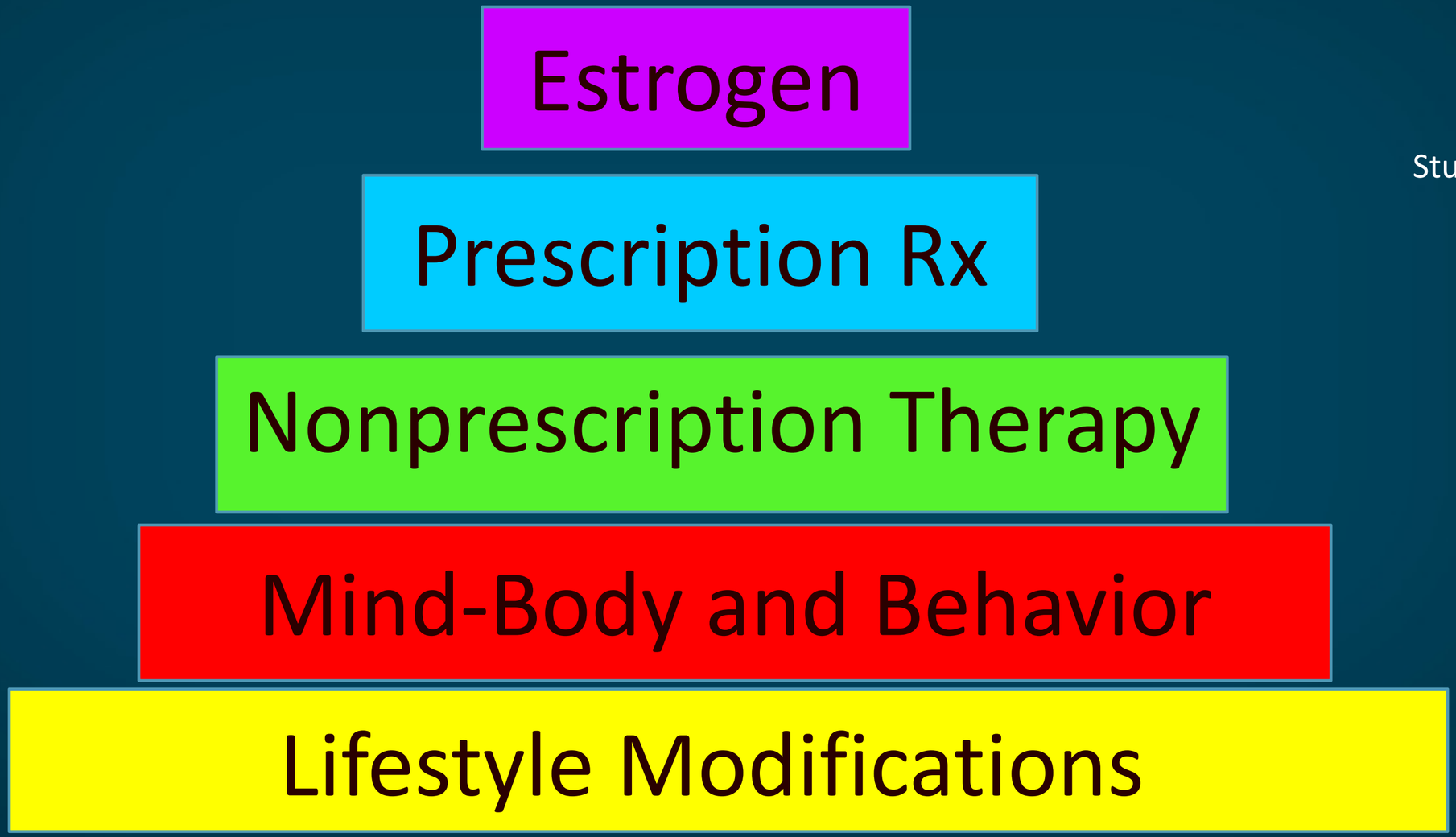
Despite these profound impacts, a survey of 1039 women ages 40 to 65 years across the US found 73% of women had not received treatment for their VMS

Not treated for VMS

VMS = vasomotor symptoms.

Khan SJ, et al. *Int J Womens Health*. 2023;15:273-287.

Treatments of Menopause-Associated Vasomotor Symptoms

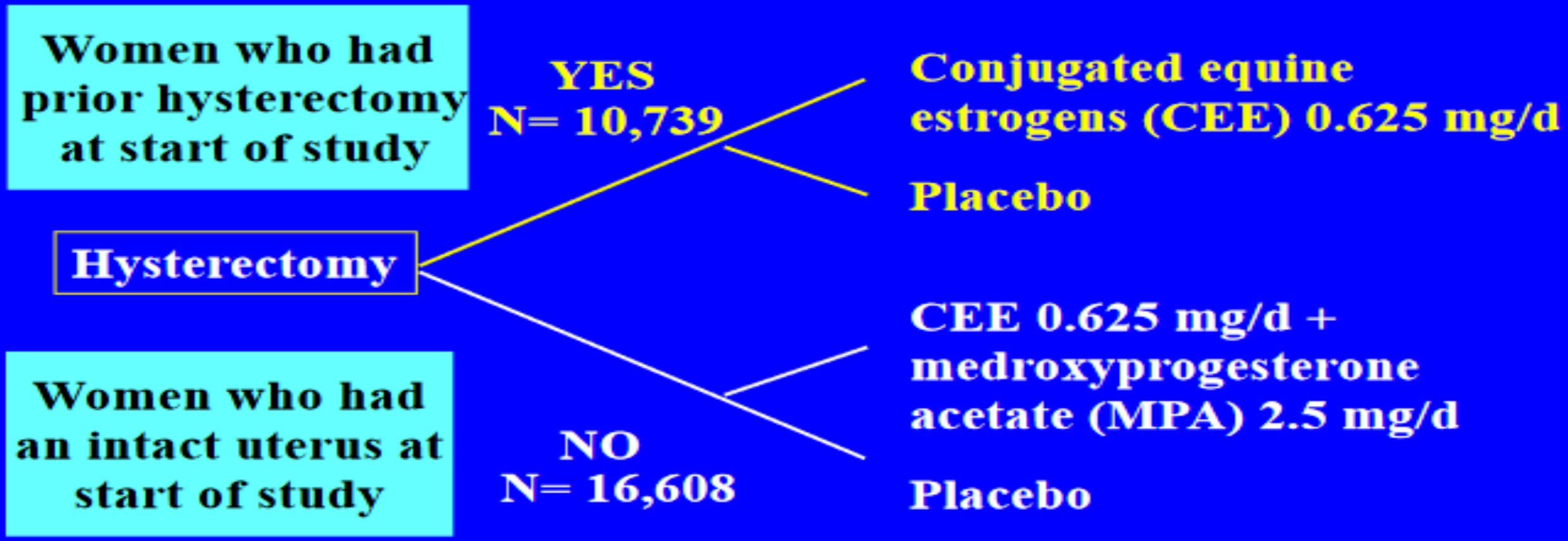


Stuenkel CEU 2024

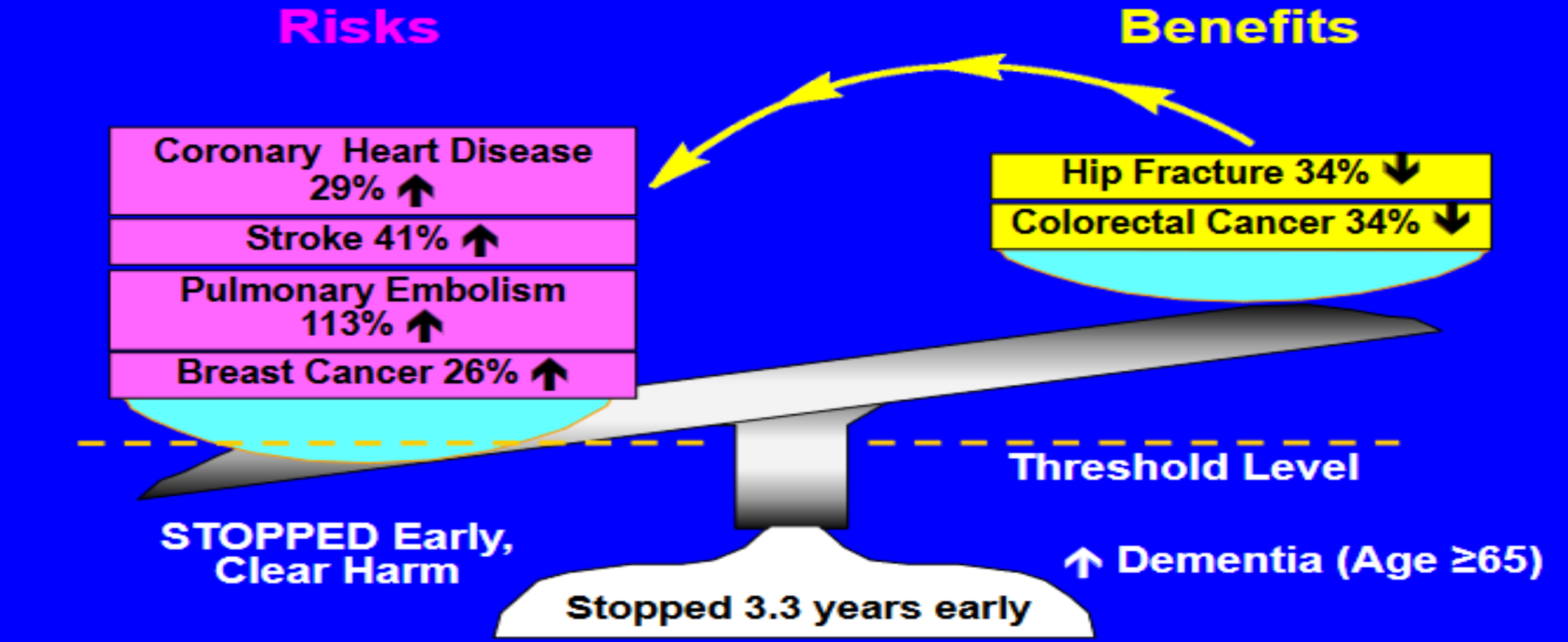
Stuenkel CA. *in Women & Health*, Elsevier, 2013; Stuenkel CA, et al, *JCEM* 2015; NAMS, *Menopause,* 2022 and 2023 .

Women's Health Initiative (WHI), Ages 50-79
Hormone Program Design

Average Age was 63

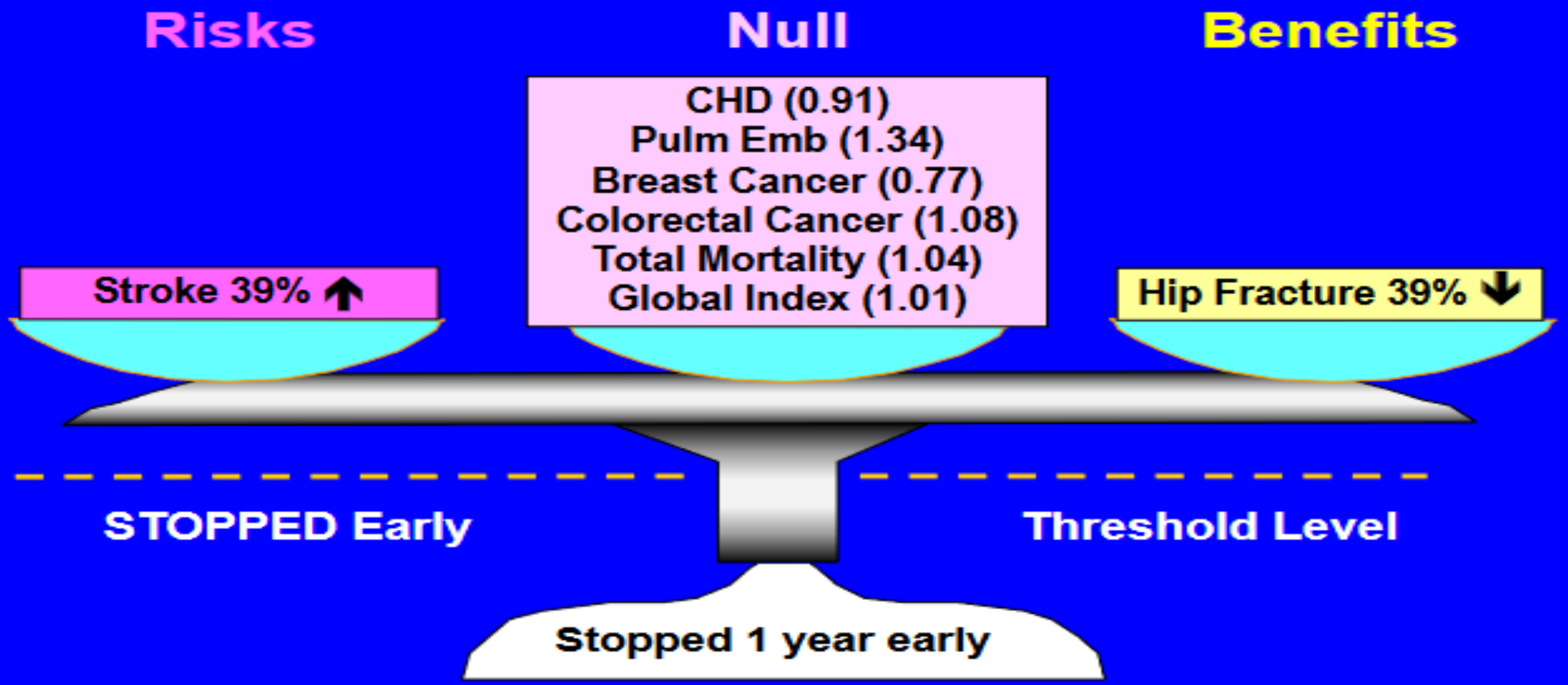


WHI Estrogen+Progestin Trial Findings, July 2002
(N=16,608; mean age 63 yrs; mean follow-up 5.2 yrs)



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

WHI Estrogen-Alone and Health Outcomes
(N=10,739; mean age 63.6 yrs; mean follow-up 6.8 yrs)



Adapted from data in: Anderson G, et al. *JAMA* 2004; 291:1701.

Women's Health Initiative study 2002

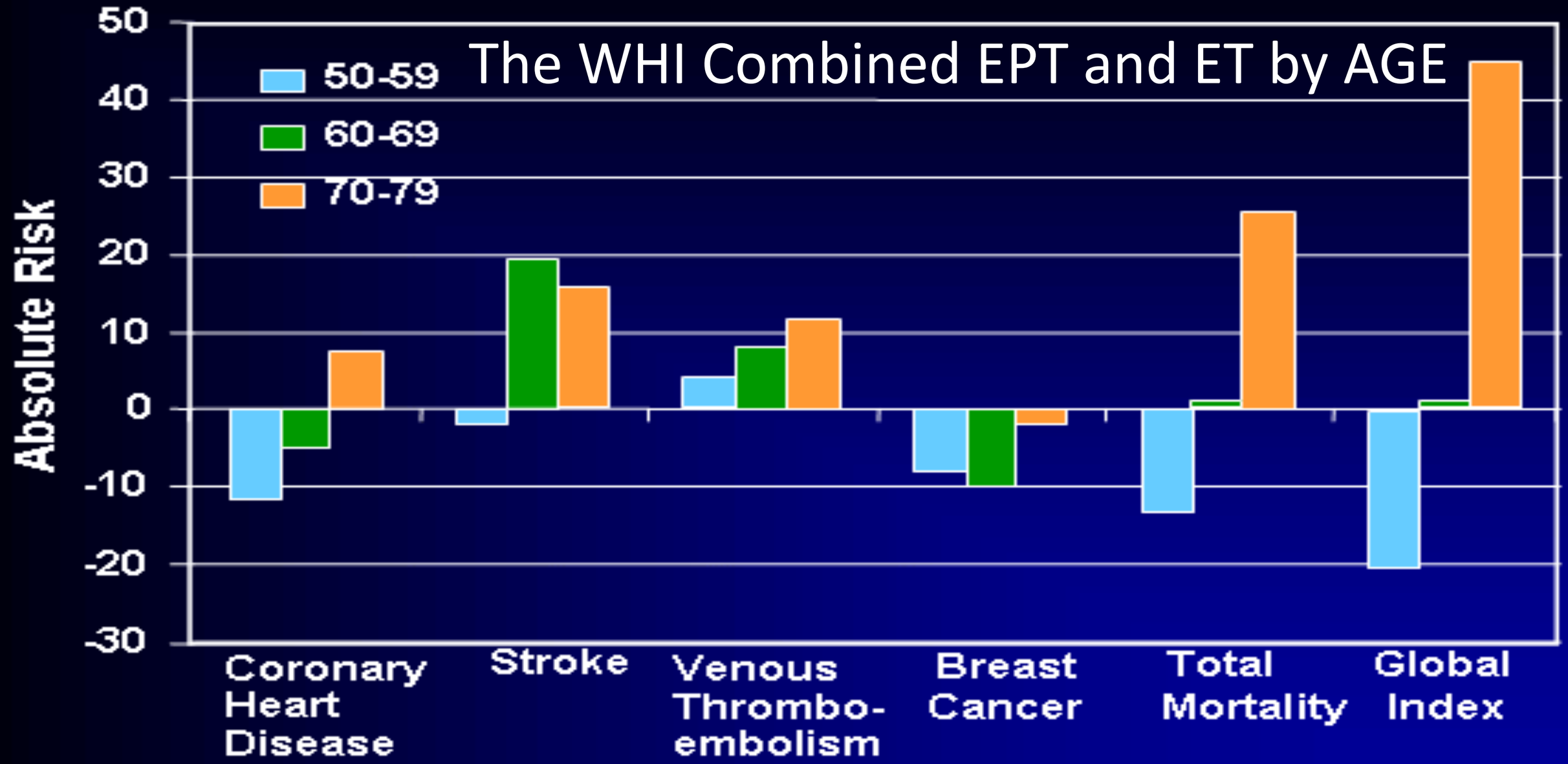
Breast cancer

Heart Disease
VTE and Stroke

Probable Dementia

<u>Fear continues driving the conversation about hormone therapy</u>

The WHI Combined EPT and ET by AGE



Writing Group for the Women's Health Initiative Investigators. *JAMA* 2004;291:1701-1712.
Rossouw et al. *JAMA* 2007;297:1465-1477.

HT and HEART (CHD): 'Timing Hypothesis'

- If initiated **early** in the menopausal transition, HT does not increase CHD risk
  - HT may reduce morbidity/mortality risk if initiated early
- **'Early':** Age 50-59 years, or < 10 years after menopause onset

The timing hypothesis-- initiation, not continuation, of hormone therapy…

- HT increases CHD risk if initiated later
  - If initiated >10 years after menopause, increase in (CHD) events
  - Findings congruent with human and non-human primate data
- Consider individual patient's risk for CVD, stroke, VTE when starting HT
- **HT not recommended for primary or secondary prevention of CVD-**

J Hsia, et al. Arch Int Med 2006
JE Rossouw et al. JAMA 2007
Manson JAMA 2013, 2017
JE Manson et al. N Eng J Med 2007
S Toh, et al. Annals Int Med 2010
USPSTF 2017
Stram DO, et al. Menopause 2011
HN Hodis, et al. Circulation 2014
MA Allison, JE Manson. Editorial. Menopause 2011
P Tuomikoski, et al. Obstet Gynecol 2014

USPSTF 201

Hormone Therapy and Premature Menopause/Primary Ovarian Insufficiency

- In women with BSO before the average age of menopause, early initiation of ET, with endometrial protection if the uterus is preserved, reduces:
  - VMS
  - Genitourinary symptoms
  - Risk for osteoporosis and related fractures
  - Likely CVD and overall mortality
  - Benefit in observational studies for CV mortality and cognition/ dementia

- **HT recommended until at least the median age of menopause (52 years)** Level II); higher doses may be needed for POI <40
- HT is not a contraceptive

The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794.

The Menopause Society™

Leading the Conversation

Can I take Hormone Therapy if I have a Family History of Breast Cancer?

- Observational evidence shows use of HT does not alter risk for breast cancer:
  - In women with a family history of breast cancer
  - In women after early surgical menopause with bilateral salpingo-oophorectomy and BRCA gene when taken to age of menopause
- Family history should be assessed when counseling women on the use of HT (Level II)
  - Use of progestins, higher doses, & longer duration increases risk
  - Heterogenously or extremely dense breasts, consider supplemental screening-screening breast ultrasound, Contrast enhanced mammogram, or FAST MRI-
  - New code for extremely dense breasts

The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794.

The Menopause Society™

Leading the Conversation

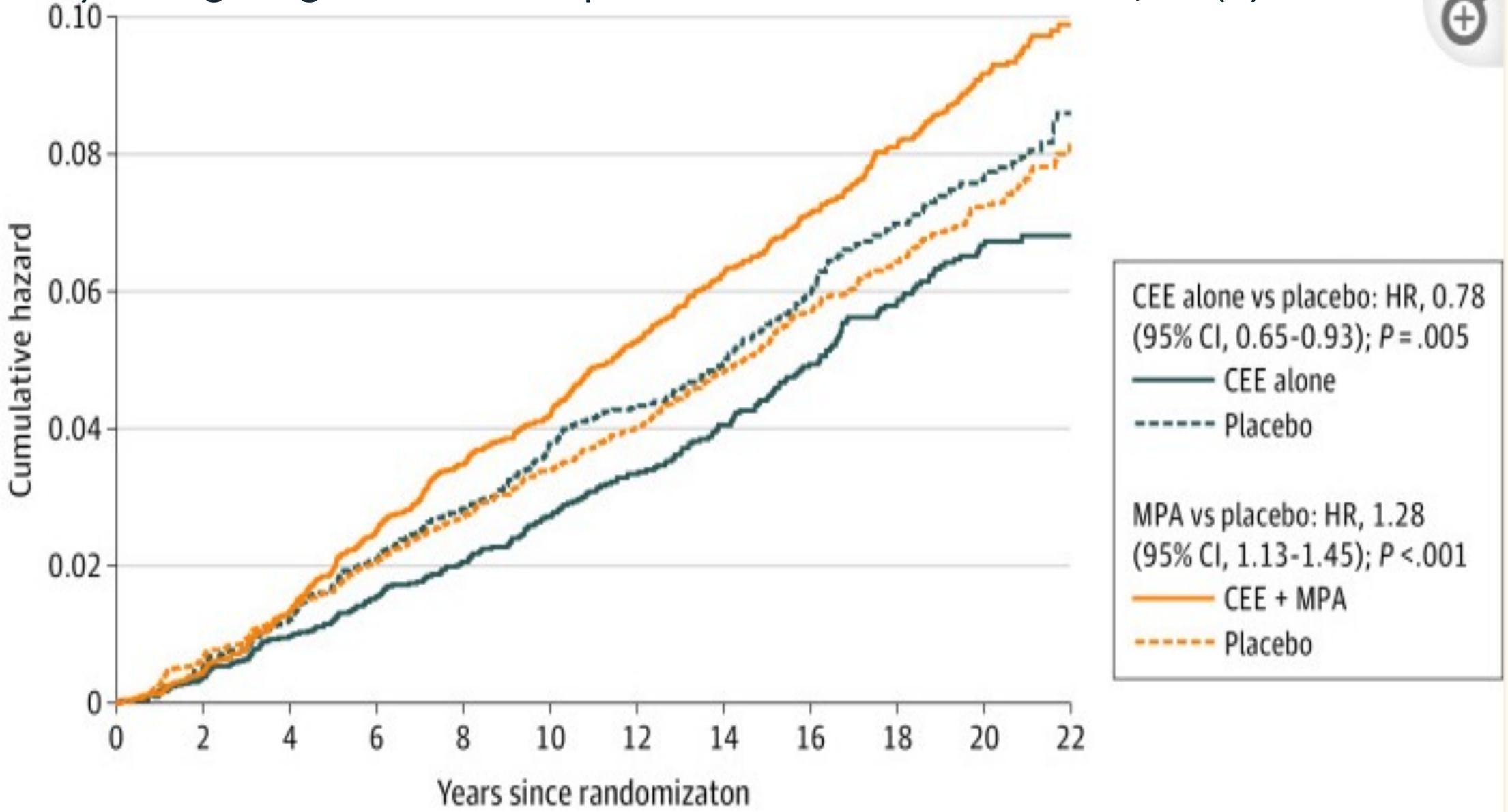
WHI Long term follow up

Among postmenopausal women, prior randomized use of estrogen alone, **conjugated estrogen (CEE)** in women with prior hysterectomy was significantly associated **with a lower risk of breast cancer incidence and mortality,**

Prior randomized use estrogen/progestin **(CEE plus MPA)** in women with an intact uterus was **significantly associated with a higher risk of breast cancer incidence and no significant difference in breast cancer mortality**

Chlebowski RT Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. *JAMA*. 2020;324(4):369-380

Chlebowski RT. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the WHI RCTs. *JAMA*. 2020;324(4):369-380.



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

Transdermal Hormone Therapy

- Based on observational data only, the use of lower doses and transdermal therapy appear to be associated with lower VTE and stroke risk, avoids liver, does not increase SHBG
- But ... the lack of comparative RCT data limits recommendations

- Need for “steady state” drug release
  - migraines, mood issues, shift work or decreased libido
- Need to bypass liver
- metabolic syndrome or DM, fatty liver, prior gastric bypass

The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794.

Concerns about Compounded Bioidentical hormone therapy

- **Unique concerns about safety surround the use** of compounded bioidentical hormone therapy
  - Lack of regulation and monitoring
  - Possibility of overdosing or underdosing
  - Lack of scientific efficacy and safety data
  - Lack of a label outlining risks

UVA Health
University Medical Center

- There is no evidence to support the use of routine serum or salivary hormone testing
- **Hormone Pellets** provide extremely high doses of hormones- no safety data
- **DUTCH- Dried Urine Test** for Comprehensive Hormones-measures hormone levels to determine which ones need to be ‘fixed’ – selling supplements

Who Should Take Hormone Therapy?

- Hormone therapy effective for relief of VMS, improves QOL, rapid eye movement (REM) sleep; bone density and reduction of fracture
- Estrogen alone if a woman has had a hysterectomy or using a progestin IUD
- Conjugated estrogen with bazedoxifene- non progestin, no increase bleeding/breast tenderness or breast density, no breast cancers at 2 years
- **Individualize decisions:** HT use, types, formulation, duration
- Not recommended if estrogen sensitive cancers
- No rule to discontinue solely based on age –but risks of breast cancer may increase
- **Extended use reasonable** if benefits > risks for VMS relief or prevention of bone loss (lower doses, transdermal)

2022 HT Position Statement The North American Menopause Society

The Menopause Society™
Leading the Conversation

Tailoring Hormone Therapy: Transdermal Estradiol

Transdermal therapies, at low doses, are *preferable** for women with:

- VTE risk
- Hypertension
- Hypertriglyceridemia
- Obesity^
- Metabolic Syndrome
- Diabetes
- History of gallbladder disease

Stuenkel CEU 2024

*No head to head RCTs with clinical outcomes comparing oral to transdermal estrogen;

Stuenkel CA, et al. *J Clin Endocrinol Metab* 2015; 100:3975-4011; p.17; ^Avoid CEE+P if BMI ≥ 30; Crandall CJ, *Menopause,* 2017;24:1145

Who Should Not Take Hormone Therapy

Contraindications for oral and transdermal hormone therapy

- Unexplained vaginal bleeding
- Liver disease
- Prior estrogen-sensitive cancer (including breast cancer)
- Prior coronary heart disease, stroke, myocardial infarction, or VTE
- Personal history or high risk of thromboembolic disease

Potential risks of hormone therapy for women <60 years include

- Rare risk of breast cancer with EPT
- Endometrial hyperplasia/endometrial cancer—inadequately opposed estrogen
- Venous thrombosis and gallbladder disease

Adverse events

Nausea, bloating, weight gain, fluid retention, mood swings (progestogen related), breakthrough bleeding, headaches, and breast tenderness

EPT = estrogen-progestin therapy; VTE = venous thromboembolism.

NAMS. *Menopause*. 2022;29(7):767-794.

Contemporary Approach to Prescribing HT and HT Risk Assessment

1. Evaluate age, time since menopause, and symptoms

<10 year from final menstrual cycle, <60 years old, and bothersome vasomotor symptoms

2. Perform ASCVD risk assessment and exclude HT contraindications

ASCVD risk factors

- Hyperlipidemia
- Hypertension
- Diabetes
- Family history of premature CVD in first-degree relative (men <55 or women <65 years of age)
- Obesity (BMI >30 kg/m^2)
- Physical inactivity
- Cigarette smoking
- Coronary calcification (moderate risk: CAC 1-99; high risk: CAC >100)
- History of preeclampsia
- History of systemic autoimmune collagen-vascular disease (e.g., lupus, rheumatoid arthritis)

Contraindications to systemic HT:

Coronary heart disease, stroke, TIA
Breast or endometrial cancer
History of pulmonary embolus, venous thrombosis or clotting disorder
Active liver disease
Undiagnosed abnormal vaginal bleeding

3. Evaluate risk category

May consider HT	***May consider HT, transdermal formulation***	***Not recommended to use HT:***
ASCVD risk <5% (low risk) and ≤1 CVD risk factor	ASCVD risk 5-10% or ASCVD risk <5% but ≥2 CVD risk factors	Age ≥60 or >10 years since menopause onset or ASCVD risk >10%

4. Ensure routine follow-up with re-evaluation of risks and benefits

O'Kelly AC, et al. *Circulation Research* 2022;130:652-672.

Non hormone Treatment for VMS Due to Menopause

Nonhormone Pharmacologic Therapies before Neurokinin Antagonists

Medication name	Drug class	Suggested dosing	Side effects	Additional considerations
Gabapentin	Gamma-aminobutyric acid (GABA) analogue	100–300 mg-600 mg at night or adding a dose in day Optimally at night	Dizziness, fatigue	Consider in concomitant migraine or sleep disorders
Paroxetine **Escitalopram**	SSRI	Paroxetine mesylate: 7.5 mg/day *** Paroxetine HCl: 10–20 mg/day Escitalopram 10-20 mg/d	Nausea, dizziness	***Only US FDA-approved nonhormone option. CYP2D6 inhibition; avoid in tamoxifen users; consider in concomitant mood disorders
Venlafaxine	SNRI	37.5–150 mg/day	Nausea, dizziness	May be safe in tamoxifen users
Oxybutynin	Anticholinergic, antimuscarinic	2.5 mg–5 mg/2x daily up to 15 mg/day	Dry mouth, urinary difficulties	Avoid in elderly; may benefit concomitant overactive bladder with VMS; side effects appear dose-dependent
Clonidine-uncommonly used	Antihypertensive; α-2 adrenergic agonist	0.05–0.1 5 mg/day	Blood pressure, drowsiness, dry mouth	Inconsistent data; less effective than SSRIs/SNRIs and gabapentinoids; significant side effects

Notes: Data from David et al and Sahni et al.
SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

***First FDA approved nonhormone was 7.5 mg/d paroxetine salt

Khan SJ, et al. *Int J Womens Health*. 2023;15:273-287.

The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society

Recommended:

- Cognitive-behavioral therapy
  Clinical hypnosis
- SSRIs/SNRIs/Gabapentin***
- NK3 Fezolinetant (Level I)***
- Oxybutynin (Levels I-II)
- Weight loss
- Stellate ganglion block (Levels II-III)

Not recommended due to lack of RCT efficacy data:

Paced respiration; Supplements/herbal remedies, 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; chiropractic interventions, clonidine; dietary modification and pregabalin)

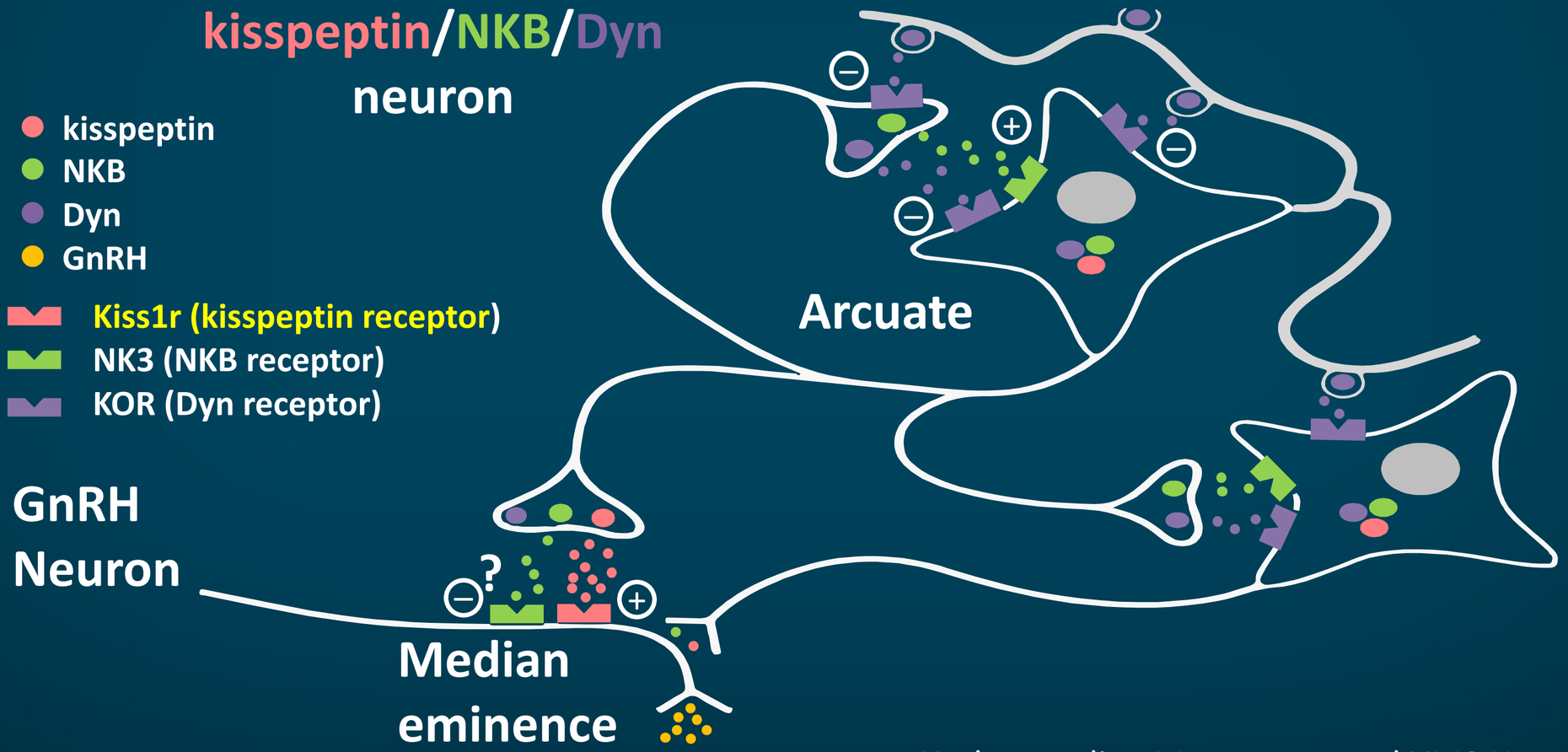
*** FDA approved 7.5 mg/d paroxetine salt
*** FDA approved Fezolinetant

The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society Menopause. 2023 Jun 1;30(6):573-590.

New and Emerging Pharmacotherapeutic Options to Better Manage VMS due to Menopause

Neurokinin

- NK-3 receptors in hypothalamic KNDy neurons become hyperactivated due to low estrogen levels and stimulate the thermoregulatory pathway–
- KNDy neurons express the neurokinin receptors NK-3 and NK-1 and their respective ligands, neurokinin B (NKB) and Substance P (SP)



Understanding Menopause and VMS Navarro ACOG 2024

Wakabayashi Y, et al. *J Neurosci*. 2010;30(8):3124-3132.

NK1 and NK3 Antagonists

NKB antagonism (NK3R receptor antagonists)

Specialized hypothalamic KNDy neurons utilize NKB signaling on NK3R

This signaling pathway appears influential in the development of hot flashes within the hypothalamic thermoregulatory neutral zone as estrogen levels decline.

Through NK3R antagonism, the signaling pathway can be disrupted and potentially attenuate VMS

Several NK3R antagonists are in phase 3 and 4 trials

- Fezolinetant – FDA approval in May 2023
- Elinzanetant- Phase 3 RCT data, phase 4 underway

Understanding Menopause ACOG 2024

FDA = US Food and Drug Administration; NK1 = neurokinin 1; NK3R = neurokinin 3 receptor; NKB = neurokinin B; VMS = vasomotor symptoms.

Khan SJ, et al. *Int J Womens Health*. 2023;15:273-287.

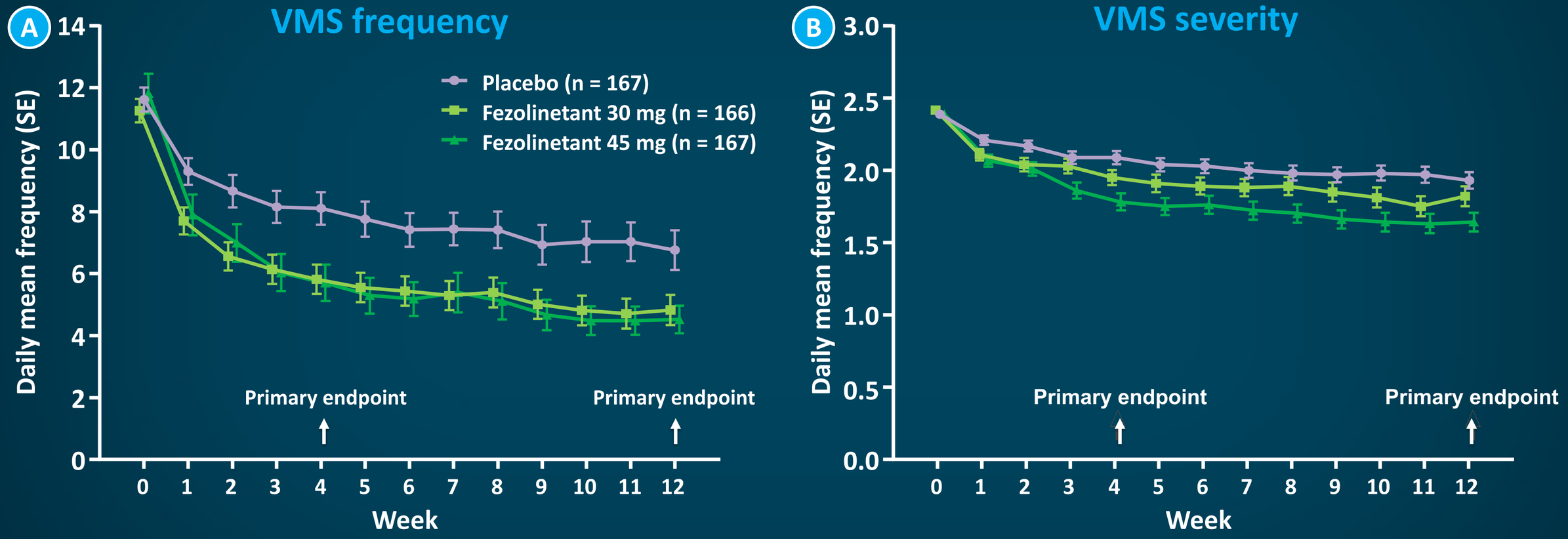
Neurokinin Receptor Antagonists

- Effective, nonhormone treatment for mod. to severe VMS
- Fezolinetant NK3R 45 mg oral daily is the first neurokinin receptor antagonist to receive FDA approval for VMS due to menopause
  - Reduced frequency of VMS about 65%, significantly > placebo, similar to 75% reduction with hormone therapy- (not tested in head to head trials)
  - Efficacy evident within one week
  - Appears to have very good safety profile including endometrial safety
  - At approval, FDA baseline LFTs and every 3 months for 9 months- ***
  - Data from NK3R antagonists fezolinetant, MLE90, and dual NK1R/NK3R antagonist NT-814/elinzanetant indicate the partial degree of gonadotropin suppression does not lead to estrogen deficiency symptoms or effects (such as bone loss)-52 week data

Skorupskaite K, Anderson RA. Hypothalamic neurokinin signalling and its application in reproductive medicine. Pharmacol Ther. 2022 Feb;230:107960. doi: 10.1016/j.pharmthera.2021.107960. Epub 2021 Jul 14. PMID: 34273412.

Fezolinetant Reduced VMS Frequency and Severity Across the 12-Week Period (skylight 2) NK3 to 52 Weeks

Percentage reduction in frequency of moderate and severe VMS per 24 hours by week (FAS)

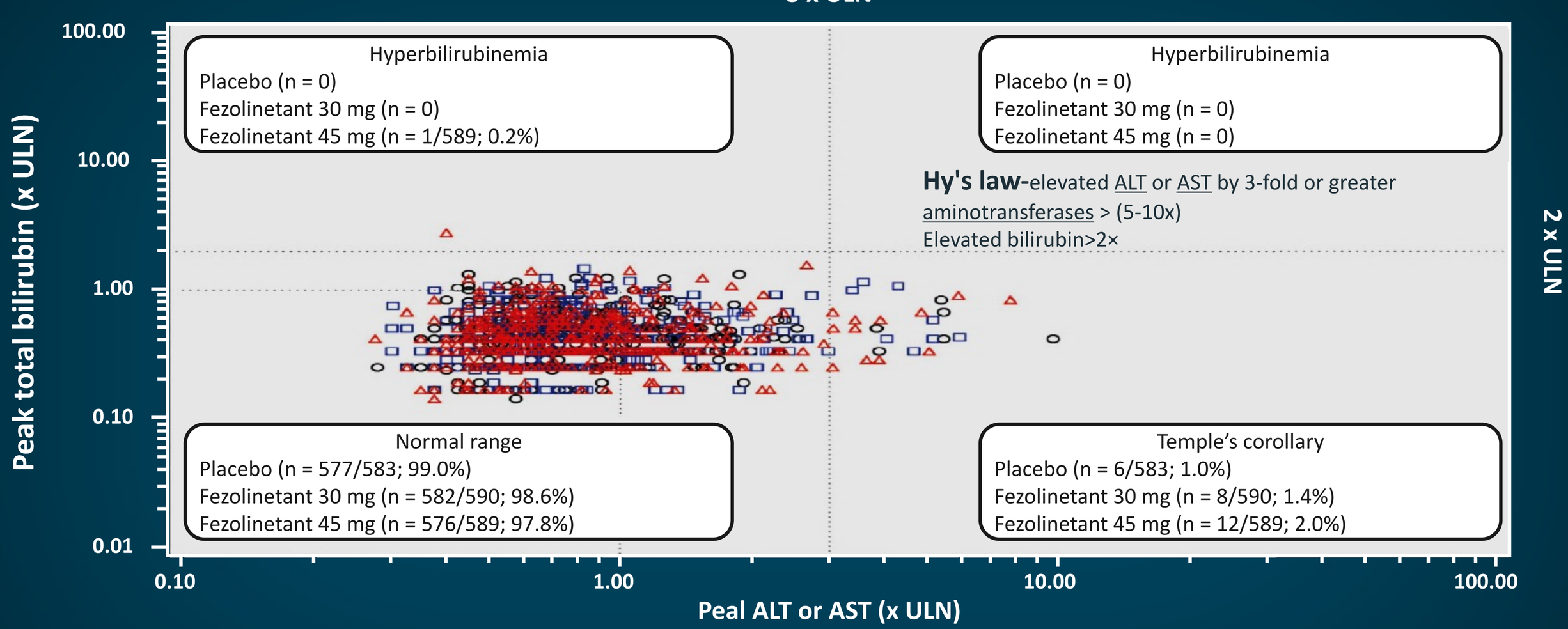


Mean (A) frequency and (B) severity of moderate and severe VMS during the 52-week treatment period (FAS and FAS-fezolinetant exposure). Genevieve Neal-Perry. Both fezolinetant doses statistically significantly reduced VMS frequency and severity at Weeks 4 and 12 vs placebo.

FAS = full analysis set; SE = standard error; VMS = vasomotor symptoms.

Johnson KA, et al. *J Clin Endocrinol Metab*. 2023;108(8):1981-1997.

Fezolinetant Evaluation of Study Drug-Induced Serious Hepatotoxicity



ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit normal.

Neal-Perry G, et al. *Obset Gynecol*. 2023;141(4):737-747.

Fezolinentant- skylight 4 52 week study 98.2% in the Fezolinetant group had liver function test results WNL compared with 99.0% in the placebo group.

Slide from Jim Simon ACOG 2024–for educational useS

FDA Drug Safety Communication FDA warning about rare occurrence of serious liver injury with use of fezolinetant for hot flashes due to menopause

A postmarketing report of a patient with elevated liver blood test values and signs and symptoms of liver injury after taking medicine for about 40 days.

Symptoms of fatigue, nausea, itching, yellow eyes and skin, light-colored stools, and dark urine within 40 days of starting Fezolinetant. The patient's liver blood test values were elevated, including abnormal liver enzymes and bilirubin levels.

After stopping the medicine, the patient's symptoms gradually went away, and blood test values slowly returned to normal.

FDA recommended increasing the frequency of liver blood testing

Monthly testing for the first 2 months after starting Fezolinetant, and then at months 3, 6, and 9

Elinzanetant (NK1,3) met primary & key secondary endpoints in pivotal OASIS 1 and 2 Phase III studies

- First dual neurokinin-1,3 (NK-1,3) receptor antagonist
  - Non-hormonal treatment of moderate to severe VMS
- Statistically significant reduction in **frequency and severity** of mod-severe VMS vs placebo in postmenopausal women
- Both studies statistically significant over placebo in:
  - Reduction in frequency of VMS at week 1
  - Improvement of sleep disturbances
  - Menopause-related quality of life
- The safety profile favorable- headaches, fatigue, no liver issues

UVA Health University Medical Center

Pinkerton JV, Simon JA, Joffe H, et al.Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618.

Mean change from baseline in frequency of moderate/severe VMS over time

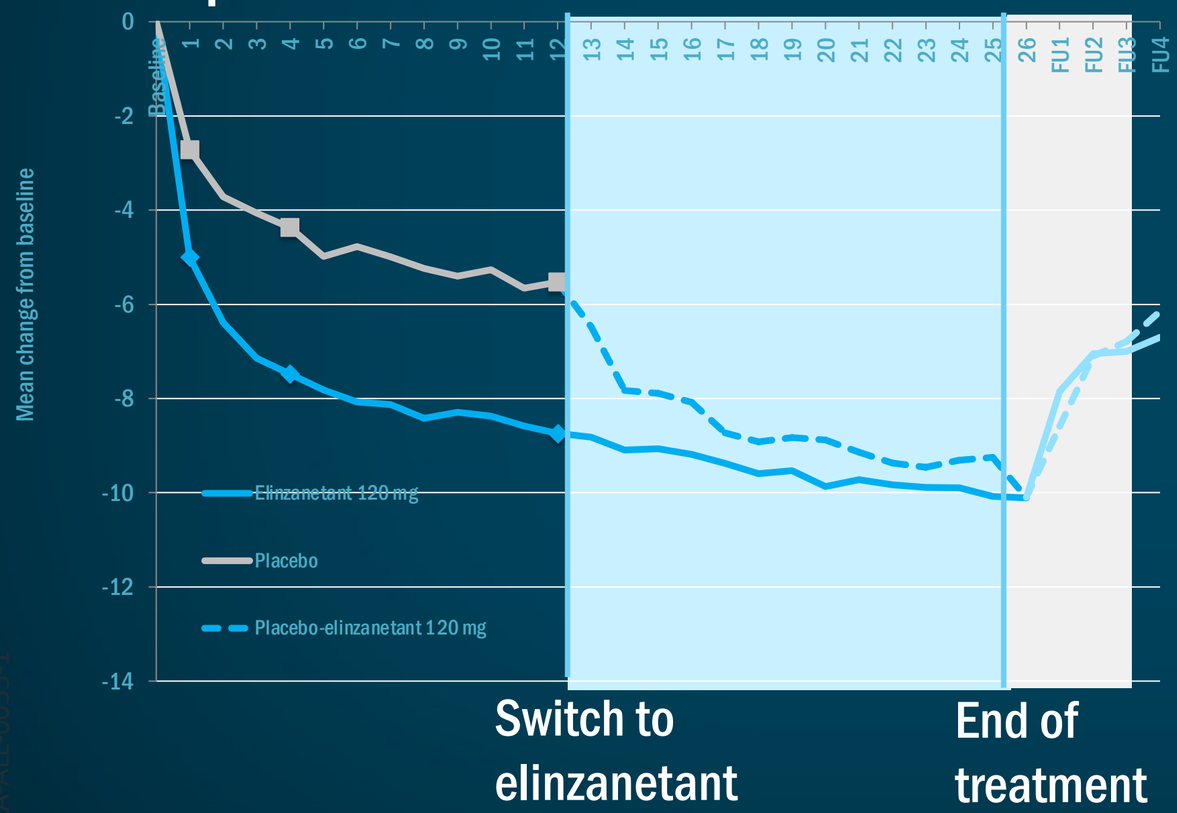
OASIS 1

Double-blind phase

Week

Elinzanetant phase

Follow up



Switch to elinzanetant

End of treatment

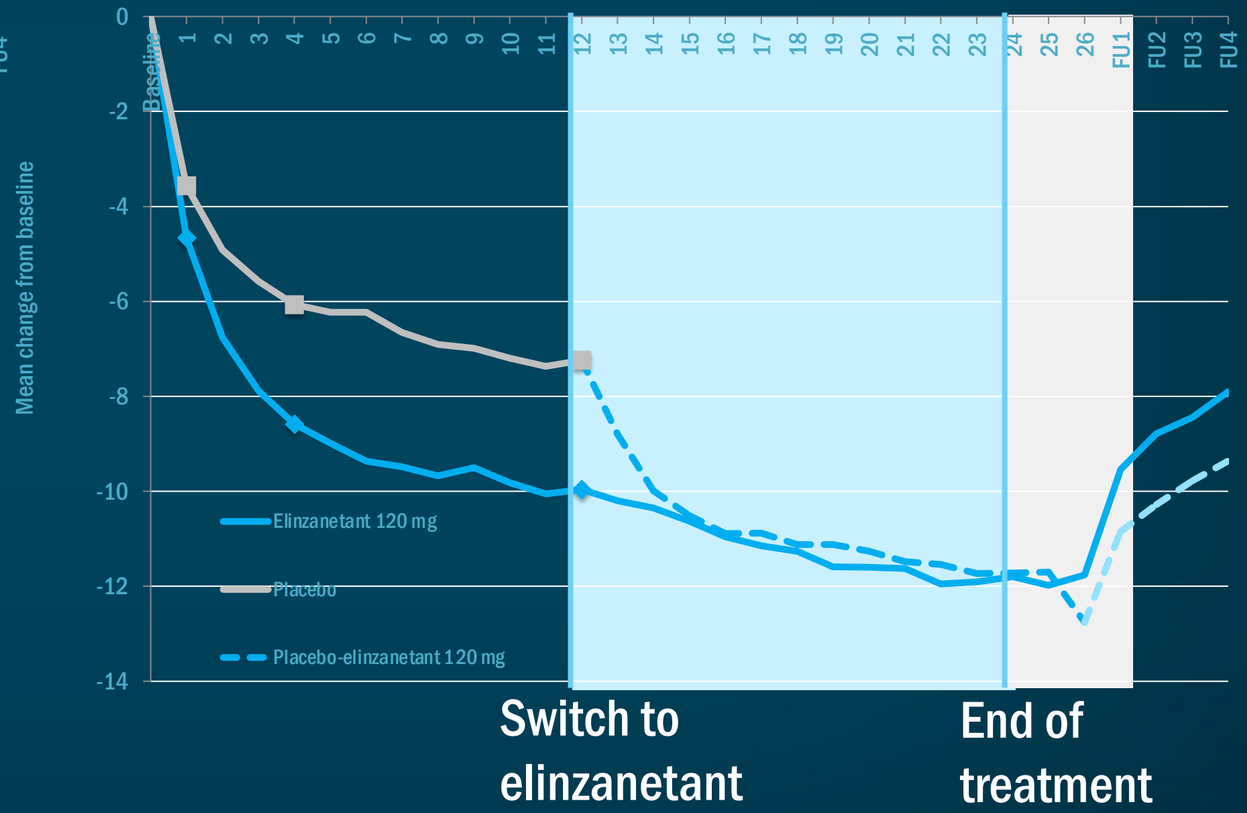
OASIS 2

Double-blind phase

Week

Elinzanetant phase

Follow up



Switch to elinzanetant

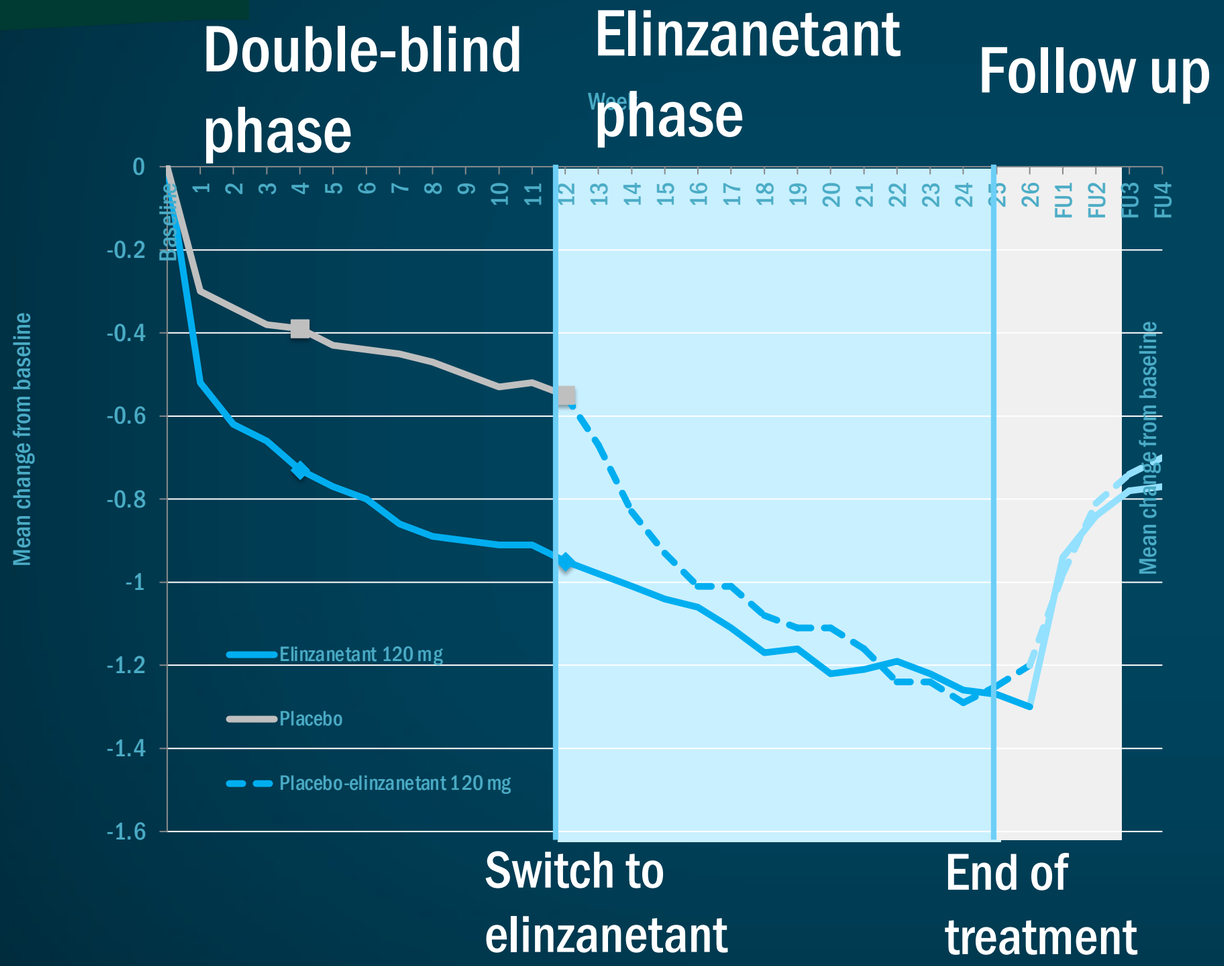
End of treatment

Simon, et al. OASIS 1 poster presented at ACOG, 2024. VMS, vasomotor symptoms.
Pinkerton, et al. OASIS 2 poster presented at ACOG, 2024.

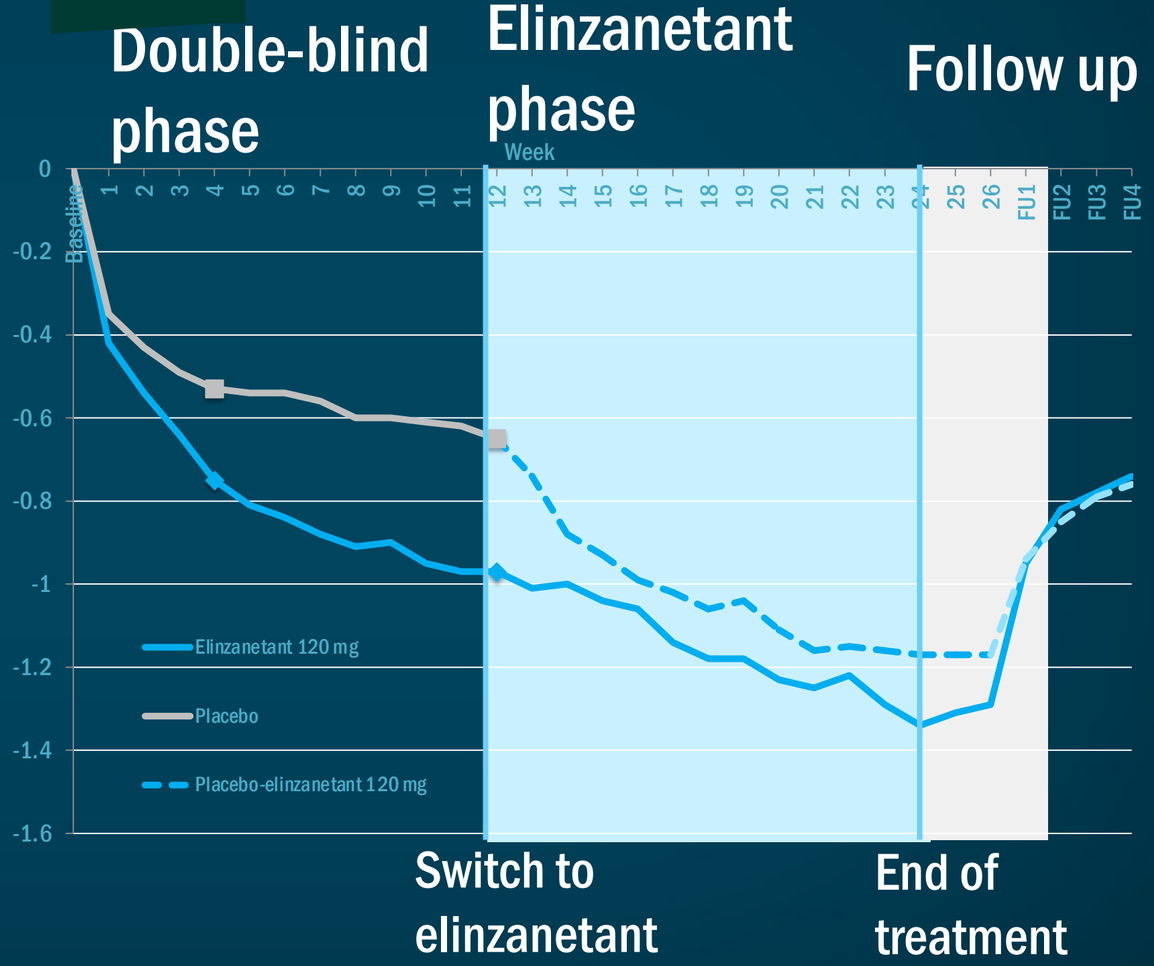
Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618.

Mean change from baseline in severity of VMS over time

OASIS 1



OASIS 2



Simon, et al. OASIS 1 poster presented at ACOG, 2024 VMS, vasomotor symptoms
Pinkerton, et al. OASIS 2 poster presented at ACOG, 2024
Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618

Most frequent TEAEs: OASIS 1 and 2

N (%) OASIS 1	Elinzanetant 120 mg week 1-12 (N=199)	Placebo week 1-12 (N=194)	Elinzanetant 120 mg week 13-26 (N=171)	Placebo-elinzanetant 120 mg week 13-26 (N=168)	Elinzanetant week 1-26 (N=367)
Headache	14 (7.0%)	5 (2.6%)	4 (2.3%)	6 (3.6%)	24 (6.5%)
Fatigue	14 (7.0%)	3 (1.5%)	0	1 (0.6%)	15 (4.1%)
Arthralgia	10 (5.0%)	10 (5.2%)	1 (0.6%)	1 (0.6%)	12 (3.3%)

N (%) OASIS 2	Elinzanetant 120 mg week 1-12 (N=201)	Placebo week 1-12 (N=199)	Elinzanetant 120 mg week 13-26 (N=171)	Placebo-elinzanetant 120 mg week 13-26 (N=180)	Elinzanetant 120 mg week 1-26 (N=381)
Headache	18 (9.0%)	5 (2.5%)	4 (2.3%)	4 (2.2%)	24 (6.3%)
Fatigue	11 (5.5%)	3 (1.5%)	1 (0.6%)	3 (1.7%)	15 (3.9%)

Simon, et al. OASIS 1 poster presented at ACOG, 2024. Pinkerton, et al. OASIS 2 poster presented at ACOG, 2024.

Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618

Rowanda Case Study Cont

Nonhormone options discussed include the following

- Low dose antidepressants- SSRI, SNRIs
  - She does not want to take antidepressants even at low doses for relief of hot flashes
- Gabapentin
  - She tried this in the past but had significant drowsiness
- Oxybutynin
  - She has dry eyes so does not want to try this route
- She has normal liver function tests
- Not taking any CYP1A2 inhibitors including cimetidine (affect metabolism of Fezolinetant)
- NK3 receptor antagonist shown effective in diverse populations, white or black race, BMI of 30 kg/m2 or higher, younger or older than age 55, smokers, former smokers, and never smokers, in US as well as in Europe

Rowanda’s bothersome hot flashes.

- Hormone therapy would be an effective therapeutic option for her.
  - Important to recognize fear of estrogen and breast cancer driving her choices.
- Race and ethnicity may play a role in whether patients trust providers recommendations and where they are obtaining their information
- Providing written or pictorial information can improve education and build trust
- Recognizing lifestyle and supplements she had tried and her goal of treatment was important to build trust.
- Good candidate for short term low dose hormone therapy or tested non hormone therapy options such as SSRIs, SNRIs, Gabapentin, but was not willing to take them
- After explaining how the neurokinin receptor antagonists worked, Rowanda was excited to try fezolinetant.

Bridging the Gap Between Evidence and Personalized Care

Treatment Indication for VMS

Baseline Health Assessment includes risk of Breast Cancer and Cardiovascular Disease

Patient <60 yr old or <10 yr from onset of menopause

Consider HT formulation, dose, and route- oral vs transdermal

Benefits outweigh risks

Initiate HT, reassess annually to determine if HT is still needed

Patient <60 yr old or <10 yr since menopause + contraindication to HT

Risks outweigh benefits

Risk breast cancer

Risk cardiovascular Disease, thromboembolism

Other comorbidities

Patient >60 yr old or >10 yr from onset of menopause

Risks outweigh benefits- Consider nonhormonal therapy

**FDA approved
Paroxetine salt 7.5 mg
Fezolinetant
Off label SSRIs, SSNRs, Gabapentin, Oxybutinin
In development
Elinzanetant

Endocrine Society Guidelines HT, NAMS for HT, Nonhormone treatments

Understanding Menopause ACOG 2024

Patient Education Resources

These society and educational web pages have information on hot flashes, hormone therapy, bone loss, and vaginal symptoms.

Healthywomen.org **Endocrine Society** **ACOG** **Red Hot Mamas**

healthywomen

ENDOCRINE SOCIETY
Hormone Science to Health

ACOG
The American College of Obstetricians and Gynecologists

REDHOTMAMAS®
outsmarting menopause™

The Menopause Society- menopause.org

The Menopause Society™
Leading the Conversation

Society for Women's Health Research

asrm
American Society for Reproductive Medicine

Let's talk Menopause

Menopause Advocacy Group

UVA Health
University Medical Center

Questions?

Question

Neurokinin receptors have a thermoregulatory affect on which of the following?

a) Ovaries
b) KNDγ neurons in the brain
c) Estrogen binding
d) Muscle movement

Question

Judy is a 48-year-old woman who has been struggling with vasomotor symptoms, specifically hot flashes and night sweats, for the past 2 years. Her symptoms are likely caused by dysregulation of the thermoregulatory zone by which type of KNDy neuron receptors?

a) KDR
b) GnRH
c) Neurokinin
d) PRA

Question

Which of the following is an FDA-approved nonhormonal drug treatment option for women with vasomotor symptoms (VMS) due to menopause?

a) Paroxetine
b) Acupuncture
c) Progesterone
d) Propranolol

Question

Based on the case study, which of the following would be a suggested pharmaceutical treatment option?

a) Fezolinetant
b) Gabapentin
c) Cognitive behavioral therapy
d) Oxybutynin

Question

Which of the following is an opportune way to provide enhance patient communication?

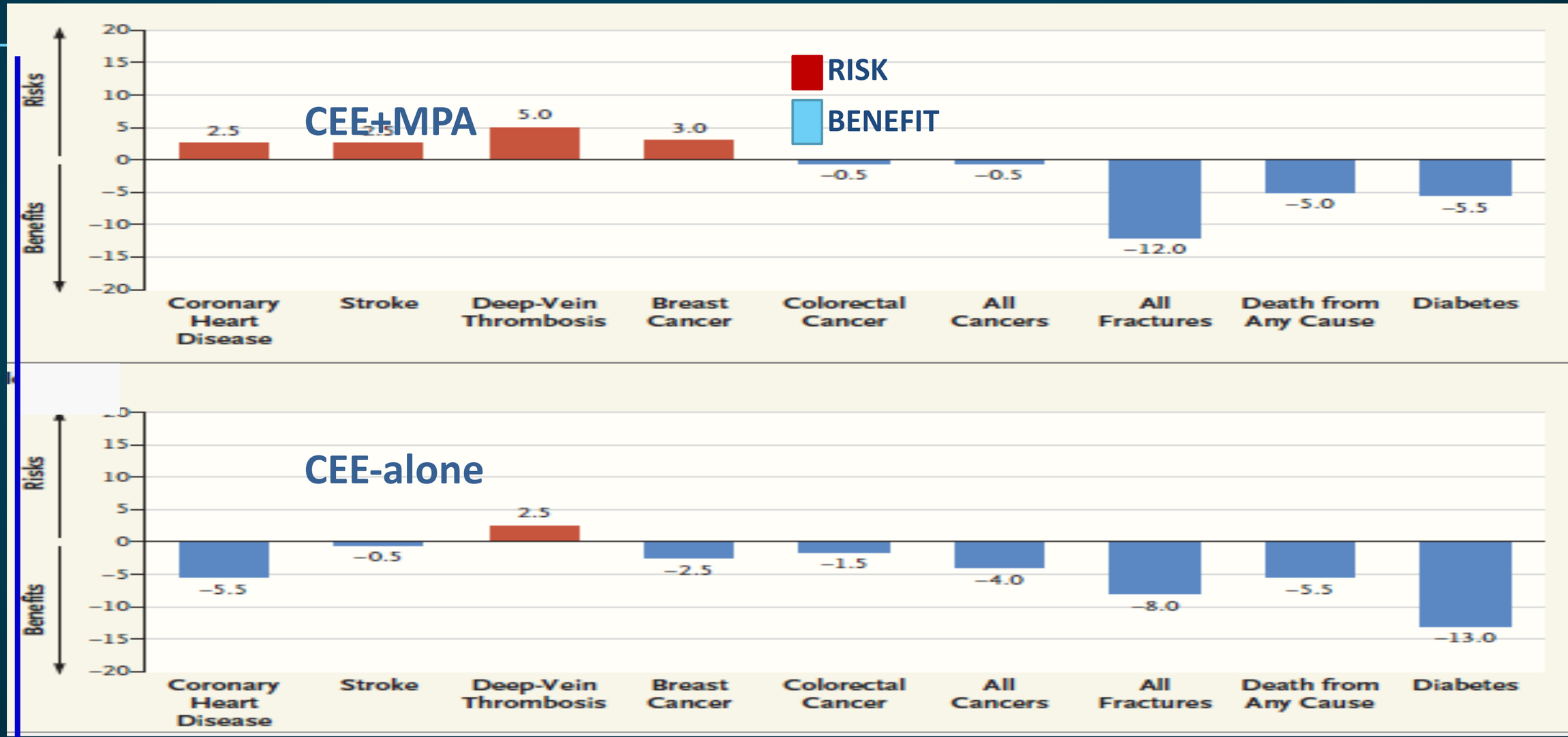
a) Build a trusting relationship
b) Create an open dialogue
c) Provide evidence-based information about hormone and nonhormone options
d) Engage in shared decision-making
e) All the above

Menopause and Workplace 55 million menopausal

- 15 % women missed work or cut back on hours b/c of menopause symptoms
- Loss of productivity costs women estimated $1.8 billion each year.
- Employers adding menopause-specific care to benefits packages to attract and retain experienced women in the workforce, but not the norm.
- Direct and indirect costs-stigma of menopause
- Workplace accommodations, absenteeism, temperature control, supportive environment, flex time, workplace culture
- Concept retain talent- invest in women being productive
- **White house Initiative on Women's Health Research-**

Benefits and Risks of MHT: *Events per 1000 Women Aged 50 to 59 Years Over 5 Years*

Intergroup Difference in Number of Events



CEE = conjugated equine estrogens; MHT = menopausal hormone therapy; MPA = medroxyprogesterone acetate.

Manson JE, et al. *N Engl J Med*. 2016;374(9):803-806.

Effect of HT on Risk of Breast Cancer: COMPLEX

- Factors: type of HT, patient risk factors, and duration of treatment
  - Progesterone appears to have less risk of breast cancer
- **WHI**—No increased risk with estrogen alone
  - A very low excess risk (<1/1000) of breast cancer for patient taking combination therapy (CEE 0.625/MPA 2.5)
  - Similar to placebo for nonprior users of HT
  - 7 fewer breast cancer/100,000 conjugated estrogen
- **DOPS**—no increased risk breast cancer
- **Collab Group et al**—observational meta-analysis, increased EPT>ET and increasing with increasing duration of use
- **NHS**—increased risk ET alone by 15 years, significant after 20 years

The2017 and then 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794.

The Menopause Society™
Leading the Conversation

Genitourinary Syndrome of Menopause (GSM)

- A collection of symptoms and signs associated with decreased estrogen levels that can involve the labia majora, labia minora, vestibule, introitus, clitoris, vagina, urethra, and bladder
- Treatment indicated if symptoms are bothersome- dyspareunia, recurrent vaginitis, frequent UTIs, overactive bladder
- Treatment individualized based on severity of symptoms and the woman's preference after discussion of treatment options and risks/ benefits
- 27% to 84% of Postmenopausal women; progresses if untreated

Portman DJ and Gass M. *Menopause* 2014; 21:1063; NAMS 2020 GSM Position Statement, *Menopause* 2020;27:976-992.