Menopause: Dilemmas & Options

Jan Shepherd, MD, FACOG

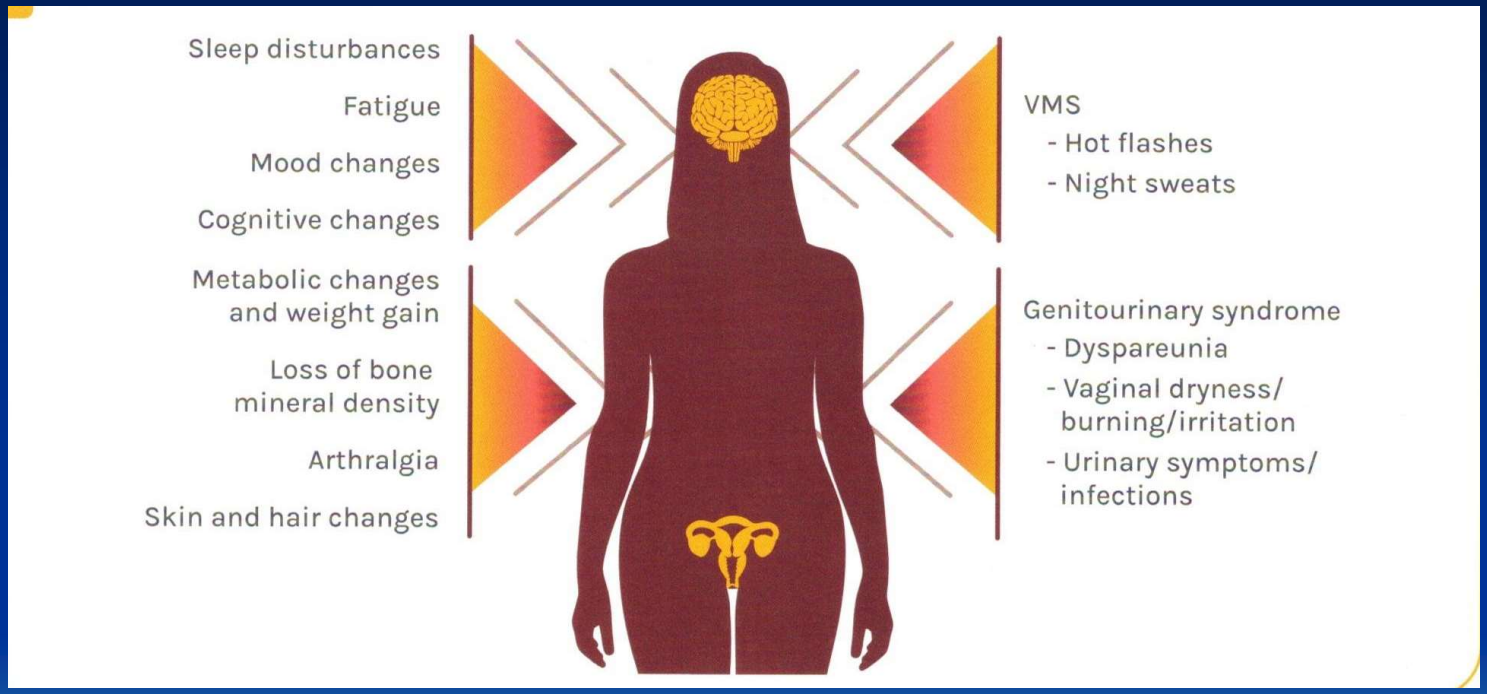
Disclosure

- I am a trainer for placement of the contraceptive implant for Organon and on the speaker's bureau for Astellas Pharma
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

Objectives

- Discuss the current risk/benefit profile of Menopausal Hormone Therapy (MHT)
- Describe contemporary best practices for prescribing MHT
- Identify evidence-based alternatives for managing menopausal symptoms

Why Are We Concerned About Menopause?



How Can We as HCPs Address These Issues?

Hormone Therapy?

WHI: The Baseline

But that data is 22 years old!

The Women's Health Initiative

- Randomized, double-blind, placebo-controlled study of Premarin and Provera (Prempro) for prevention of CHD
- Involved 16,600 postmenopausal women at 40 sites in the US
- Halted after 5.2 years because breast cancer risk reached a predetermined threshold

Results of WHI

	Prempro Incidents per 10,000 women/year	Placebo	RR (95%CI)	% Change
CHD	37	30	1.29 (1.02-1.63)	↑ 29%
Strokes	29	21	1.41 (1.07-1.85)	↑ 41%
DVT/PE	34	16	2.11 (1.58-2.82)	↑ 111%
Breast Ca	38	30	1.26 (1.00-1.59)	↑ 26%
Colon Ca	10	16	0.63 (0.42-0.92)	↓ 37%
Hip fracture	10	15	0.66 (0.45-0.98)	↓ 34%

JAMA 2002;288:321.

Questions Raised about WHI

- Average age 63 - does this data apply to newly menopausal women?
- One-size-fits-all approach
  - Only Premarin .625 and Provera 10 mg studied
  - What about other forms and doses of HT?
- Only E+P studied - does progestin play a role in risk?

WHI Premarin-Only Arm

(10,739 women post hysterectomy)

	Premarin Incidents per 10,000 women/year	Placebo	RR (95% CI)	% Change
CHD	49	54	0.91 (.75-1.12)	↓ 9%
Stroke	44	32	1.39 (1.1-1.77)	↑ 39%
DVT or PE	28	21	1.33 (.99-1.79)	↑ 33%
Breast Ca	26	33	0.77 (.59-1.01)	↓ 23%
Colon Ca	17	16	1.08 (.75-1.55)	↑ 8%
Hip fracture	11	17	0.61 (.41-.91)	↓ 39%

JAMA 2004;291:1701.

WHI: What do we think we learned?

RISKS

- Venous thrombosis
- Stroke
- CHD (combined therapy)
- ↑ Breast cancer (combined therapy)

BENEFITS

- Symptom relief
- Vulvovaginal health
- Osteoporosis and fracture prevention
- ↓ Colon cancer (combined therapy)

Newer Data

Diabetes

Heart Disease

Stroke

Breast Cancer

Reduced Onset Type 2 Diabetes

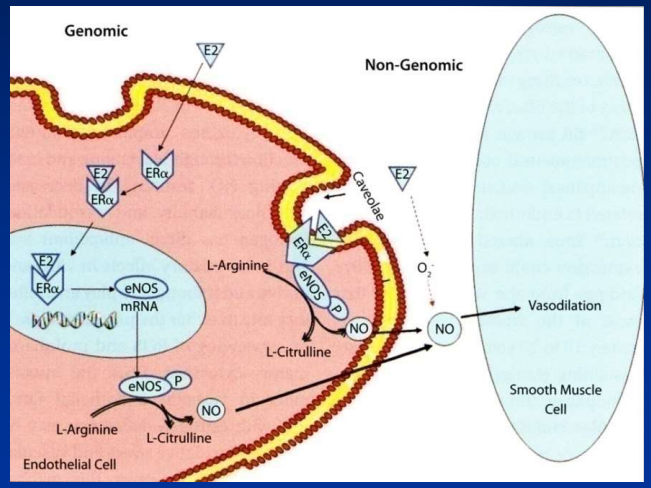
	RR	95% CI	% Change
HERS[1]	0.65	0.48-0.89	- 35%
WHI/HT[2]	0.79	0.67-0.93	- 21%
WHI/ET[3]	0.88	0.77-1.01	- 12%

Estradiol improves insulin-mediated glucose uptake
"One of the major benefits of instituting HT early in menopause"[4]

1. Ann Intern Med 2003;138:1-19. 2. Diabetalogia 2004;47:1175-87. 3. Diabetalogia 2006;49:459-68.
4. J Clin Endocrinol Metab 2015;100:4456-62.

Effects of Estrogen on Vasculature

- Direct
  - Binds to endothelial receptors → NO release → Vasodilation
  - ↑ Prostacyclin → ↓ platelet aggregation



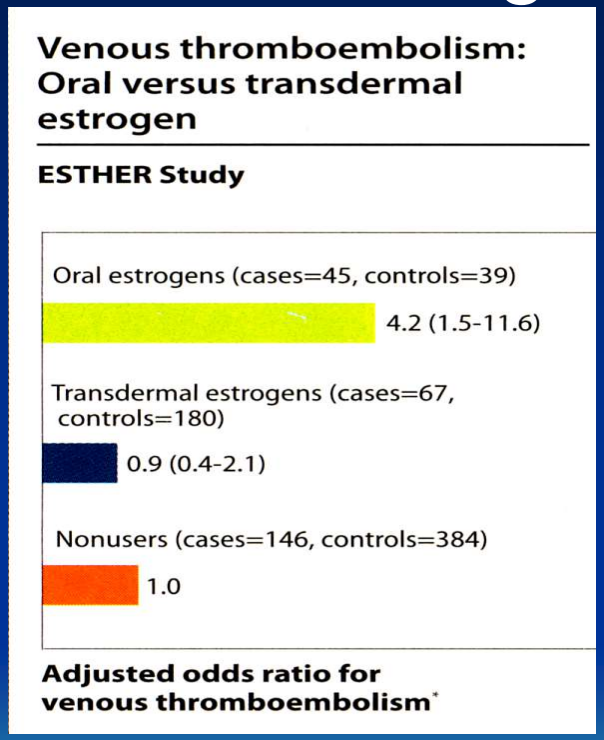
- Biochemical
  - ↑ HDL-C, ↓ LDL, ↑ triglycerides (oral)
  - ↑ C-reactive protein (oral)

Thrombogenic Effects of Estrogen

- First-pass effects
  - ↑ Factors VII and X, APC resistance
  - ↓ Antithrombin, Proteins C and S
- Explains increased DVT/VTE
- Some oral estrogens appear to be more thrombogenic than others*
  - OR 2.08 of VTE with CEE vs. estradiol

*JAMA Intern Med 2014;174:25-31.

No increase in DVT/VTE with Transdermal Estrogen[1,2,3,4]



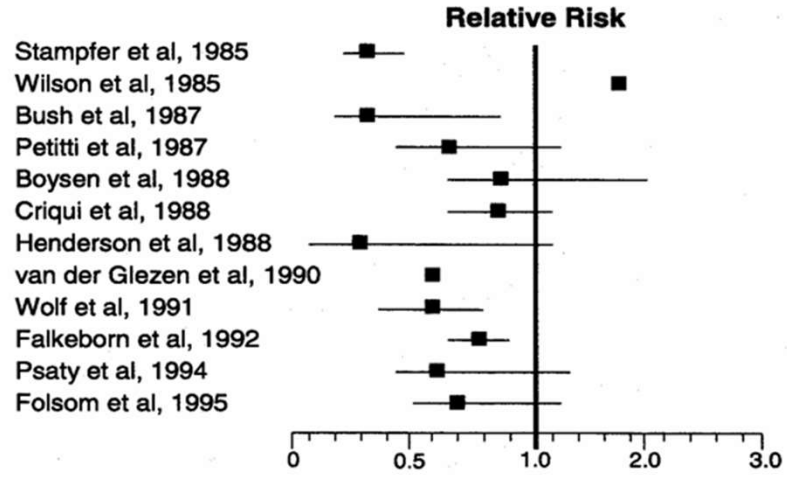
1. Circulation 2007;115:840. 2.Menopause 2011;18:1052. 3. Menopause 2011;18:488. 4. BMJ 2019;364:bmj.k4810.

Potential Effects of Progestin

- Can reverse estrogen's positive effect on lipid profile
- May block estrogen's positive effect on vasculature
- Likely explains differences between EPT and E-only arms of WHI

But Why Were Results on CVD So Different than Previous Studies?

Summary of Observational Studies of ERT/HRT and CVD



Adapted from Wagner. *J Reprod Med.* 2000;45:245.

WHI vs. Previous Studies

- Women in observational studies prior to WHI
  - Chose MHT
  - Presumably because they were going through menopause (~age 51), having hot flashes
  - Demonstrated significant ↓ CHD
- WHI participants were average age 63
  - Twelve years post menopause
  - No significant hot flashes
- Could these 2 groups react differently to MHT?

WHI Review of Data (EPT)[1]

	Overall risk CHD	≤ 2 years into study	8 years into study
All women	1.48	2.06	1.28
> 10 years postmenopause	1.86	2.42	1.58
< 10 years postmenopause	0.66	1.29 (NS)	0.53

Cochrane Review of studies including women < 10 yrs postmenopausal:
RR of CHD 0.52 (95% CI 0.29-0.96)[2]

1. Ann Int Med 2010;152(4):211-217. 2. Cochrane Syst Rev 2015;3:CD00229.

HT and Risk of Coronary Heart Disease
Timing Hypothesis

- Estrogen appears to have a positive effect on preserving healthy endothelium
- Estrogen appears to have a negative effect on damaged endothelium
- Therefore
  - Likely ↓ risk when begun at menopause
  - Likely ↑ risk when started postmenopausally

Newer Data on Stroke Risk

- Population-based case control study from UK Database[1]

	Cases	Controls	RR (95% CI)
Transdermal	103	441	0.95 (0.75-1.20)
≤ 50 µg estradiol	76	384	0.81 (0.62-1.05)
> 50 µg estradiol	27	57	1.89 (1.15-3.11)
Oral	618	2025	1.28 (1.15-1.42)
≤.625mg CE, 2mg E	515	1753	1.25 (1.12-1.40)
>.625mg CE, 2mg E	103	272	1.48 (1.16-1.90)

- French nested case control study[2]
  - RR oral MHT 1.58; RR transdermal MHT 0.83

1. BMJ 2010;340:e2519. 2. Stroke 2016;47:1734-41.

Effects of E and P on the Breast

- Persistent high endogenous estrogen is known to be associated with breast cancer
- Mitotic activity in ductal epithelial cells is stimulated by estrogen, but peaks during the luteal phase (progesterone-dominant)

HT and Risk of Breast Cancer

- Older observational studies
  - Average RR 1.35
  - ↑ Risk with ↑ duration of therapy
  - Little or no risk with estrogen alone
- WHI
  - RR 1.24 (CI 1.00 – 1.59)
  - No risk with estrogen alone

WHI 20 Year Follow Up

- Breast cancer risk with combined therapy (16,608 women)
  - Annualized incidence 0.45% EPT, 0.36% placebo: **HR 1.26 (CI 1.13-1.45)**
  - Annualized mortality 0.045% EPT, 0.035% placebo: **HR 1.35 (CI .94-1.95 - difference not statistically significant)**
- Breast cancer risk with estrogen alone (10,739 hysterectomized women)
  - Annualized incidence 0.30% ET, 0.37% placebo: **HR .78 (CI: .65-.93)**
  - Annualized mortality 0.031% ET, 0.046% placebo: **HR .60 (CI: .37-.97)**

JAMA 2020;324(4):369-380.

UK Database

- Review of 100,000 women with breast cancer and 450,000 control women in British primary care data base
- Matched for mammography history, BMI, ETOH use, ethnicity, etc.
- OR of breast ca with ever use of EPT 1.26 (identical to WHI)
  - **Attributable risk in women aged 50-59 who used for ≥ 5 years: 15/10,000**
- OR of breast ca with ever use of ET 1.06
  - **Attributable risk in women aged 50-59 who used for ≥ 5 years: 3/10,000**
- Risk increased with duration, significant decrease 5 yrs after stopping
- Risk lower in obese women
- **No risk** with vaginal estrogen

JAMA 2020;324(4):369-380.

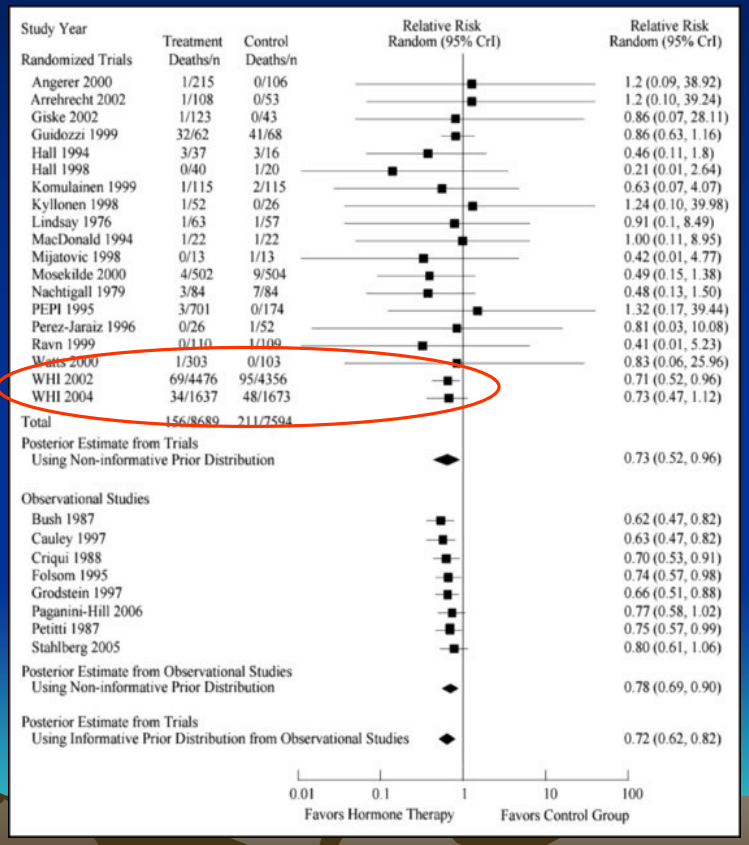
Evidence Suggests:

- There is a small increased risk of breast cancer with combination HT, which increases with duration of use
- E alone has little or no impact
- Vaginal estrogen does not increase risk

"The attributable risk of breast cancer in women on EPT is slightly greater than that observed with one daily glass of wine, less than with two daily glasses, and similar to the risk reported with obesity, low physical activity, and other medications."

NAMS Position Statement, July 2022

Hormone Therapy and Mortality
Meta-Analysis for Women < Age 60



Am J Med 2009;122:1016-22.

What do we think we know about MHT?

RISKS

- Venous thrombosis (oral)
- Stroke (?oral)
- CAD (combined therapy, older women)
- Breast cancer

(combined therapy, esp. prolonged use)

BENEFITS

- Symptom relief
- Vulvovaginal health
- Osteoporosis prevention
- ↓ Colon cancer (EPT)
- ↓ Diabetes

Likely ↓ CAD if begun < age 60

Likely ↓ mortality if begun < age 60*

*JAMA 2017;318(10):927-38.

"Benefits are most likely to outweigh risks for symptomatic women who initiate HT when aged younger than 60 years or within 10 years of menopause. (Level I evidence)"

NAMS Position Statement, July 2022

"Reluctance to treat menopausal symptoms has derailed and fragmented the clinical care of midlife women, creating a large and unnecessary burden of suffering. Clinicians who stay current regarding hormonal and nonhormonal treatments can put menopause management back on track by helping women make informed treatment choices."

N Engl J Med 2016;374:803-6.


MARK WOOD
"H..has your hot flush gone yet, c..can we close the window now?"


Poor Millie, that was one heck of a hot flash!.

Options for MHT

Most Important Factors to Consider

- Timing – initiate within 10 years of menopause or by age 60
- Dose – lowest effective
- Method of Delivery – transdermal or transvaginal preferred

Lowest Effective Potency

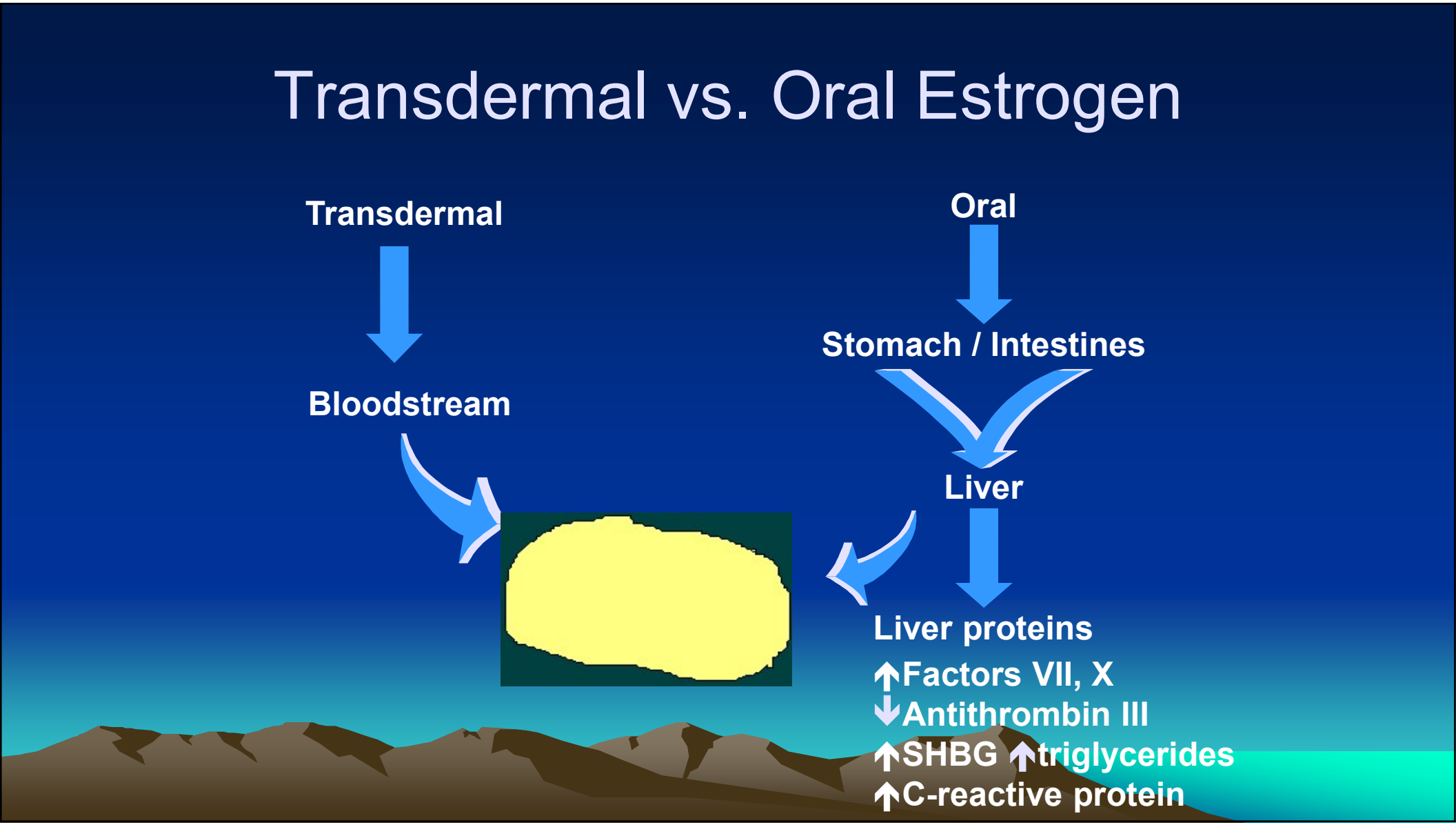
- estradiol (bioidentical): e.g. generic, Estrace, Bijuva, Activella, transdermal preparations - 1.0
- conjugated estrogens: e.g. Premarin, Prempro, Menest, Enjuvia - 2.5-3.5
- ethinyl estradiol: e.g. Femhrt, OCPs - 80-200

Novel Delivery Systems

- Estrogen-only and combination patches
- Vaginal ring for systemic therapy (Femring®)
- Gel, cream, mist

- All contain estradiol
- Provide steady blood levels

Transdermal vs. Oral Estrogen



Recommend Transdermal Estrogen for

- Women with obesity
- Spontaneous or estrogen-induced hypertriglyceridemia
- Smokers
- Hypertensive women
- Women with sexual dysfunction

All Women Who Choose MHT!

Vaginal Preparations

- Preferred if vaginal dryness/dyspareunia only symptoms (Genitourinary Syndrome of Menopause)
- Blood levels remain in postmenopausal range
- Preparations
  - Premarin cream
  - Estradiol cream, tablets
    - *Lowest dose:* Imvexxy® – 4 µg vaginal inserts
  - Estring® (3-month low-dose estradiol vaginal ring)

Ospemifene (Osphena®)

- SERM: E2 agonist in vulvovaginal tissue
- Proven to ↓ vaginal pH, ↑ maturation index, and decrease dyspareunia
- Dose - 60 mg po qd with food
- Contraindicated with estrogen-dependent cancer, and history of VTE, MI, or stroke
- Side effects: hot flashes (7.5%), vaginal discharge (3.8%), muscle cramps (3.2%)

Menopause 2013;20(6):623-30.

Intrarosa®/Prasterone®

- DHEA 6.5 mg vaginal insert applied qhs
- Indicated for moderate to severe postmenopausal dyspareunia
- Proven to ↓ vaginal pH, ↑ maturation index, and ↓ pain with intercourse[1]
- Safe for endometrium (cannot convert DHEA to estrogen) and no ↑ serum E or T[2]
- Warning/Precaution: h/o breast cancer

1. Menopause 2016;23(3):243-56.
2. J Steroid Biochem Mol Bio 2016;159:142-53.

Progestins

- In increasing order of potency
  - Micronized progesterone (Prometrium)
  - Norethindrone acetate (Aygestin, Activella, Femhrt)
  - Medroxyprogesterone acetate (MPA, Provera)

Hormone	Relative Potency
Progesterone	1.0
19-nor-testosterone	5.6
MPA	8.1

Breast Cancer Risk with Synthetic Progestins

UK Database: Women with breast cancer matched 1/10 to women without breast cancer

HRT Exposure	Control Group N = 431,830	Case Group n = 43,183	Adjusted OR (95%CI) for breast cancer
No estrogen	373,019	36,391	1.0 (ref.)
Animal-derived estrogen	28,184	3,311	1.01 (0.96-1.06)
Bioidentical estrogen	21,579	2,487	1.04 (1.00-1.09)
No progestin	410,256	40,352	1.0 (ref.)
Synthetic progestin	21,434	2,817	1.28 (1.22-1.35)
Bioidentical progestin	125	12	0.99 (0.55-1.79)

Obstet Gynecol 2022;139:1103-10.

TSEC (Duavee®)
Tissue Selective Estrogen Complex

- Conjugated estrogens 0.45 mg plus bazedoxifene 20 mg
- Bazedoxifene - a SERM
  - Strong E2 antagonist in endometrium and breast
  - Strong E2 agonist in bone
- Duavee → ↓ hot flashes, maintains or improves bone, no progestin required
- DVT/PE risk = oral estrogen alone
  - Contraindicated with history of DVT/PE or breast ca

Menopause 2016;23:1204-13.

Alternatives to Hormone Therapy

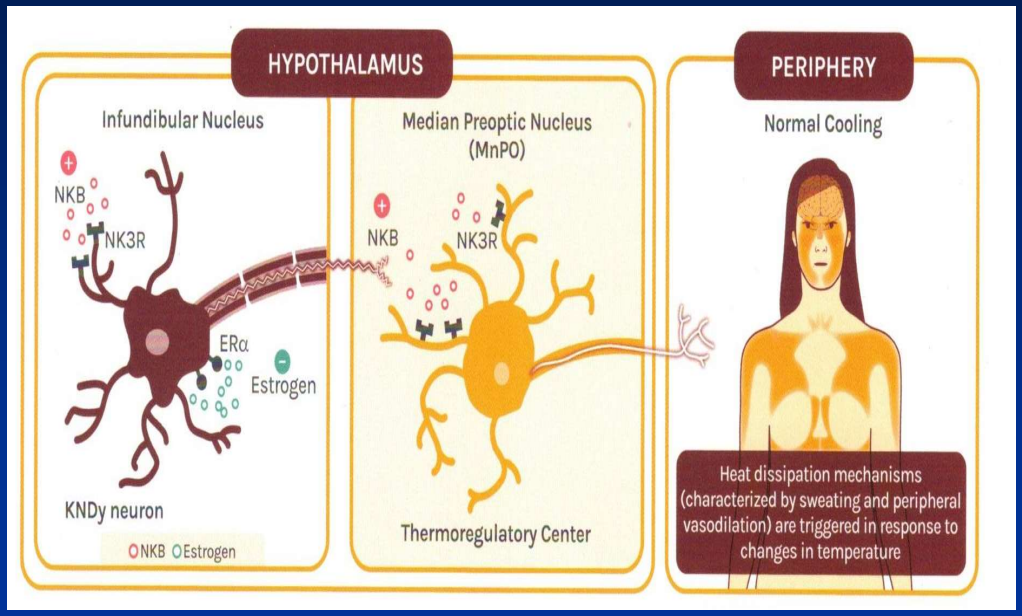
Medications for Hot Flashes

Agent	Dose	% ↓ In Hot Flashes	Placebo Effect (%)
Paroxetine *On-label* Brisdelle	7.5 mg qhs	62	46
Citalopram*	10-20 mg	58	18
Escitalopram*	10-20 mg	55	36
Venlafaxine*	37.5-150 mg	51	15
Desvenlafaxine*	100-150 mg	64	41
Gabapentin*	900-2400 mg	45	29
Oxybutynin*	2.5-5.0 mg	60-77	27

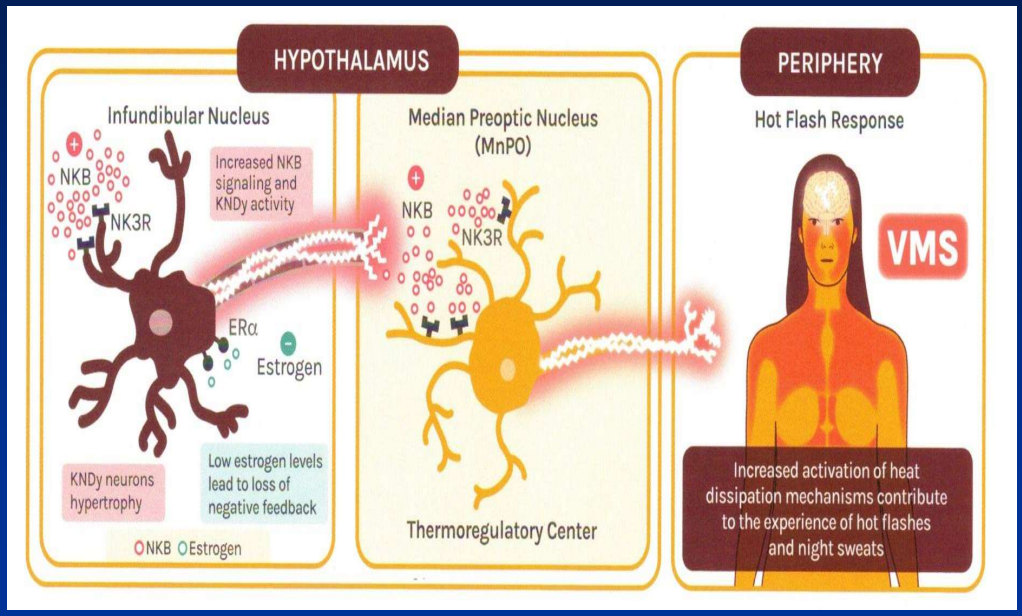
*Off label

NAMS Position Statement, June 2023

NEW: Neurokinin Receptor Antagonists



Before Menopause



After Menopause

Blocking the NK receptors with an antagonist reestablishes balance

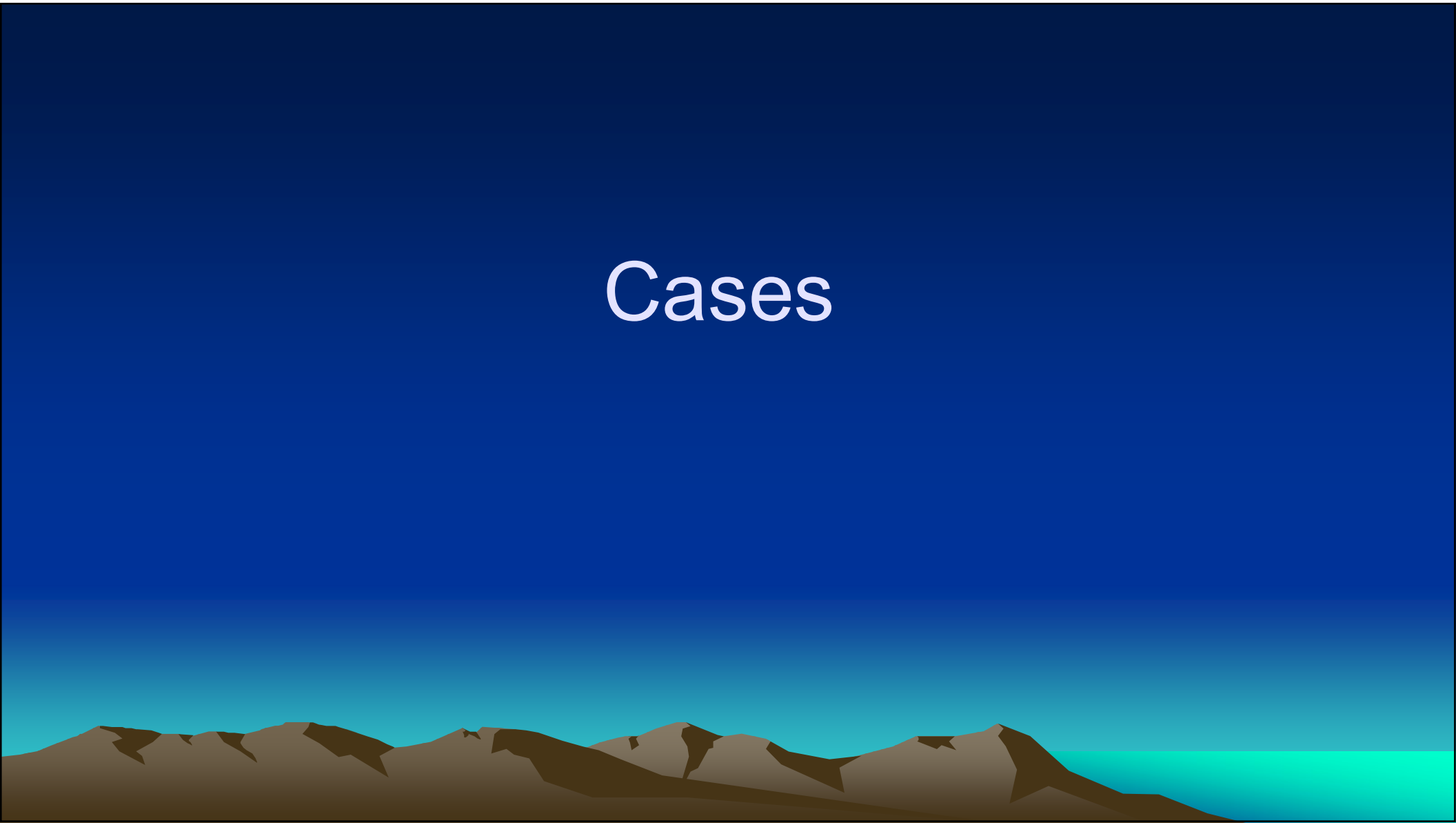
Fezolinetant (Veozah ®)

- Nonhormonal treatment for hot flashes
  - Directly targets the underlying neural mechanism
- One 45 mg. tab qd
- Decreases frequency and severity of hot flashes in one week[1,2]
- Side effects: abdominal pain (4.3%), diarrhea (3.9%), insomnia (3.9%), back pain (3.0%), hot flush (2.5%), ↑ ALT and/or AST (2.3%)
- Obtain serum ALT, AST, and bilirubin before prescribing and at 3, 6, and 9 months

Coming soon: Elinzanetant

1. Lancet 2023; 401: 1091–102. 2. J Clin Endocrinol Metab 2023.

Cases



Eleanor is a 54-year-old g0 on tamoxifen after lumpectomy, radiation, and chemotherapy for ER + breast cancer who presents complaining of severe hot flashes.

What Can You Prescribe to Help Eleanor with Her Symptoms?

- Venlafaxine or Desvenlafaxine
- Gabapentin
- Oxybutynin (short term)
- Fezolinetant (off label)

BUT Avoid SSRIs with Tamoxifen

- SSRIs (esp. paroxetine) block CYP2D6 → reduce conversion of tamoxifen to its active forms
- Evidence for decreased survival of breast cancer patients treated with the combination*

*BMJ 2010;340,c693.

Eleanor returns to clinic, saying that your prescription helped relieve her hot flashes. She is now ready to resume having intercourse with her partner but finds she can't because of severe pain due to vulvovaginal dryness.

How Can You Help Eleanor with this Issue?

- Lubricants and Moisturizers
- Prasterone (vaginal DHEA)
- Estring ® or 4-10 µg estradiol vaginal tablets/inserts
- Refer her for Laser Therapy

Vaginal Estrogen and Breast Cancer

- ACOG: *"Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms."*[1]
- Danish national review: No increased recurrence or mortality with vaginal estrogen in postmenopausal ER+ breast cancer patients with or without tamoxifen, advised caution with aromatase inhibitors[2]
- Recently supported by two additional large (42,000 patients, 49,000 patients) observational studies[3,4]

1. ACOG Committee Opinion #659. 2. J Natl Cancer Inst 2022;114:1347-55.
3.Obstet Gynecol 2023;142:660-8. 4. JAMA Oncol 2023;10:103-108.

Laser Therapy

- Laser beams create tiny wounds in the vaginal epithelium stimulating collagen remodeling and regeneration
- Demonstrated improvement in dysurea, vaginal dryness, dyspareunia, and sexual function[1]
- Some randomized controlled sham studies have not shown difference in outcomes between groups[2]
- Lack of data on safety and long-term efficacy,[3] adverse events[4]
- Not FDA-approved/covered by insurance
- Expensive and require retreatment

1. Obstet Gynecol 2023;142:555-70. 2. JAMA 2021;326:361-9.
3. FDA Safety Communication July 2018. 4. Menopause 2019;26:423-7.

Helen is a 54-year old woman who started MHT one year ago for management of hot flashes. The .05 mg estrogen patch relieved her symptoms but she couldn't tolerate the Prometrium you prescribed with it. Over the past year, she has also had significant side effects from Provera, Aygestin, and combination patches. She wishes to continue the estrogen but you are concerned about protecting her uterus.

How Can You Manage Helen's Problem?

- Place a Mirena®
- Prescribe conjugated estrogens plus bazedoxifene (Duavee®)
- Avoid allowing her to use estrogen only with an u/s exam of her endometrial stripe annually
- Avoid dosing the progestin every 3 months

Continuous or Sequential?

Progestin Regimen (5 years or more)	Endometrial Cancer RR (95% CI)
Continuous	0.36 (0.19-0.62)
Sequential	1.69 (1.43-1.96)
3-Month Intervals	3.76 (2.90-4.79)

No significant difference in risk by progestin used or method of delivery

Obstet Gynecol 2009;114:1197-1204.

Joan is a 65-year-old woman on PremPro .45 since menopause 10 years ago. States she feels miserable every time she tries to discontinue the therapy and wants you to prescribe it again this year.

What Can You Do for Joan?

- Consider alternative therapies for her hot flashes
- Discuss risks vs. benefits and continue the therapy if patent chooses. Both ACOG and NAMS say there is no absolute time limit on MHT.
- Lower her dose to PremPro .3
- Change her to a .0375 patch and Prometrium

MHT after Age 65

NIH study of >10 million women's Medicare records

ET

- 19% ↓ mortality
- ↓ Cancer: 16% breast, 13% lung, 12% colorectal cancer
- 11% ↓ MI, 5% ↓ CHF, 3% ↓ VTE, 4% ↓ atrial fibrillation
- 2% ↓ dementia

EPT

- 10-19% ↑ breast cancer
- ↓ Cancer: 45% endometrium, 21% ovary
- 5% ↓ ischemic heart disease, 5% ↓ CHF, 5% ↓ VTE

Risk reductions greater with lower doses, vaginal or transdermal preparations, estradiol rather than conjugated estrogens

Anne, a 60-year-old g2p2, presents for AE. She continues on .05 estradiol patch with 100 mg progesterone po without problems. Her only complaint is ↓ libido. States her husband is still very interested in sex, but although she used to be, she now could totally do without it. She's heard that testosterone might help and would like to try it if possible. Will you prescribe it?

First: Consider Other Causes of ↓ Desire

Psychosocial

- Recent sexual trauma
- Other sexual dysfunction
- Body image disruption
- Relationship conflict
- Life events/Chronic stress

Physical

- General health issues
- Drug and/or alcohol abuse
- Clinical depression
- Endocrinopathies (esp. hypothyroid)
- Urinary incontinence
- Medication side Effects

Decreased Sexual Desire Screener available online

Role of Androgens

- Testosterone replacement
  - Often indicated after oophorectomy
- Use of testosterone in postmenopausal women

(Does Androgen Insufficiency Syndrome exist?)

  - No correlation between serum androgen levels and libido
  - Moderate evidence for a therapeutic effect of supplemental T in treatment of HSDD
  - Insufficient data for use of T for any other symptom, clinical condition, or disease prevention

Global Consensus Statement on Use of Testosterone in Women
J Clin Endocrin Metab 2019;104:4660-4666.

"Robust support for a trial of testosterone treatment... when clinically indicated in postmenopausal women."

Lancet Diabetes Endocrinol 2019;7:754-66.

"Testosterone therapy, *in doses that approximate physiologic testosterone concentrations levels for premenopausal women,* exerts a beneficial effect on sexual function, particularly HSDD."

Global Consensus Statement on Use of Testosterone in Women
J Clin Endocrin Metab 2019;104:4660-4666.

Adverse Effects of Androgens

- Hirsutism, acne, lower voice (irreversible)
- Data suggest no breast cancer risk with short-term therapy, long-term risk unknown
- Liver damage (oral or supraphysiologic level)
- Adverse lipid profile (oral or supraphysiologic level)
- Teratogenic (can masculinize a female embryo) if given during early pregnancy

→ Weigh potential benefits vs. potential risks

Global Consensus Statement on Use of Testosterone in Women
J Clin Endocrin Metab 2019;104:4660-4666.

Options for Androgen Therapy

- Estratest, Estratest hs (brand discontinued)
  - esterified estrogens + methyltestosterone
  - FDA approved but off label for this indication
- Testosterone
  - No FDA-approved form available for women
  - ↓ doses (~1/10) of male formulations (off label)
  - Compounded transdermal therapy
    (e.g. 1% testosterone cream)

What about Pellets?

FDA-Approved MHT

- Mean estradiol 93.45
- Mean testosterone 15.59
  - (only 4.6% of pts prescribed T)
- Side effects 14.8%
- Abnormal uterine bleeding 15.2%
- Hysterectomy 6.3%

Pellet Hormone Therapy

- Mean estradiol 237.70
  - 4 pts E >1000
- Mean testosterone 194.04
  - 9 pts T >400
- Side effects 57.6%
- Abnormal uterine bleeding 55.3%
- Hysterectomy 20.3%

Review of Pennsylvania hospital electronic records

Menopause 2021;28:867-874.

Flibanserin (Addyi®)

- FDA approved August 2015 for generalized HSSD in premenopausal women
  - Off label postmenopause, but evidence for efficacy*
- Mixed antagonist/agonist to serotonin/dopamine
- 100 mg qhs, efficacy peaks at 8 weeks
- Black Box: Can ↓ bp → syncope, especially combined with alcohol or CYP3A4 inhibitors
- *NOW* – Alcohol no longer contraindicated
  - Avoid alcohol within 2 hours of taking
- *NOW* – REMS certification no longer required

*J Sex Med 2017;14(6):834-842.

Alternative Therapies

- Phytoestrogens, isoflavones
- Black cohosh
- Ginseng, ginkgo
- Omega-3 fatty acids, Vitamin E
- Acupuncture, Yoga

↓

None proven superior to placebo

Most evidence for Cognitive Behavioral Therapy and Hypnosis

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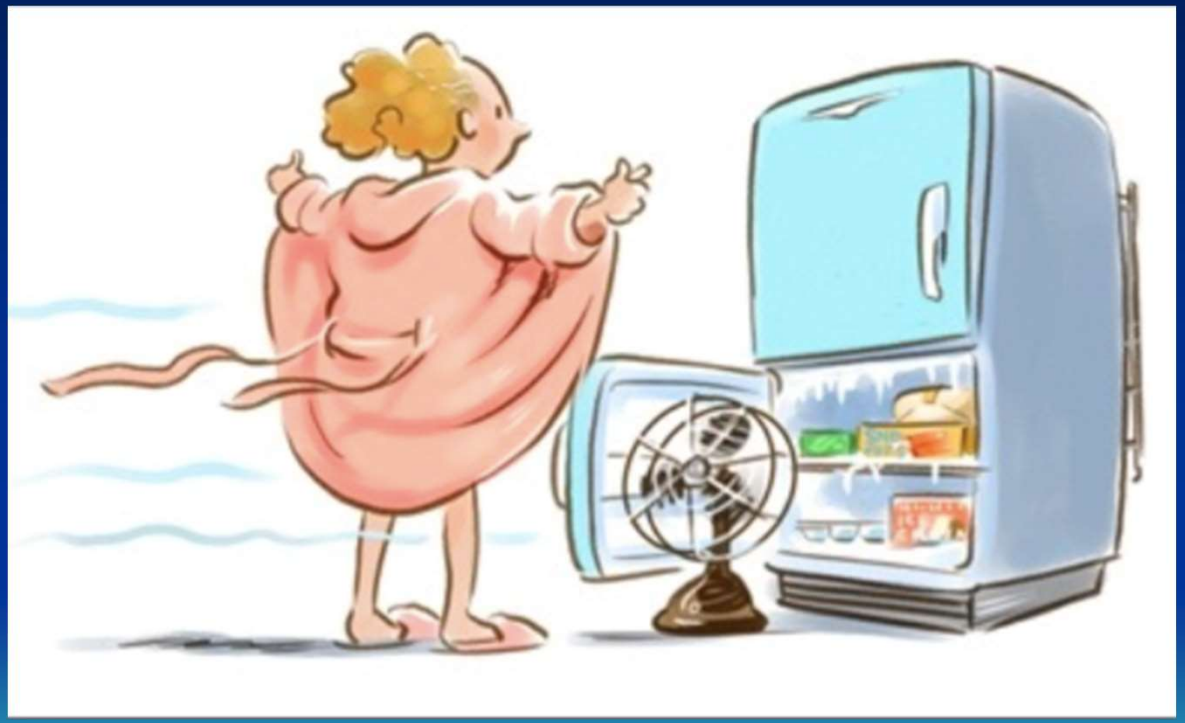
Lifestyle Interventions



Lifestyle Interventions

- Cooler environment
- Avoid triggers (e.g. red wine, spicy foods)
- Aerobic exercise
- Smoking cessation
- Weight loss*

*NAMS Position Statement, June 2023

3 Most Important Health Measures for Postmenopausal Women

- Weight-bearing exercise
- Healthy diet rich in fruits and vegetables
- Adequate Calcium & vitamin D