What are my options?

NONHORMONE AND HORMONE MANAGEMENT OF VASOMOTOR SYMPTOMS

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Disclosures

Relevant Disclosures:

The Menopause Society Board of Directors

Consultant: Astellas

No conflicts of interest

References:

I will discuss clinical studies of off label use of pharmaceuticals for vasomotor symptoms.

This presentation references people born with ovaries. I may use the terms women, she, and her. These terms may not capture the diversity of all those experiencing menopause. We need more research to explore how diverse people experience menopause.

59 years old

LMP: age 52

Symptoms: night sweats, soaks bedsheets, disrupted sleep

Gyn hx: sexually active, some dryness

PMH: HTN, well managed with lifestyle changes, previously used Amlodipine

Social: denies tobacco use, exercises daily, strength training 3x per week

Fam Hx: Mother dx with Breast cancer at age

Allergies: Black cohosh

Treatment: Exercise, dietary changes, cooling bed linens, bedside fan

"I want a natural treatment…"

PRIMAL QUEENS HANDPICKED 6 BEEF ORGANS FOR OPTIMAL FEMALE NUTRITION

Kidney (more Iron than kale*)

Liver (more Vitamin A than lettuce*)

Heart (more CQ10 than cauliflower*)

Uterus (more Vitamin B12 than spinach*)

Ovaries (more Selenium than oats*)

Fallopians (more Zinc than broccoli*)

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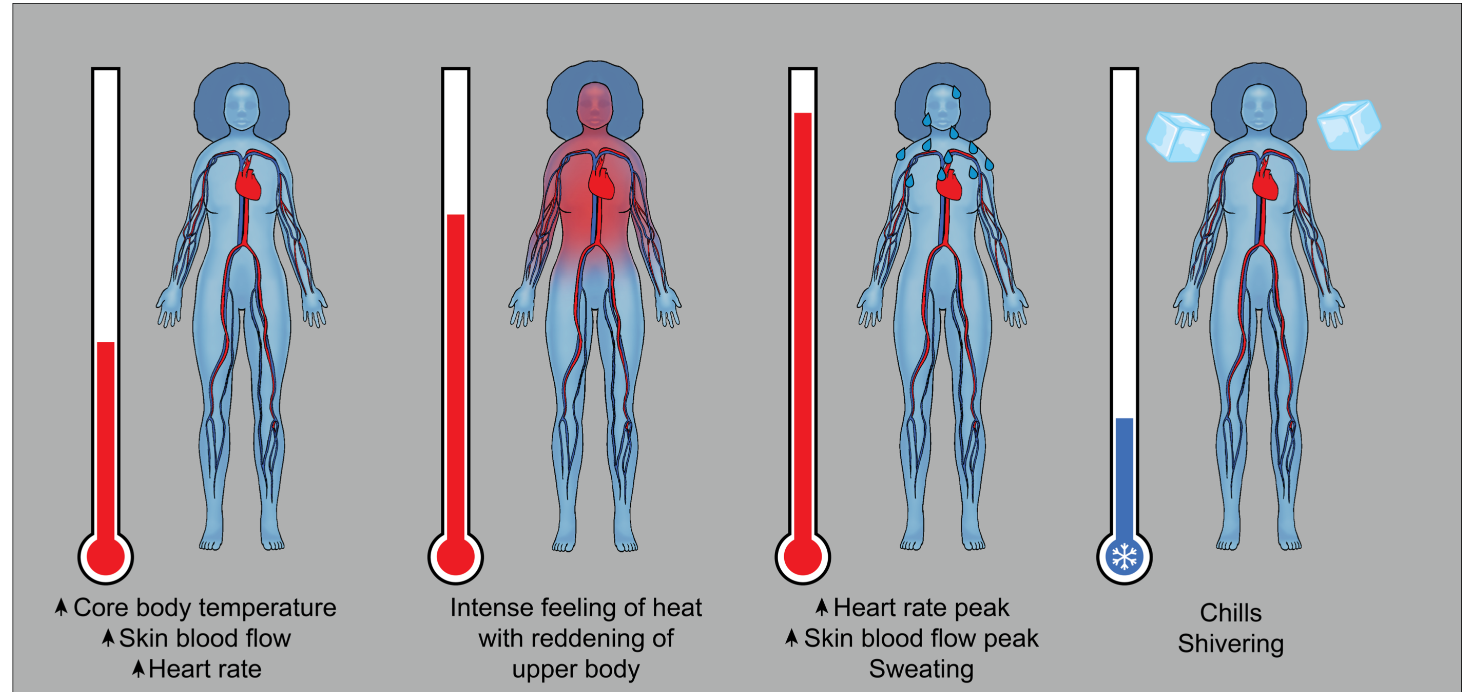
Hormone Therapy

2030: 1.3 billion Menopausal women

$600 Billion industry

Vasomotor Symptoms (VMS)

- Mild: **sensation of heat** without sweating
- Moderate: sensation of **heat with sweating**, able to continue activity
- Severe: sensation of heat with sweating, causing **cessation of activity**



Impact

Health

Economic

Duration of Hot Flashes

Shorter	Longer	Median Years
Postmenopause with symptom onset	Pre/perimenenopause at symptom onset	3.4 v 11.8
Japanese/Chinese	African American race	4.8/5.4 vs 10.1
Non-Hispanic White	Hispanic	6.5 v 8.9
Education≥College	Education<College	7.7 v 9.9
Stress never/almost never	Stress at least sometimes	8.9 v 10.8
No depression	Depression	7.7 v 11.0
No anxiety	Anxiety (mild-severe)	5.0 v 7.4
	Financial strain	
	Poor social support	
	Obesity	
	Smoking	
	Single	

Gold EB, et al. *Am J Epidemiol*. 2000;152(5):463-473; Thurston RC, et al. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501; Shobeirl F, et al. *J Menopausal Med*. 2016;22(1):78-85; Wilson LF, et al. *Maturitas*. 2016;91:1-7; Herber-Gast GC, et al. *Am J Clin Nutr*. 2013;97(5):1092-1099.

Treatment Options

Hormone

- Estrogen
- Estrogen + Progesterone
- Estrogen + SERM

Non-hormone

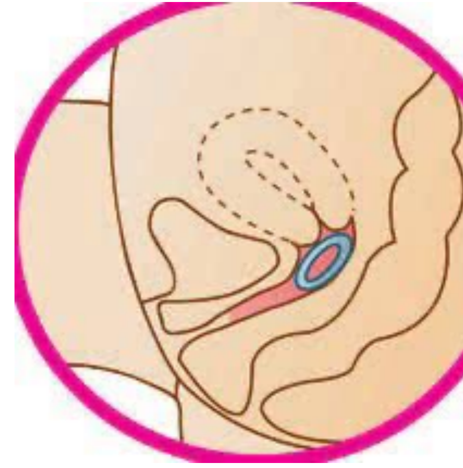
- Pharmaceutical therapies
- Behavioral and lifestyle changes
- Dietary supplements

Estrogen

FDA APPROVED: 1ST LINE THERAPY FOR VMS

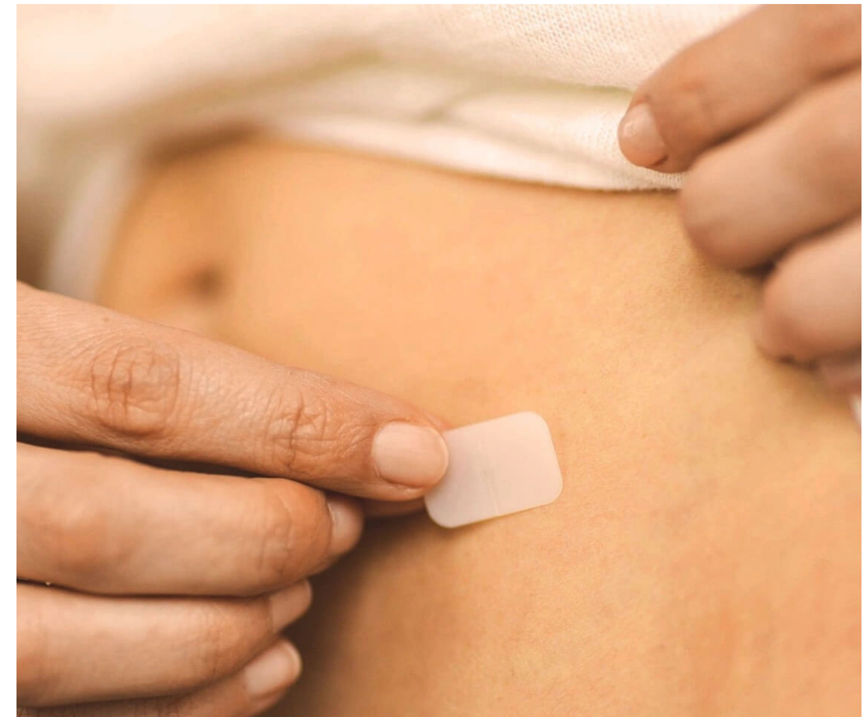
REDUCES VMS FREQUENCY, INTENSITY

Non-Oral Estrogen Therapy



Transdermal/Topical/Vaginal

- Patch, gel, spray, and emulsion
- Avoids first-pass hepatic metabolism
- More stable serum levels
- Minimal effect on SHBG; minimized negative impact to sexual function
- Reduced risk of VTE/stroke compared to oral ET in observational studies



Endometrial Protection

Types of Progestogen Therapy

Micronized Progesterone

- Compound identical to endogenous progesterone
- Prometrium is the only FDA-approved bioidentical progestogen
- Contraindicated in women with peanut allergy
- Bedtime dosing advised because of sedating effects

Progestin

- Synthetic products with progesterone-like activity
  - Medroxyprogesterone acetate (MPA) is the most commonly used and studied in the United States for endometrial protection
  - Norethindrone aceta (NETA)

Schussler P, et al. *Psychoneuroendorinology*. 2008;33(8):1124-1131. Montplaisir J, et al. *Menopause*. 2001;8(1):10-16.

Methods of EPT Administration

Continuous-cyclic (sequential)

- Daily estrogen with progestogen added cyclically for 12-14 d each month
- 80% of women will experience bleeding with progestogen withdrawal

Continuous-combined

- Daily estrogen and progestogen
- Low rates of endometrial hyperplasia
- Higher rates of amenorrhea
- Decreased breakthrough bleeding after 2 yrs

Ettinger B, et al. *Obstet Gynecol*. 1994;83(5pt1):693-700; Ettinger B, et al. *Obstet Gynecol*. 2001;98(2):205-211; Odmark IS, et al. *Menopause.* 2005;12(6):699-707. Steiner AZ, et al. *Obstet Gynecol.* 2007;109(3):581-587. Prempro [package insert]. Philadelphia, PA: Wyeth; 2009. Furness S, et al. *Cochrane Database Syst Rev*. 2012;(8):CD000402. Casper RF, et al. *J Soc Gynecol Investig*. 1996;3(5):225-234.

Alternative Progestogen Options

- Levonorgestrel-containing IUD
- May provide endometrial cancer protection
- Off label
- Long-term efficacy data is needed

Warren MP, et al. *Am J Obstet Gynecol*. 1999;180(1 pt 1):42-48. Luo L, et al. *Cochrane Database Syst Rev*. 2018;12:CD009458.

ET Combined With an Estrogen Agonist/Antagonist

- Tissue-selective estrogen complex (TSEC)
- Daily estrogen combined with a daily selective estrogen-receptor modulator (SERM)
- Approved for treatment of VMS and prevention of osteoporosis
- Amenorrhea rates similar to placebo
- Safety profile comparable to placebo

Archer DF, et al. *Fertil Steril*. 2009;92(3):1039-1044. Pinkerton JV, et al. *Obstet Gynecol*. 2013;121(5):959-968. Pinkerton JV, et al. *J Clin Endocrinol Metab*. 2014;99(2):E189-E198. Pickar JH, et al. *Menopause*. 2018;25(9):1033-1045.
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Transdermal Hormone Therapy

Medications	Available doses*
Transdermal estrogen formulations for menopausal hormone therapy commonly prescribed in the United States	
Weekly estradiol patch	0.014 mg, 0.025 mg, 0.0375 mg, 0.05 mg, 0.06 mg, 0.075, 0.1 mg
	Standard: 0.0375–0.05 mg
	Low: 0.025 mg
	Ultra-low: 0.014 mg
Twice weekly estradiol patch	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
	Standard: 0.0375–0.05 mg
Combination transdermal estrogen-progestin formulations available*	
Estrogen	Progestin
Estradiol 0.05 mg	Norethindrone 0.14 mg, 0.25 mg
Estradiol 0.045 mg	Levonorgestrel 0.015 mg

*Daily release note

Oral Hormone Therapy

Medications	Available doses
Oral estrogen formulations for menopausal hormone therapy commonly prescribed in the United States	
Estradiol	0.5 mg, 1.0 mg, 2.0 mg
	Standard: 1.0 mg
	Low: 0.5 mg
Conjugated equine estrogen	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg
	Standard: 0.625 mg
	Low: 0.3 mg, 0.45 mg
Combination oral estrogen-progestogen formulations available	
Estradiol (0.5 mg, 1.0 mg)	Drospirenone (0.25 mg, 0.5 mg)
Estradiol (0.5 mg, 1.0 mg)	Norethindrone acetate (0.1 mg, 0.5 mg)
Estradiol (1.0 mg)	Norgestimate (0.09 mg)
Estradiol (1.0 mg)*	Progesterone (100 mg)*
Ethinyl estradiol (2.5 µg, 5 µg)	Norethindrone acetate (0.5 mg, 1.0 mg)
Conjugated equine estrogen (0.3 mg, 0.45 mg, 0.625 mg)	Medroxyprogesterone acetate (1.5 mg, 2.5 mg, 5 mg)
Oral progestogen formulations for menopausal hormone therapy commonly prescribed in the United States	
Medroxyprogesterone acetate	2.5 mg, 5 mg, 10 mg
Progesterone*	100 mg, 200 mg

*Formulation contains peanut oil; hypnotic effect, so should be taken at bedtime.

Non-Hormone Prescription Therapies for VMS

- FDA-approved prescription treatments
  - Paroxetine 7.5 mg daily
  - Fezolinetant 45 mg daily
- Off-label prescription therapies
  - Selective serotonin reuptake inhibitors
  - Serotonin-norepinephrine reuptake inhibitors
  - Gabapentin
  - Oxybutynin

Carroll DG, et al. *Int J Womens Health*. 2015;7:615-624; Reddy SY, et al. *Obstet Gynecol*. 2006;108: 41-48; Rada G, et al. *Cochrane Database Syst Rev*. 2010;CD004923; Simon JA, et al. *Menopause*. 2016;23(11):1214-1221.

Non-Hormone Pharmaceuticals

Fezolinetant	45 mg daily	Single dose, no titration needed
Selective Serotonin Reuptake Inhibitors		
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)
Serotonin Norepinephrine Reuptake Inhibitors		
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
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)
Oxybutynin	2.5-5 mg mg/d	Start with 2.5 mg daily and increase to 5 mg twice daily after one week

NON-HORMONES: RECOMMENDED

- Cognitive-behavioral therapy (Level I)
- Clinical hypnosis (Level I)
- Fezolinetant (Level I)
- Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (Level I)
- Gabapentin (Level I)
- Oxybutynin (Levels I-II)
- Weight loss (Levels II-III)
- Stellate ganglion block (Levels II-III)

Level I: Good and consistent scientific evidence.
Level II: Limited or inconsistent scientific evidence.
Level III: Consensus and expert opinion.

NON-HORMONES: NOT RECOMMENDED

- Paced respiration (Level I)
- Supplements/Herbal remedies (Levels I-II)
- Cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation (Level II)
- Soy foods and soy extracts, soy metabolite equol (Level II)
- Cannabinoids (Level II)
- Chiropractic interventions and acupuncture (Levels I-III)
- Clonidine (Levels I-III)
- Dietary modification (Level III)
- Pregabalin (Level III)

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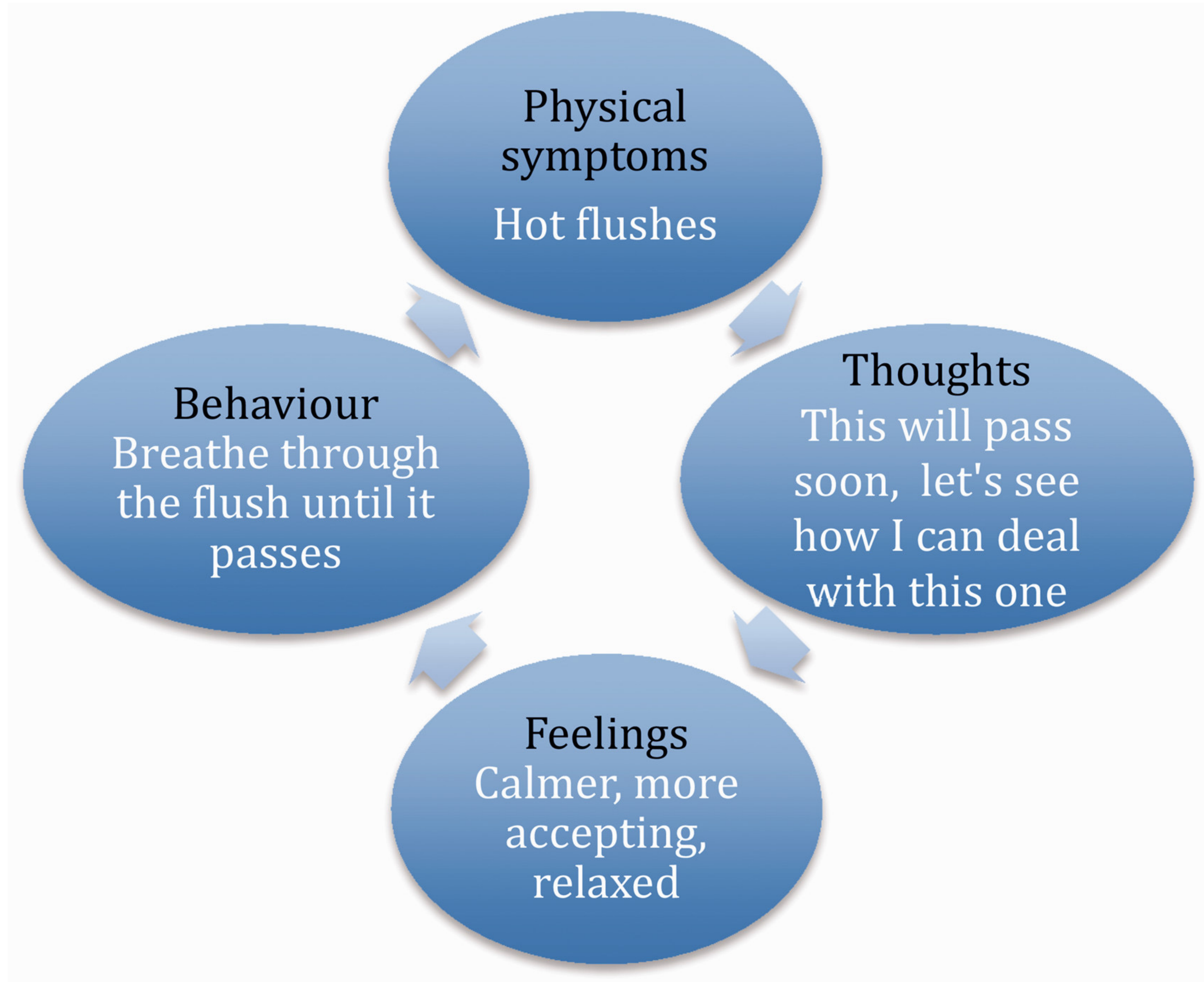
Exercise

- Not recommended for treating VMS
- Recommended for overall health: CV, Bone

Weight loss
Reduces VMS

Cognitive Behavior Therapy (CBT)

Reduces VMS



Dietary Supplements

Not recommended

Black Cohosh

Not recommended

Not recommended

Cannabinoids

Not recommended

Stellate Ganglion Blockade

Recommended in select individuals

NON-HORMONES: NOT RECOMMENDED

- Paced respiration (Level I)
- Supplements/Herbal remedies (Levels I-II)
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Level I: Good and consistent scientific evidence.
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Level III: Consensus and expert opinion.

ELISE’S TREATMENT OPTIONS

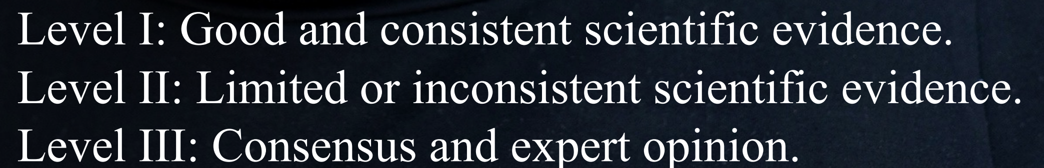
- Estrogen-Progestogen Therapy (Level I)

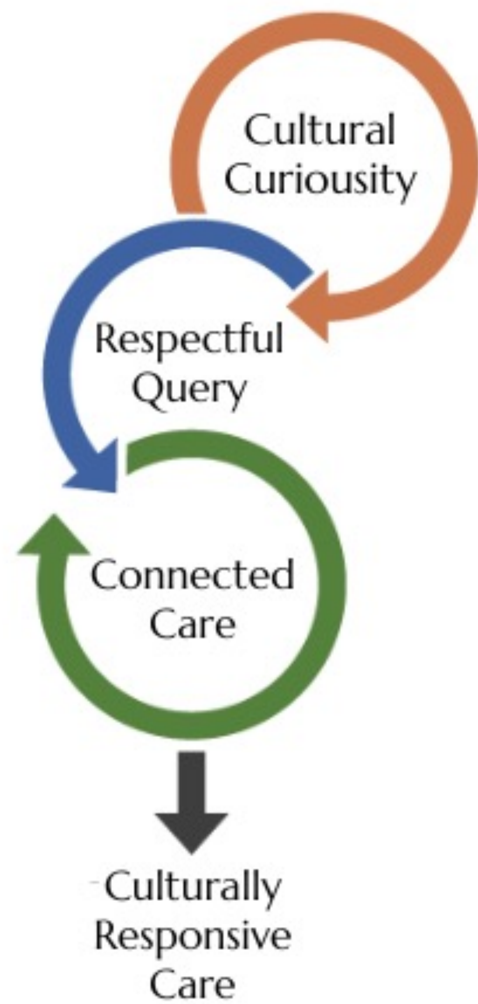
- SSRIs/SNRIs(Level I)
- Fezolinetant (Level I)
- Gabapentin (Level I)
- Oxybutynin (Levels I-II)

- Cognitive-behavioral therapy (Level I)
- Clinical hypnosis (Level I)

- Weight loss (Levels II-III)

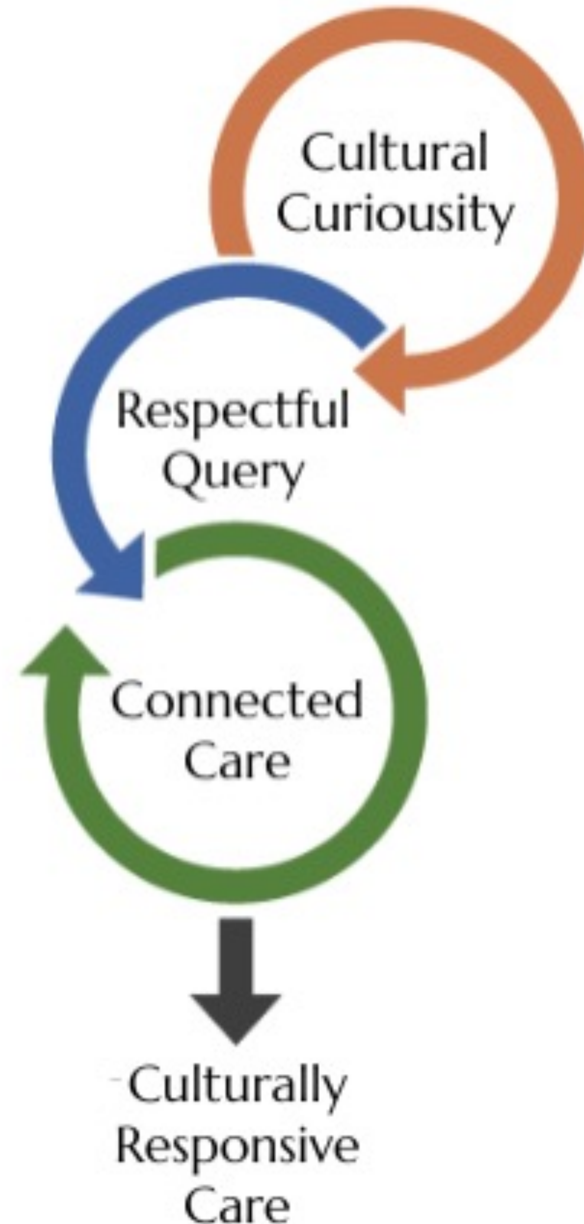
- Stellate ganglion block (Levels II-III)




Cultural
Curiousity
Respectful
Query
Connected
Care
Culturally
Responsive
Care

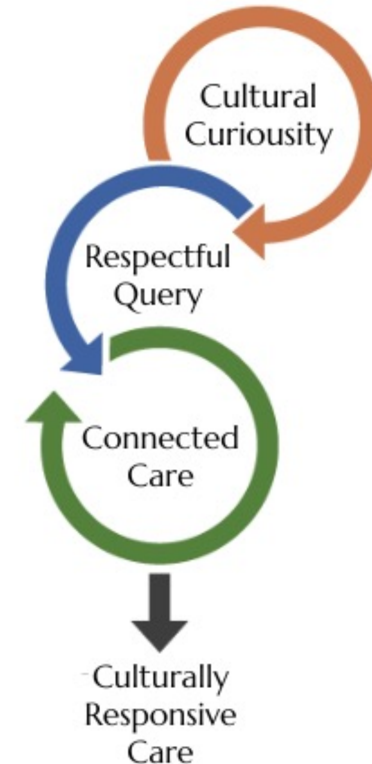
Cultural Curiosity

"I am sorry you've had such a challenging time with your symptoms. Everyone's experiences menopause symptoms differently. I would like to understand more about your unique experience and your preference for natural treatment options…"



Respectful Query

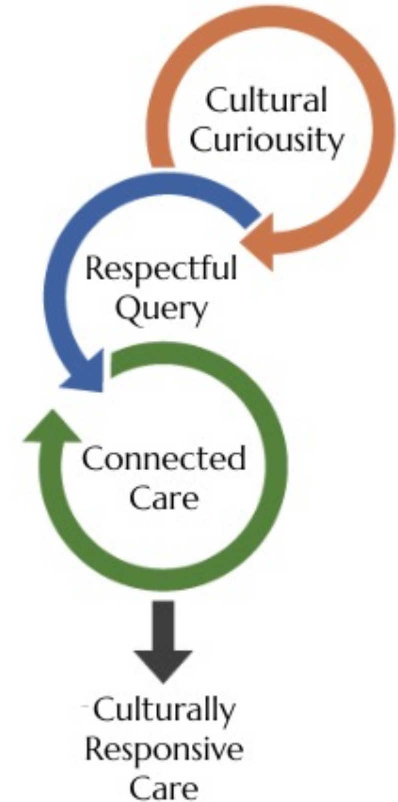
- How and what do you feel about going through menopause?
- What advice have you received about menopause?
- Are there any cultural practices related to menopause that are important for you to observe?
- Do you have a spiritual, religious or faith practice that influences your health care?
- How do you manage your menopausal symptoms? Foods, herbs, behaviors?



- *We all want to live our best lives. Are there things that get in the way of you taking care of yourself and living your best life?*

Connected Care

"Elise, I like to be sure that all of my patients receive information about all available and effective treatment options. You may not be interested in some of them, but I want to be sure that you have complete information before making a decision. Are you ok with me reviewing non-natural therapies?"



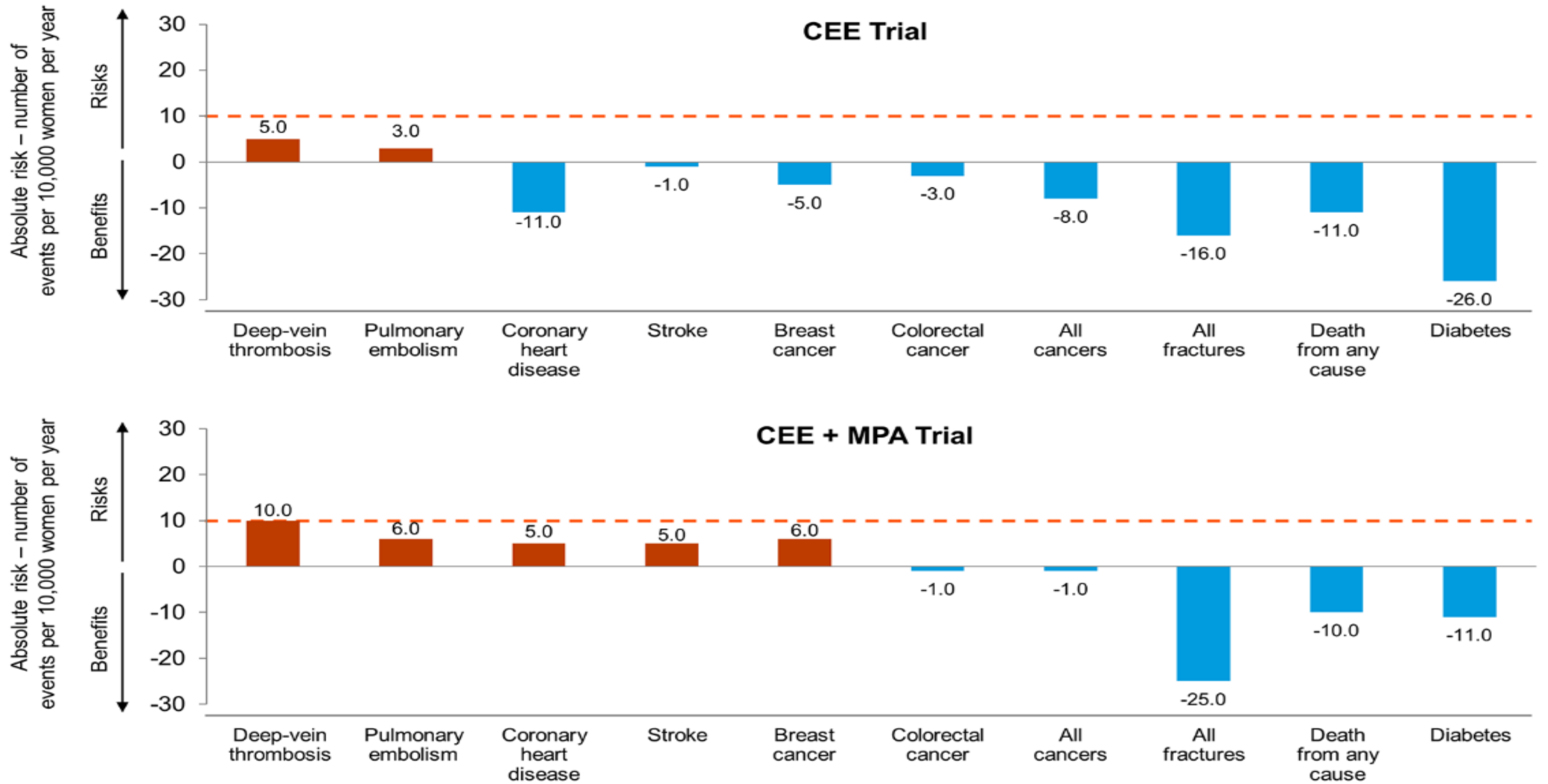
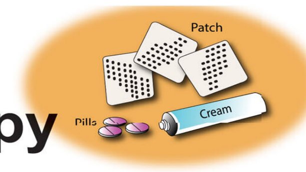
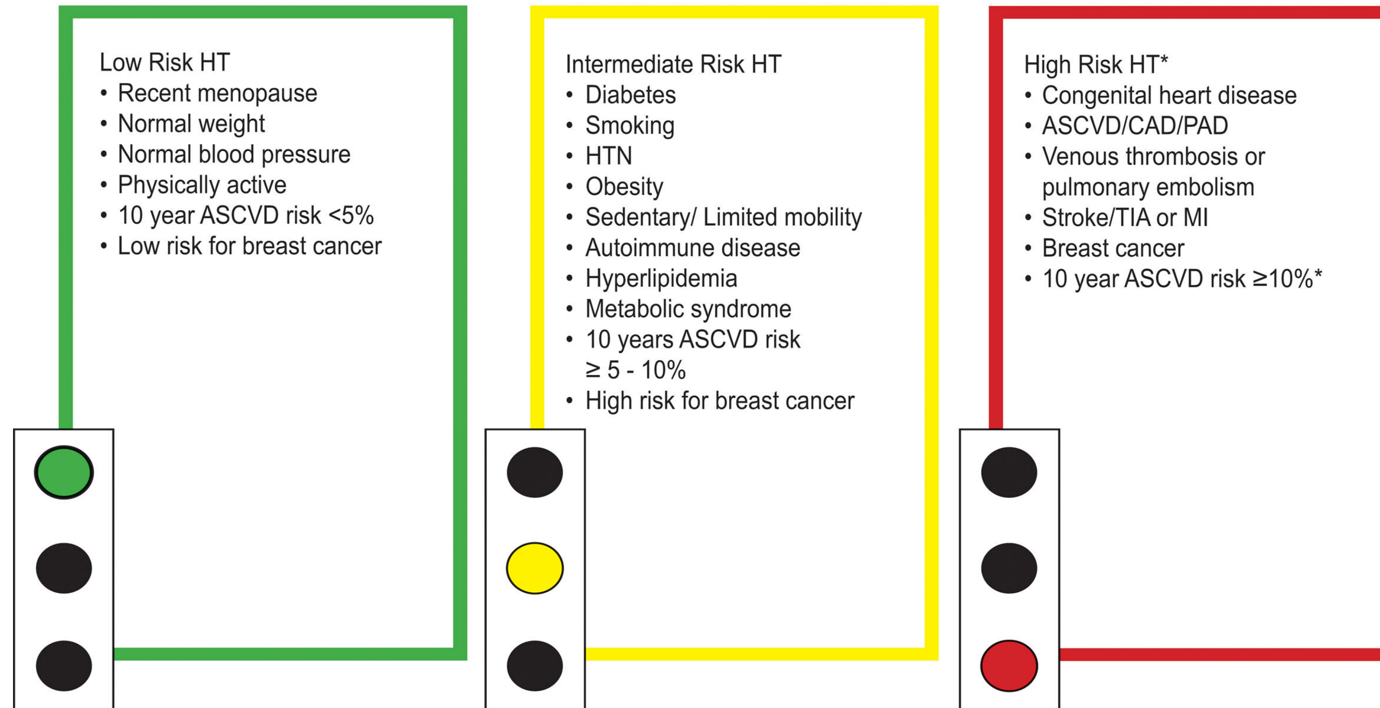


Fig. 1. Benefits and risks of the two hormone therapy formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (CEE + MPA), evaluated in the Women's Health Initiative for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line). Adapted from Manson JE, et al. *JAMA* 2013;310:1353-1368.

Menopausal Hormone Therapy





Leslie Cho. Circulation. Rethinking Menopausal Hormone Therapy: For Whom, What, When, and How Long?, Volume: 147, Issue: 7, Pages: 597-610, DOI: (10.1161/CIRCULATIONAHA.122.061559)

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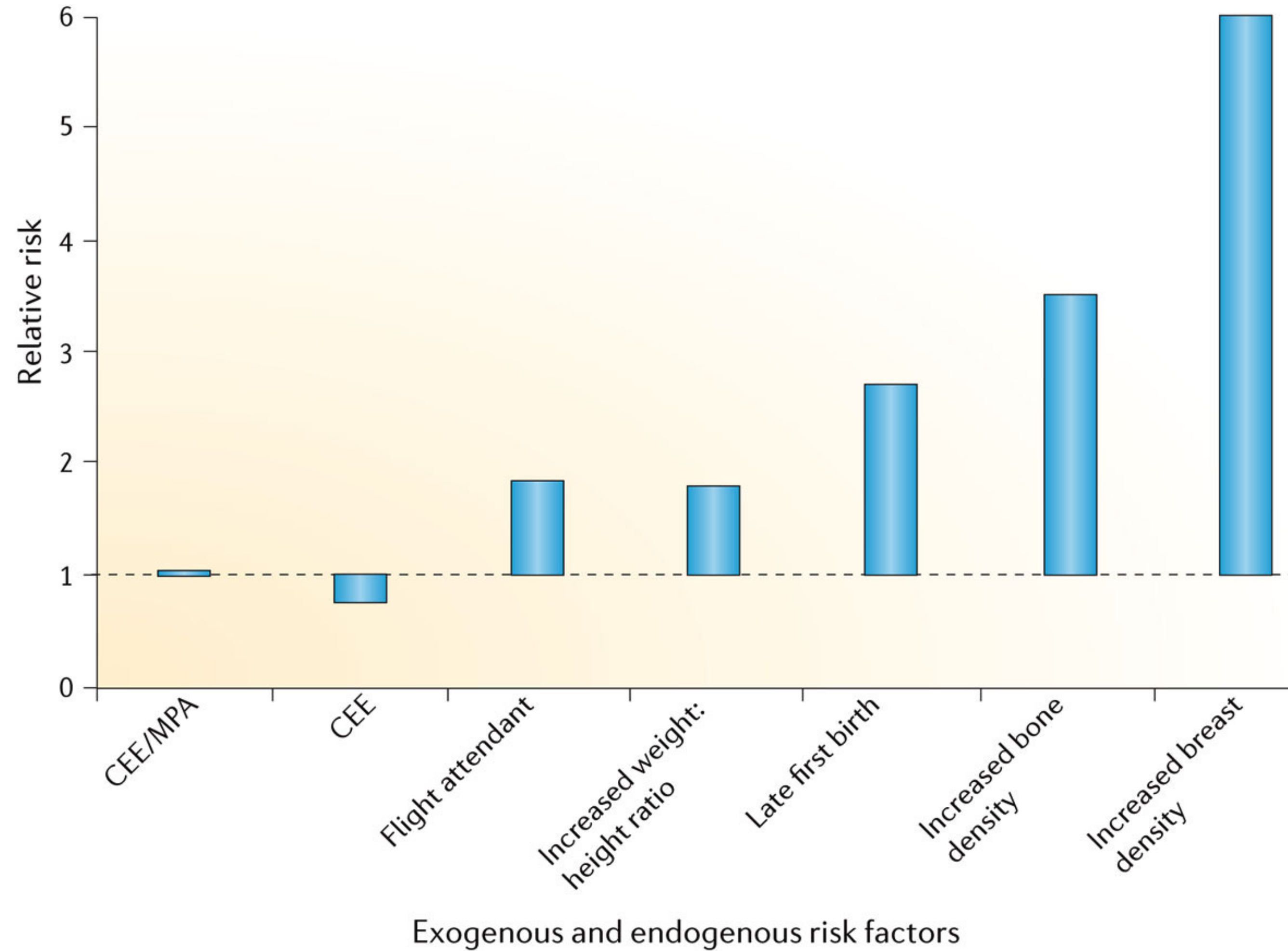
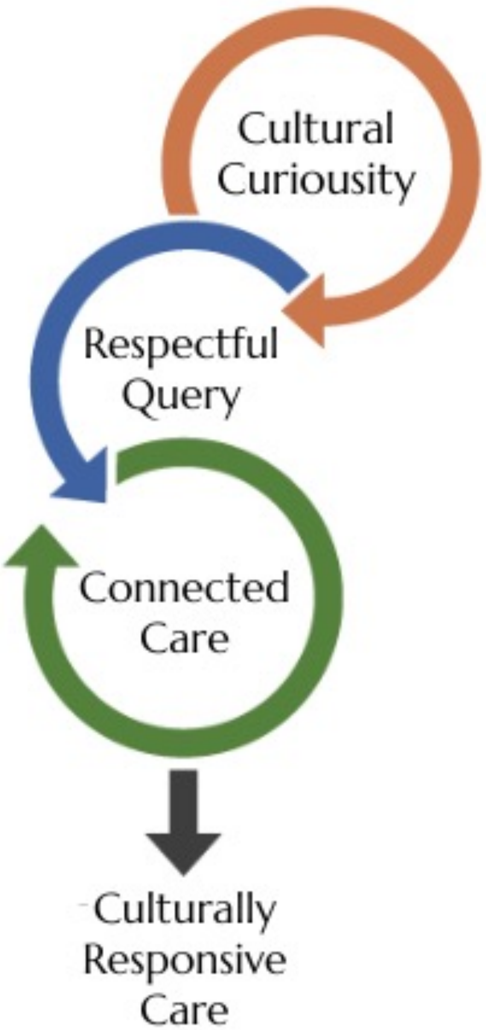
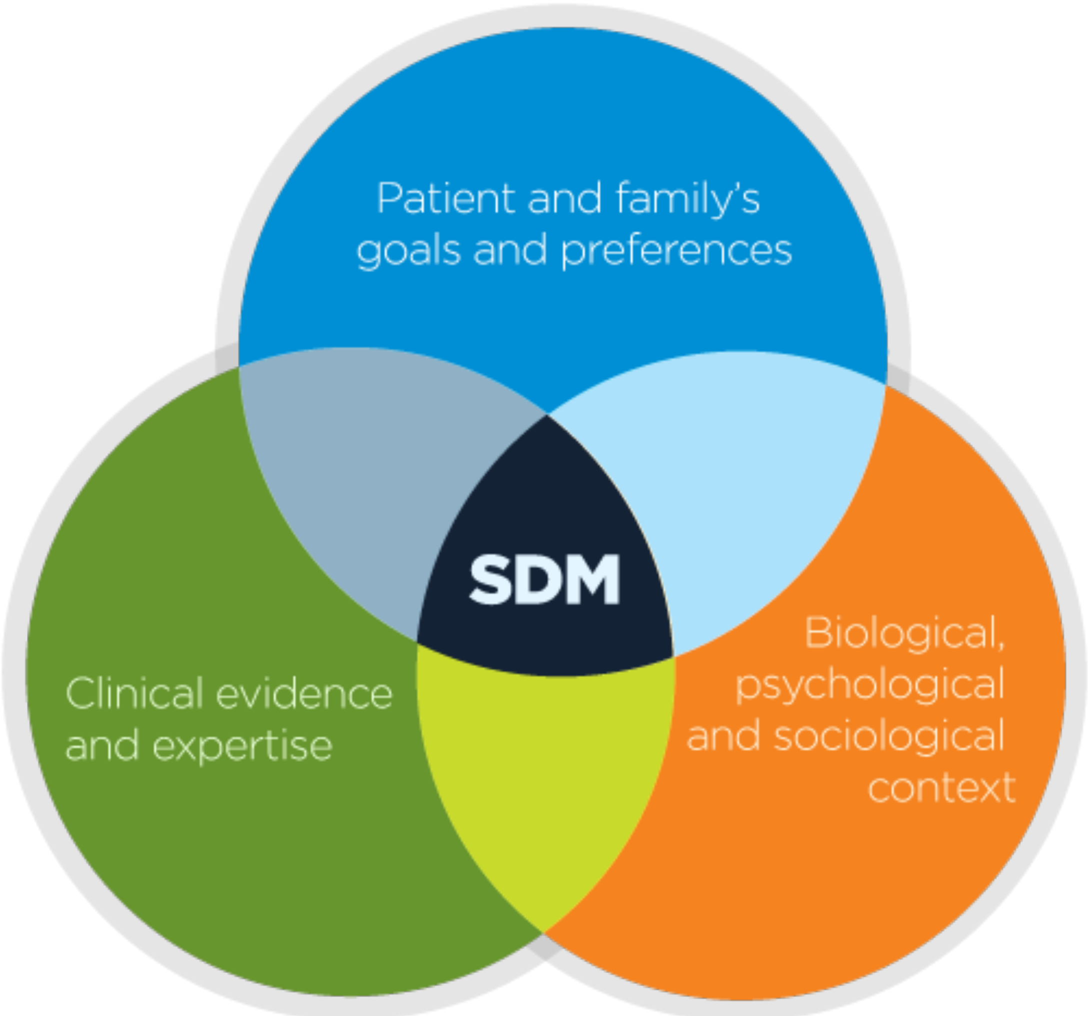
Breast Cancer Risk



Lobo, R. A. (2016) Hormone-replacement therapy: current thinking
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2016.164



Decision-making process



ELISE'S DECISION…

Nonhormone Treatments for Hot Flashes and Night Sweats

Hot flashes and night sweats, also called vasomotor symptoms (VMS), are feelings of warmth that can be associated with flushing and sweating. They are very common during menopause, occurring in up to 80% of women and lasting a mean of 7 to 10 years. Vasomotor symptoms may also contribute to sleep and mood issues that can negatively affect quality of life.

Women may choose to use hormone therapy (HT) to treat their VMS, but for those who cannot because of medical conditions (such as breast cancer or a history of heart attack, stroke, or blood clot) or for those who choose not to use HT, there are nonhormone options available to provide relief.

Nonhormone treatment options

Recommended

The treatments with research showing that they are effective for treating VMS include

- **Clinical hypnosis:** a mind-body therapy that involves a deeply relaxed state and individualized mental imagery and suggestion. This includes mental imagery for coolness as well as dissociation from VMS, along with a focus on future positive imagery.
- **Cognitive-behavioral therapy:** a form of biofeedback that includes education about the physiology of VMS as well as how thoughts and emotions may affect physical sensations, training in relaxation and paced breathing, identifying and challenging negative beliefs about VMS, monitoring and modifying triggers of VMS, and relaxation exercises.
- **Fezolinetant:** a neurokinin B antagonist that works in the brain to reduce VMS and is FDA approved for VMS management.
- **Gabapentin:** a drug used to treat seizures or nerve pain but has also been found to reduce VMS in multiple studies. Bedtime dosing may be a good choice for women with sleep issues because drowsiness is an adverse event. It can also help with pain and migraine.
- **Oxybutynin:** an antimuscarinic, anticholinergic therapy that is used for the treatment of overactive bladder and urinary urge incontinence and has been found to reduce VMS at low doses. Thus, it could be used to treat both urinary symptoms and VMS.
- **SSRIs/SNRIs:** multiple formulations have been studied and found to be beneficial for VMS management, including paroxetine, escitalopram, citalopram, venlafaxine, and desvenlafaxine, often at lower doses than those used for treatment of anxiety or depression. Only paroxetine mesylate 7.5 mg daily is FDA approved for VMS management specifically. These treatments may be ideal for women with coexisting mood or anxiety symptoms.
- **Stellate ganglion block:** a widely used treatment for pain, including for migraine and complex regional pain syndrome, that involves an injection of an anesthetic agent by a pain specialist targeting a bundle of sympathetic nerves in the front of your neck. It can be considered in select women but is associated with potential risks.
- **Weight loss:** weight loss has been shown to reduce VMS.

Not recommended

Deciding About Hormone Therapy Use

Many women experience hot flashes, vaginal dryness, and other physical changes with menopause. For some women, the symptoms are mild and do not require any treatment. For others, symptoms are moderate or severe and interfere with daily activities. Hot flashes improve with time, but some women have bothersome hot flashes for many years. Menopause symptoms often improve with lifestyle changes and nonprescription remedies, but prescription therapies also are available, if needed. Government-approved treatments for bothersome hot flashes include hormone therapy (HT) containing estrogen, as well as a nonhormone medication (paroxetine).

Hormone therapy involves taking estrogen in doses high enough to raise the level of estrogen in your blood in order to treat hot flashes and other symptoms. Because estrogen stimulates the lining of the uterus, women with a uterus need to take an additional hormone, progestogen, to protect the uterus. Women without a uterus just take estrogen. If you are bothered only by vaginal dryness, you can use very low doses of estrogen placed directly into the vagina. These low doses generally do not raise blood estrogen levels above postmenopause levels and do not treat hot flashes. You do not need to take a progestogen when using only low doses of estrogen in the vagina. (The *MenoNote* "Vaginal Dryness" covers this topic in detail.)

Every woman is different, and you will decide about whether to use HT based on the severity of your symptoms, your personal and family health history, and your own beliefs about menopause treatments. Your healthcare professional will be able to help you with your decision.

Potential benefits

Hormone therapy is one of the most effective treatments available for bothersome hot flashes and night sweats. If hot flashes and night sweats are disrupting your daily activities and sleep, HT may improve sleep and fatigue, mood, ability to concentrate, and overall quality of life. Treatment of bothersome hot flashes and night sweats is the principal reason women use HT. Hormone therapy also treats vaginal dryness and painful sex associated with menopause. Hormone therapy keeps your bones strong by preserving bone density and decreasing your risk of osteoporosis and fractures. If preserving bone density is your only concern, and you do not have bothersome hot flashes, other treatments may be recommended instead of HT.

Potential risks

As with all medications, HT is associated with some potential risks. For healthy women with bothersome hot flashes aged younger than 60 years or within 10 years of menopause, the benefits of HT generally outweigh the risks. Hormone therapy might slightly increase your risk of stroke or blood clots in the legs or lungs (especially if taken in pill form). If started in women aged older than 65 years, HT might increase the risk of dementia. If you have a uterus and take estrogen with progestogen, there is no increased risk of cancer of the uterus. Hormone therapy (combined estrogen and progestogen) might slightly increase your risk of breast cancer if used for more than 4 to 5 years. Using estrogen alone (for women without a uterus) does not increase breast cancer risk at 7 years but may increase risk if used for a longer time.

Some studies suggest that HT might be good for your heart if you start before age 60 or within 10 years of menopause. However, if you start HT further from menopause or after age 60, HT might slightly increase your risk of heart disease. Although there are risks associated with taking HT, they are not common, and most go away after you stop treatment.