Menopause – The Heat Goes On!

(21 years after the publication of the Principal Results from the WHI.)

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Learning Objectives

1. Develop an approach to evaluate the patient experiencing vasomotor instability.
2. Identify the options for treatment of the patient with vasomotor instability.
3. Provide patient education on the potential risks and benefits of hormone therapy (HT) and non-hormone therapy.

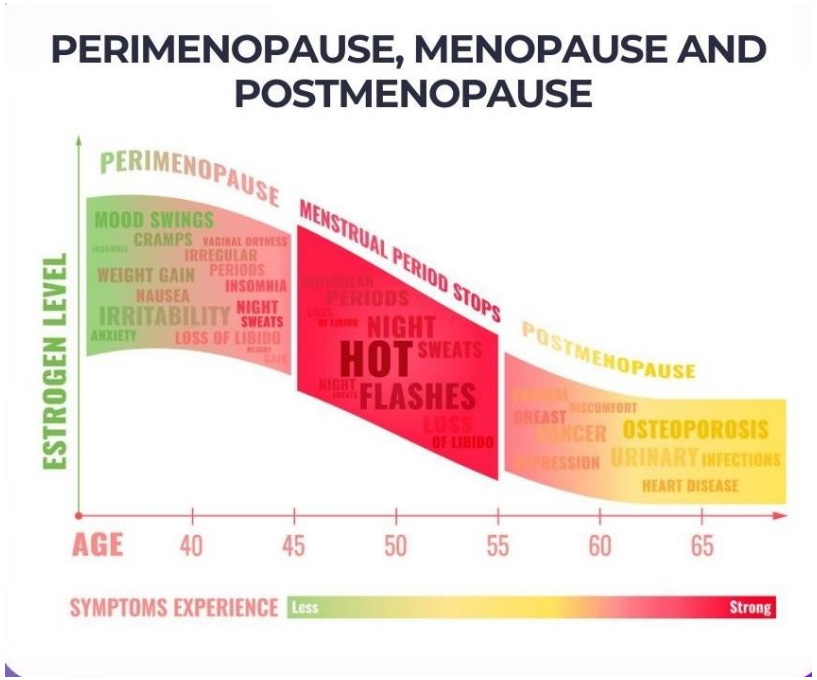
Question

Which of the following hormonal changes is indicative of menopause diagnosis in a 52-year-old woman presenting with irregular menstrual cycles and hot flashes?

1. Increase in estradiol production
2. Decrease in luteinizing hormone (LH Levels)
3. Surge in progesterone levels
4. Rise in follicle-stimulating hormone (FSH) levels

Defined and Diagnosed

Clinical Diagnosis



Menopause –

- The time that marks the end of menstrual cycles
- Confirmed after 1 year of no periods
- Median age 51.3 (Range 45-55)

Three stages -

- Perimenopause (Climacteric; **Menopausal Transition**)
  - Hormonal changes and clinical symptoms occur over a period leading up to and immediately following menopause. Ovaries begin to atrophy, leading to a decline in E/P
- Menopause
- Postmenopause

No indication for FSH.

- The diagnosis of perimenopause and menopause does not require laboratory testing in the majority of cases.
- (consistently elevated to 30 mIU/mL or higher)

Do not routinely test FSH levels to establish menopausal status

- ✓ **Conditions which can be diagnosed without testing serum FSH in otherwise healthy women > 45 years of age with menopause symptoms.**
  - Perimenopause based on vasomotor symptoms and irregular periods
  - Menopause in women who have not had a period for greater than 12 months and are not using hormonal contraception
  - Menopause based on symptoms in women without a uterus
- ✓ **Do not use these laboratory tests and imaging to diagnose perimenopause in women > 45 years.**
  - Anti Mullerian hormone
  - Inhibin A & B
  - Estradiol
  - Antral follicle count
  - Ovarian volume
- ✓ **Do not use FSH if a woman is on the combined estrogen or progestogen contraception or using high dose progestogen.**

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ConsumerReportsHealth
AMERICAN ACADEMY OF OPHTHALMOLOGY
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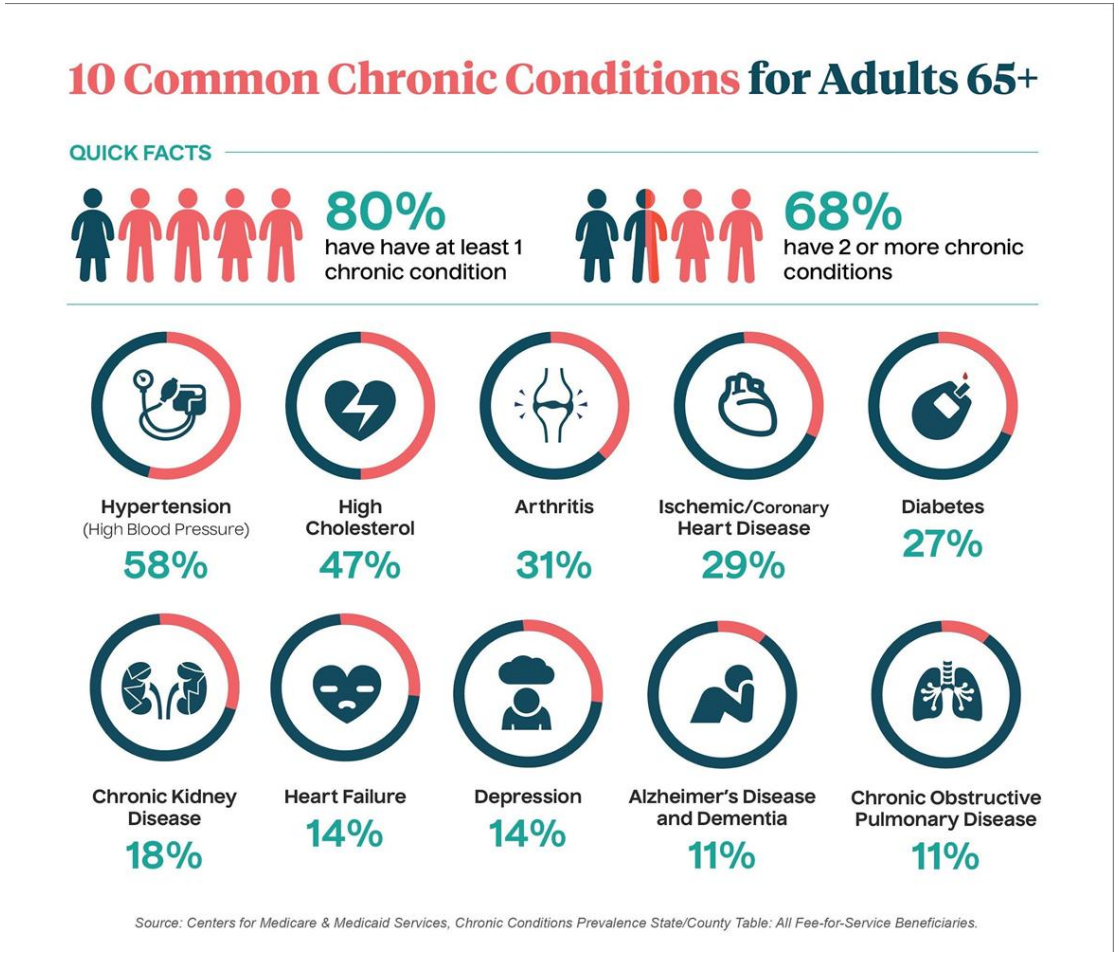
Consider using an FSH test to diagnose menopause ONLY in the following situations:

- **Women 40 – 45 years** with menopause symptoms including a change in their menstrual cycle
- **Women < 40 years** where a premature menopause is suspected

Chronic Disease and Aging

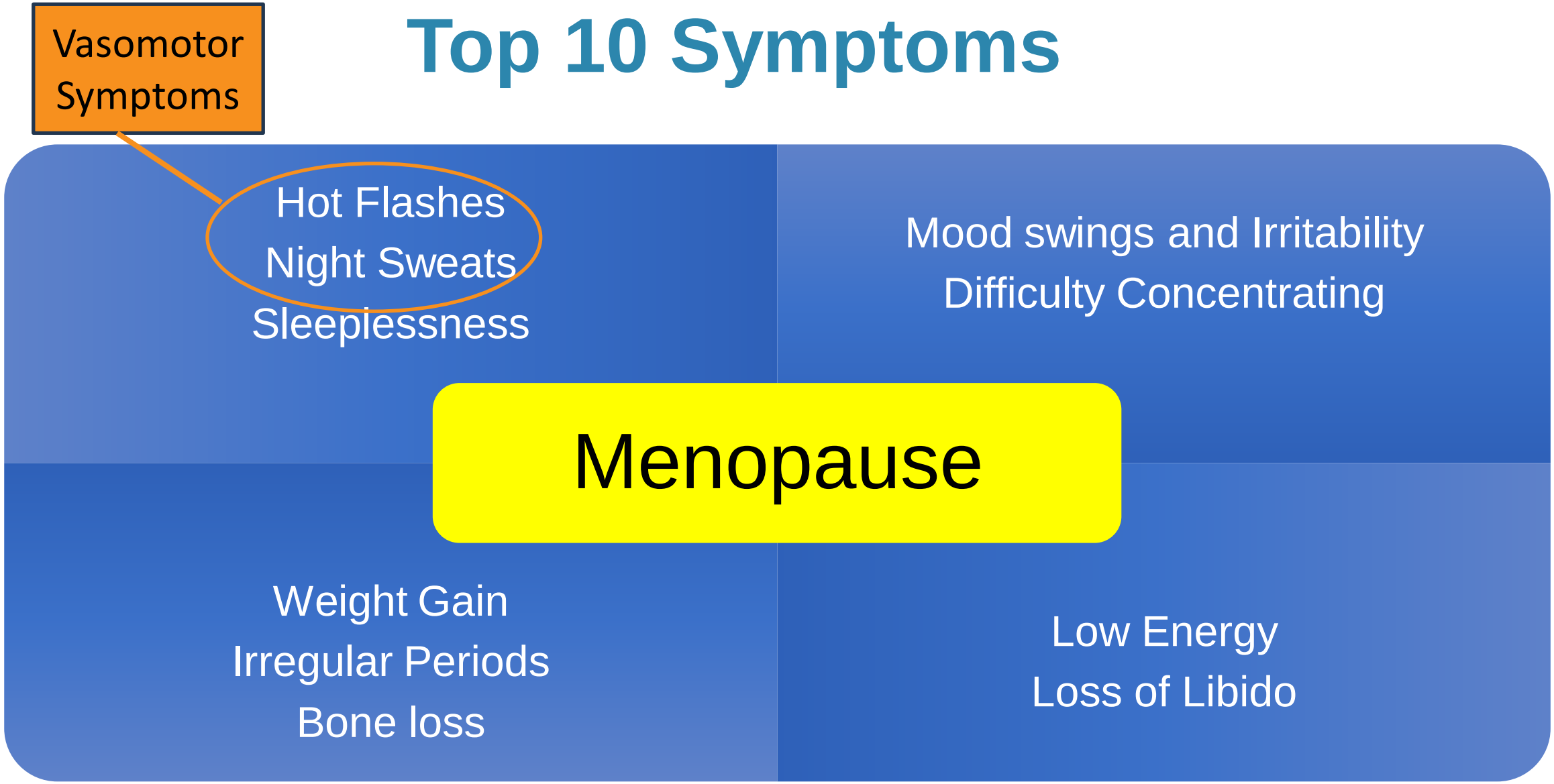
- Prevalence and incidence of most chronic conditions increase with age.
- The excess risk for these conditions that can be attributed to menopause ALONE is uncertain.




Symptoms


MENOPAUSE

Top 10 Symptoms



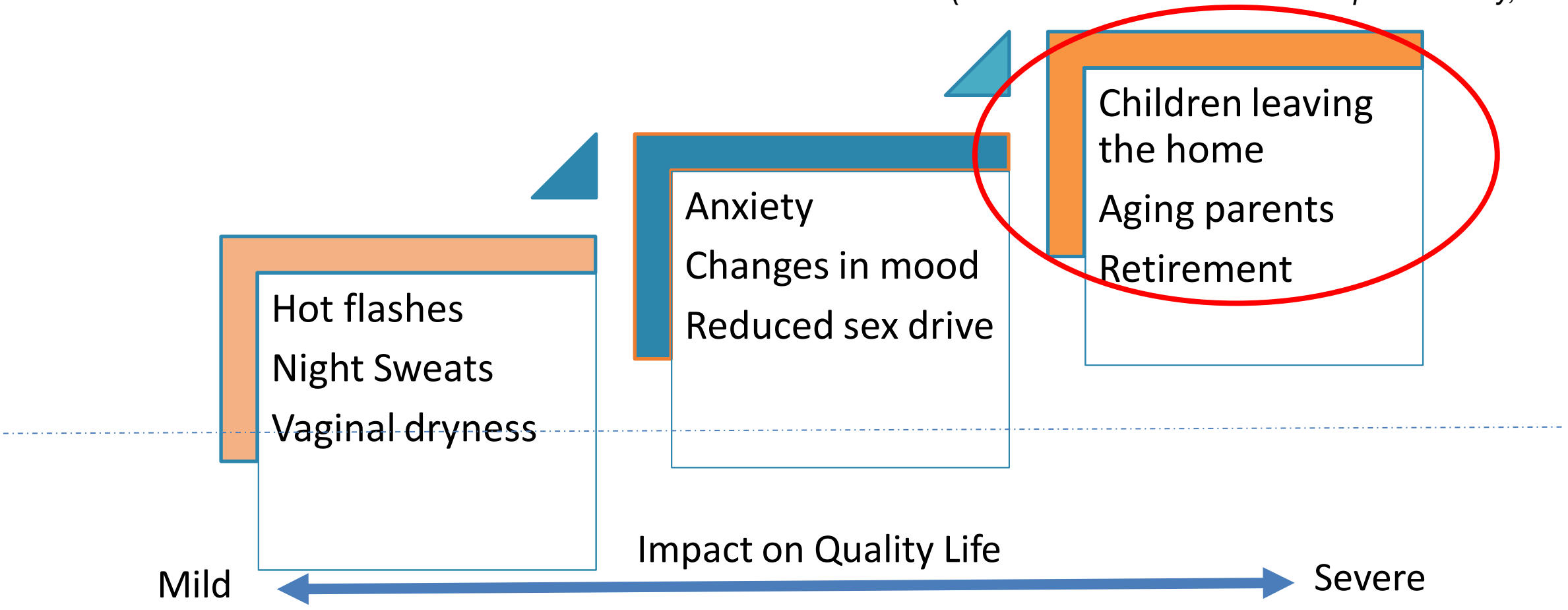
Symptoms

- **Cognitive Changes***
  - Substantial biologic evidence supports the importance of estrogen to cognitive function.
  - Decline in cognitive function was not observed in the SWAN study, but increases in anxiety and depression had independent, unfavorable effects on cognitive performance.
- **Joint Pain**
  - Unclear if the pain is related to estrogen deficiency or a rheumatologic disorder
- **Breast pain** – common in early transition and diminishes in late transition
  - Probably due to the fluctuations in serum estradiol concentrations
- **Menstrual migraines** (if you have them historically)
  - Worsen in frequency and intensity during the menopausal transition

**Greendale GA, Derby CA, Maki PM. Perimenopause and cognition. Obstet Gynecol Clin North Am 2011; 38:519.*

- **Only about 6%** of women receive counseling and treatment for the consequences of menopause.
- Research of both primary care physicians and gynecologists found that the discussion of menopause is initiated **by the patient** 91% of the time.
- Yale U study of insurance claims revealed that although 60% of women suffering from significant symptoms of menopause seek medical attention, three-quarters of them are NOT being treated.
- 2021 Survey – 73% of respondents experiencing menopause symptoms were NOT treating them.

(Bonafide Health "State of Menopause Study," 2021)

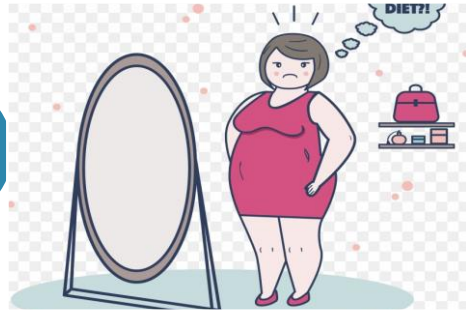


It’s Very Personal

Menopause is not just a physiological experience. It also has deep cultural meaning…

Getting “old.” This can trigger many feelings. Some derive meaning and wisdom from menopause, while others may experience depression

Cultural values and assumptions about menopause can affect **how a woman feels** about this natural body process. The way she reacts to this may affect her relationships and lifestyle. e.g., a woman who believes menopausal weight gain is inevitable might stop exercising



Conversely, a woman who takes joy in the wisdom she believes comes with age, **might feel better about herself**. She may, therefore, feel **more adventurous** or sexual than ever before

Vasomotor Symptoms

- After menopause, up to 85% of women experience hot flashes as a result of vasomotor instability

- Probably hypothalamic origin
  - *Menopause*
  - Thyroid disease
  - Panic or anxiety disorder
  - Insulinoma
  - Autoimmune disorders
  - Pheochromocytoma
  - Carcinoid syndrome
  - Tamoxifen and raloxifene

Vasomotor Symptoms

Description

- Sudden sensation of extreme heat in the upper body, particularly the face, neck, and chest.
- Typically last 1-5 minutes
  - Perspiration, flushing, chills, clamminess, anxiety, and, on occasion, heart palpitations
- May interfere with sleep and cause chronic sleep disruption.

Influences on Hot Flashes

- **Cultural**
  - More prevalent in African American and Latin American women than in white women
  - Less common in Chinese and Japanese women
- **Other variables associated with increased reporting of hot flashes**
  - **Cigarette smoking**
  - *Potential risk factors with "inconsistent" association*
    - *Maternal history*
    - *Early age of menarche and menopause onset*
    - *History of irregular menses*
    - *Higher BMI*
    - *Alcohol use*
    - *Hot/humid weather*

Sleep Disturbance

- Hot flashes are more common at night
- Can occur in the absence of hot flashes
  - Early menopausal transition 32-40%
  - Late menopausal transition 38-46%
- Anxiety and depression symptoms may contribute
  - Subjective sleep disturbance
- Take-Home: peri- or postmenopausal women who report sleep disturbances, treating the vasomotor symptoms may decrease sleep disturbances, *but this may not resolve all sleep problems, as there are many other things that can disturb sleep, such as* ***primary sleep disorders, anxiety, and depression***

Vasomotor Symptoms

Description

- Sudden sensation of extreme heat in the upper body, particularly the face, neck, and chest
- Typically last 1-5 minutes
  - Perspiration, flushing, chills, clamminess, anxiety and on occasion, heart palpitations
- May interfere with sleep and cause chronic sleep disruption
- Historically estimated to persist 6 months to 2 years

…and they last…

- Study of Women's Health Across the Nation (SWAN)
  - Longitudinal observational study of the menopause transition
- 1449 participants
  - Women who were married or partnered, better educated, less financially stressed, and had greater social support had shorter duration of symptoms.
  - Physical activity and alcohol intake did not affect symptom duration

Avis NE et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015 Feb 16; [e-pub].(http://dx.doi.org/10.1001/jamainternmed.2014.8063)

RESULTS

Group	Mean Duration (years)
1449 with frequent vasomotor symptoms (VMS) (occurring on ≥6 of the preceding 14 days)	7.4
Subset (881) with identifiable final menstrual period (FMP), early onset of symptoms (i.e., during pre- or perimenopause) • Longer overall VMS • Post FMP persistence	 11.8 9.4
Post menopausal onset of VMS	3.4
Persistence by race and ethnicity: Black Hispanic Non-Hispanic white Chinese Japanese	 10.1 8.9 6.5 5.4 4.8

What can we say?

- Bothersome VMS may persist for more than “a few” years
- New twist to the guidelines for HT “lowest effective dose, shortest duration”
  - Women may need a range of options for a decade or more
    - Hormonal and nonhormonal therapies
    - Behavioral and lifestyle adaptations
  - SWAN results help us individualize counseling as we educate women about the risks and benefits of each treatment strategy

Avis NE et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015 Feb 16; [e-pub].(http://dx.doi.org/10.1001/jamainternmed.2014.8063)

What can we say?

- Hot flashes are **more than just a nuisance**
  - Financial consequences of untreated VMS on women, workplace, society
- Deciding whether to seek treatment for VMS is a **personal decision**
- Some women may find VMS only irritating; others may avoid treatment because they lack awareness of the range of remedies or are concerned about its safety and side effects.
- Challenge for clinicians: provide an objective assessment of the efficacy, risks, and benefits of available treatments versus no treatment

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 person-years.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

Author Information and Financial Disclosures appear at the end of this article.

For editorial comment see p 366.

- 18 years of follow-up data

- 21 years since the publication of this primary prevention trial
- *suggest that the results from the observational studies were overstated and the positive findings were a result of confounding biases*

65% of women will not consider using HRTs to treat their menopause symptoms.
(Bonafide Health "State of Menopause Study," 2021)

TREATMENT REGIMEN

Vasomotor Symptoms

Estrogen-containing HT	Nonhormonal medications	Nonpharmacologic
• Uterus – E+P • No Uterus – E alone	• SSRIs • SNRIs • Gabapentin	• CBT* • Hypnosis*

*effective for short-term reduction of vasomotor, symptoms and associated sleep disturbances

Data are lacking to support the effectiveness of other nonpharmacologic treatments such as herbal or botanical supplements, exercise, and acupuncture.

Hormonal Medications

Effective in Treating VMS

- Systemic HT with estrogen alone or in combination with progestin, is THE MOST EFFECTIVE therapy for vasomotor symptoms related to menopause [SOR: A]
  - Estrogen: oral, transdermal, and vaginal forms
  - Progesterone-based hormone therapy: oral tablets, transdermal patches (combined with estrogen), levonorgestrel-releasing IUS (used off-label for endometrial protection), vaginal inserts (dehydroepiandrosterone[DHEA])
- Data DO NOT SUPPORT the use of the following:
  - Progesterone-only medications
  - Testosterone
  - Compounded bioidentical hormones

Formulations and Shared-Decision Making

- **Oral** and **transdermal** estrogen formulations
  - Designed for SYSTEMIC delivery
  - VMS
    - Generally preferred
    - Similarly effective compared with placebo
    - Observational studies suggest transdermal estrogen-containing HT does **NOT** increase the risk of VTE compared with oral estrogen
- **Vaginal** estrogen formulations
  - Minimally absorbed
    - **Exception: high-dose estradiol vaginal ring (Femring),** FDA-approved for vasomotor **and** vaginal symptoms

Estrogen-Only Therapies for Vasomotor Symptoms of Natural Menopause

Medication	Dosage (mg)[1]	FDA- approved indications	Bioidentical	Cost
ORAL **Estrace** (estradiol)	0.5, 1, 2 daily for 21 day, then seven days off[2]	Vasomotor symptoms, vulvovaginal atrophy, osteoporosis prevention	Yes	$125 (21 tablets)
Menest (esterified estrogen)	0.3, 0.625, 1.25, 2.5 daily for 21 days, then seven days off[2]	Vasomotor symptoms, vulvovaginal atrophy	No	$65 (21 tablets)
Premarin (conjugated equine estrogen)	0.3, 0.45, 0.625, 0.9, 1.25 (daily for 25 days, then five days off)[2]	Vasomotor symptoms, vulvovaginal atrophy, osteoporosis prevention *(0.3 to 0.625 mg only)*	No	$165 (25 tablets)

[1]Dosing should be individually adjusted to the lowest effective dose for the shortest duration.

[2]Add a progestin for the final 10 to 14 days of a 28- to 30-day cycle if the patient has an intact uterus.

Estrogen-Only Therapies for Vasomotor Symptoms of Natural Menopause

Medication	Dosage (mg)[1]	FDA- approved indications	Bio-identical	Cost
Transdermal patch (estradiol) **Climara**	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 (mg delivered per day) Apply one patch/week[3]	Vasomotor symptoms, vulvovaginal atrophy, osteoporosis prevention	Yes	$65 for four 0.0375-mg patches
Minivelle	0.025, 0.0375, 0.05, 0.075, 0.1 (mg delivered per day) Apply one patch per week[3,4]	Vasomotor symptoms, vulvovaginal atrophy, osteoporosis prevention	Yes	$245 for eight 0.025-mg patches
Vivelle-Dot	0.025, 0.0375, 0.05, 0.075, 0.1 (mg delivered per day) Apply one patch **twice** per week[3,4]	Vasomotor symptoms, vulvovaginal atrophy, osteoporosis prevention	Yes	$35 for eight patches

[3] Consider adding a progesterone-based therapy for patients with an intact uterus

[4] Consider using for three weeks, then one week off, for patients with an intact uterus.

Estrogen-Only Therapies for Vasomotor Symptoms of Natural Menopause

Medication	Dosage (mg)[1]	FDA- approved indications	Bio-identical	Cost
Transdermal gel (estradiol) **Divigel 0.1%**	0.25, 0.5, 0.75, 1, 1.25(mg per packet) Apply one packet to upper thigh daily[3]	Vasomotor symptoms	Yes	$185
Elestrin 0.06%	0.52(mg per single pump) Apply one pump to upper arm or shoulder daily[3]	Vasomotor symptoms	Yes	$260 for one package of two gel pumps
Estrogel 0.06%	0.75(mg per single pump) Apply one pump to entire arm (wrist to shoulder) daily[3]	Vasomotor symptoms, vulvovaginal atrophy (NOT preferred if this is the only indication)	Yes	$130

[3] Consider adding a progesterone-based therapy for patients with an intact uterus

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Estrogen-Only Therapies for Vasomotor Symptoms of Natural Menopause

Medication	Dosage (mg)[1]	FDA- approved indications	Bio-identical	Cost
Transdermal spray (estradiol) Evamist	1.53(mg per single spray) Apply one spray to inner forearm once daily (maximum of three sprays per day) and do not rub in; wait one hour before getting the area wet[3]	Vasomotor symptoms	Yes	$90
Vaginal ring (estradiol) Femring	0.05, 0.1(mg per ring) Insert one ring into vagina every three months[3]	Vasomotor symptoms (NOT preferred if this is the only indication)	Yes	$260 for one package of two gel pumps

[3] Consider adding a progesterone-based therapy for patients with an intact uterus

[4] Consider using for three weeks, then one week off, for patients with an intact uterus.

Combination Estrogen/Progesterone Hormone Therapy and Alternatives for Vasomotor Symptoms of Natural Menopause

Medication	Dosage (mg)[1]	Brand (generic) 1m
Activella (amabelz, mimvey; estradiol/norethindrone acetate)	0.5/0.1, 1/0.5 po qD	$300 ($30)
Angeliq (estradiol/drospirenone)	0.5/0.25, 1/0.5 po qD	$200 (--)
Bijuva (estradiol/progesterone)	1/100 po qD	$240(--)
Climara Pro (estradiol/levonorgestrel)	Transdermal patch q week	$240 (--)
Combipatch (estradiol/norethindrone acetate)	0.05/0.14, 0.05/0.25 Transdermal patch 2x/w	$250 (--)
Fyavolv (ethinyl estradiol/norethindrone acetate)	0.0025/0.5 po qD	--($20)
Jinteli (ethinyl estradiol/norethindrone acetate)	0.005/1 po qD	$30 (--)
Prefest (estradiol/norgestimate)	1/0.09 po qD (estrogen alone for three days followed by estrogen/progestogen for three days, then repeat)	$215 (--)

Combination Estrogen/Progesterone Hormone Therapy and Alternatives for Vasomotor Symptoms of Natural Menopause

Medication	Dosage (mg)[1]	Brand (generic) 1m
Premphase (conjugated estrogen/medroxyprogesterone)	0.625/5 po q D (estrogen alone for days 1 through 14, then add progestogen for days 15 through 28)	$230 (--)
Prempro (conjugated estrogen/medroxyprogesterone)	0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5.0 po qD	$225 (--)
Levonorgestrel-releasing intrauterine system (off-label use)	52 mg; initially releases 21 mcg/day; declines to 11 mcg/day after five years Inserted per manufacturer protocol - up to 5 years for heavy menstrual bleeding, 8 years for contraception	$1,170/device
Prometrium (micronized progesterone)	200 po q D for 12 days/month	$710 ($10)
Provera (medroxyprogesterone)	2.5, 5, 10 po once daily for continuous use, or 10to 14 days per month (starting day 15 through 19 if cyclic estrogen use)	$90 ($10)

Conjugated Estrogens/Bazedoxifene (Duavee)

Dosage: 0.45mg/20mg tablet PO daily

- Combines conjugated estrogen with bazedoxifene, a selective estrogen receptor modulator
- Bazedoxifene stimulates estrogen receptors in bone and has antagonistic effects in the breast and uterus
  - improves bone mineral density (lumbar spine and hip; effect on fractures not known
  - lowers the risk of uterine cancer due to SERM's varying mechanism of action in tissues
- Labeled for the treatment of **moderate to severe vasomotor symptoms** associated with menopause **and prevention of postmenopausal osteoporosis**.
  - Will maintain bone mineral density in the lumbar spine and hip, but its **effect on fractures is not known.**
- May be better tolerated than conjugated estrogens/medroxyprogesterone
- Precludes the need for endometrial protection with progesterone
- **Cost $210/month**

Estrogen Alone or Combined with Progestin

- Cochrane meta-analysis, 24 RCTs; 3329 participants
  - 75% reduction in weekly hot flush frequency
  - 87% reduction in symptom severity
- Postmenopausal Estrogen/Progestin Interventions trial; 875 women
  - Significant reduction in self-reported vasomotor symptoms
    - Estrogen alone – 58%
    - Estrogen plus progesterone – 62%

MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD002978. DOI: Greendale GA et al., Obstet Gynecol 1998:92:982-8.

Bioidentical Synthetic Hormones

Plant derived, chemically similar or structurally identical to those produced by the body

- FDA Approved – but **NO** evidence to suggest greater effectiveness over standard estrogens
  - Estradiol
  - Estrone
  - Micronized progesterone
- Non-FDA regulated
  - Compounded preparations; purity, potency, and quality are concern
  - Overdosage and underdosage possible because of variable bioactivity and bioavailability

NAMS Position Statement

- Compounded bioidentical HT presents **safety concerns** such as minimal government regulation and monitoring, overdosing or underdosing, presence of impurities or lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks.
- Salivary hormone testing to determine dosing is **unreliable**.
- **Prescribers of compounded bioidentical HT** should document the medical indication for compounded HT over government-approved therapies, such as allergy or the need for dosing or a formulation not available in FDA-approved products

Contraindications to Hormone Therapy

- Unexplained vaginal bleeding
- History of Stroke
- Active estrogen-sensitive cancer (e.g., breast, endometrial); history of estrogen-sensitive cancer is a relative contraindication
- History of thromboembolism
- Personal history or strong family history of thromboembolic disorders
- History of coronary artery disease
- Active Liver Disease

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions *2024*

- The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women.
  Grade: D Recommendation
- The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women *who have had a hysterectomy*.
  Grade: D Recommendation

Hormone Therapy

*Women's Health Initiative Study**

Increases the risk

- Breast cancer (26%)§
- CVA (41%)
- MI (29%)§
- Venous thromboembolic events*§

Proven benefits

- Reduced risk of osteoporosis and related fractures (34%)
- Decreased colon cancer risk (37%)
- Improvement of vasomotor symptoms

Previous thromboembolic disease is the only **ABSOLUTE contraindication to HT. Heart disease, breast cancer , and endometrial cancer are **RELATIVE** contraindications.*

*§ **Among women receiving estrogen ONLY, there was increased risk of thromboembolic events, but NOT an increased risk of CV events or breast cancer diagnosis**.*

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

Risks

** -Women aged 65 years and older*

(Majority of trials – conjugated equine estrogen alone or in combination with medroxyprogesterone acetate)

Estimated Event Rate Difference Associated with Combined Estrogen and Progestin Use vs. Placebo in Postmenopausal Women	
Outcome	**Absolute event rate difference per 10,000 woman-years**
Harms	
Breast Cancer (invasive)	9 (diagnosed) (5-7 years of treatment; NO increase in breast cancer deaths)
Coronary Heart Disease	8
Dementia (probable)*	22
Gallbladder disease	21
Stroke	9
Venous thromboembolism	21
Urinary incontinence	876 (Systemic estrogen increases the risk of stress, urge, mixed Incontinence 2-3x; if already have incontinence, can make it worse.)

WHI – 18 years of Follow-Up

- **Breast Cancer**
  - (-) Uterus (hysterectomy) - use of conjuga
    alone significantly decreased the over
  - (+) Uterus - use of combination conjugated
    estrogen/medroxyprogesterone was asso
    increased risk of breast cancer but **NOT**
    mortality

…and I have a uterus!

- Adding a progestin to estrogen therapy in those with a uterus is important to reduce endometrial cancer risk
- Safest form of progesterone and optimal dosing schedule?
  - Daily vs. Cyclic (dosing 10-14 days/month)

Progesterone

- **WHI**
  - included only combination hormone therapy with **medroxyprogesterone** used daily orally
- **Micronized progesterone**
  - May be less thrombogenic than other progestins
  - May be associated with higher risk of endometrial cancer

- **Current Guidelines:**
  - Micronized progesterone
    - 200 mg PO daily 12-14 days/month
  - Observational studies
    - Have suggested that the risk of breast cancer may be less with the use of micronized progesterone compared with synthetic progestogens, but the bioavailability of oral and transdermal progesterone is poor.
    - Needs to be adequately dosed for endometrial protection.
    - Improperly formulated or dosed or delivery issues with estrogen plus micronized progesterone combinations have potentially serious health consequences, including increased risk of endometrial neoplasia

WHI – 18 Years of Follow-Up

During 5-7 years of treatment:

- No significant increases in the risk of death from <u>all causes or cardiovascular death</u> among women receiving conjugated estrogen alone **or** conjugated estrogen/MPA during **5-7 years** of treatment

** -Women aged 65 years and older*

Risks

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VTE	21
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Risks

(Majority of trials – conjugated equine estrogen alone or in combination with medroxyprogesterone acetate)

Estimated Event Rate Difference Associated with Combined Estrogen and Progestin Use vs. Placebo in Postmenopausal Women	
Outcome	**Absolute event rate difference per 10,000 woman-years**
Benefits	
Diabetes	-14
All fractures (hip and vertebral)	-44
Colorectal cancer	-6

Gartlehner G, Patel S, Viswanathan M, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: An Evidence Review for the US Preventive Services Task Force. Evidence synthesis no. 155. AHRQ publication no. 15-05227-EF-1. Rockville, Md.: Agency for Healthcare Research and Quality; 2017.

Risks

(Majority of trials – conjugated equine estrogen alone or in combination with medroxyprogesterone acetate)

Estimated Event Rate Difference Associated with Estrogen Use Alone vs. Placebo in Postmenopausal Women	
Outcome	**Absolute event rate difference per 10,000 woman-years**
Harms	
Dementia (probable)*	12
Gallbladder disease	30
Stroke	11
Venous thromboembolism	11
Urinary incontinence	1,261

** -Women aged 65 years and older*

Risks

(Majority of trials – conjugated equine estrogen alone or in combination with medroxyprogesterone acetate)

Estimated Event Rate Difference Associated with Estrogen Use Alone vs. Placebo in Postmenopausal Women	
Outcome	**Absolute event rate difference per 10,000 woman-years**
Benefits	
Breast cancer (invasive)	-7
All fractures (hip and vertebral)	-53
Diabetes	-19

Gartlehner G, Patel S, Viswanathan M, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: An Evidence Review for the US Preventive Services Task Force. Evidence synthesis no. 155. AHRQ publication no. 15-05227-EF-1. Rockville, Md.: Agency for Healthcare Research and Quality; 2017.

Other Approaches to Prevention of Chronic Disease

- **Reduce risk of breast cancer**
  - Tamoxifen or Raloxifene in women at increased risk of breast cancer who do not have contraindications and are at low risk of adverse medication effects
- **Reduce risk of cardiovascular disease**
  - Behavioral counseling to promote a healthful diet and physical activity in adults who are overweight or obese and have additional CV disease risk factors
- **Reduce risk of cardiovascular disease and colorectal cancer**
  - Low-dose aspirin therapy in appropriate candidates

U.S. Preventive Services Task Force. Medications for risk reduction of primary breast cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;159(10):698–708.

U.S. Preventive Services Task Force. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(8):587–593

U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement.Ann Intern Med. 2016;164(12):836–845.

Effectiveness

- **Compared to placebo**
  - Reduces number and severity of hot flashes
  - Decreases pain with intercourse
  - Reduces vaginal dryness
  - Improvements
    - Sexual functioning
    - Menopause-related quality of life
    - Sleep quality

Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/ conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril. 2009;92(3):1025-1038.

NAMS Position Statement

Hormone Therapy:

Remains the **most effective** treatment for *vasomotor symptoms* (VMS) and the *genitourinary syndrome of menopause* (GSM)

Risks differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used

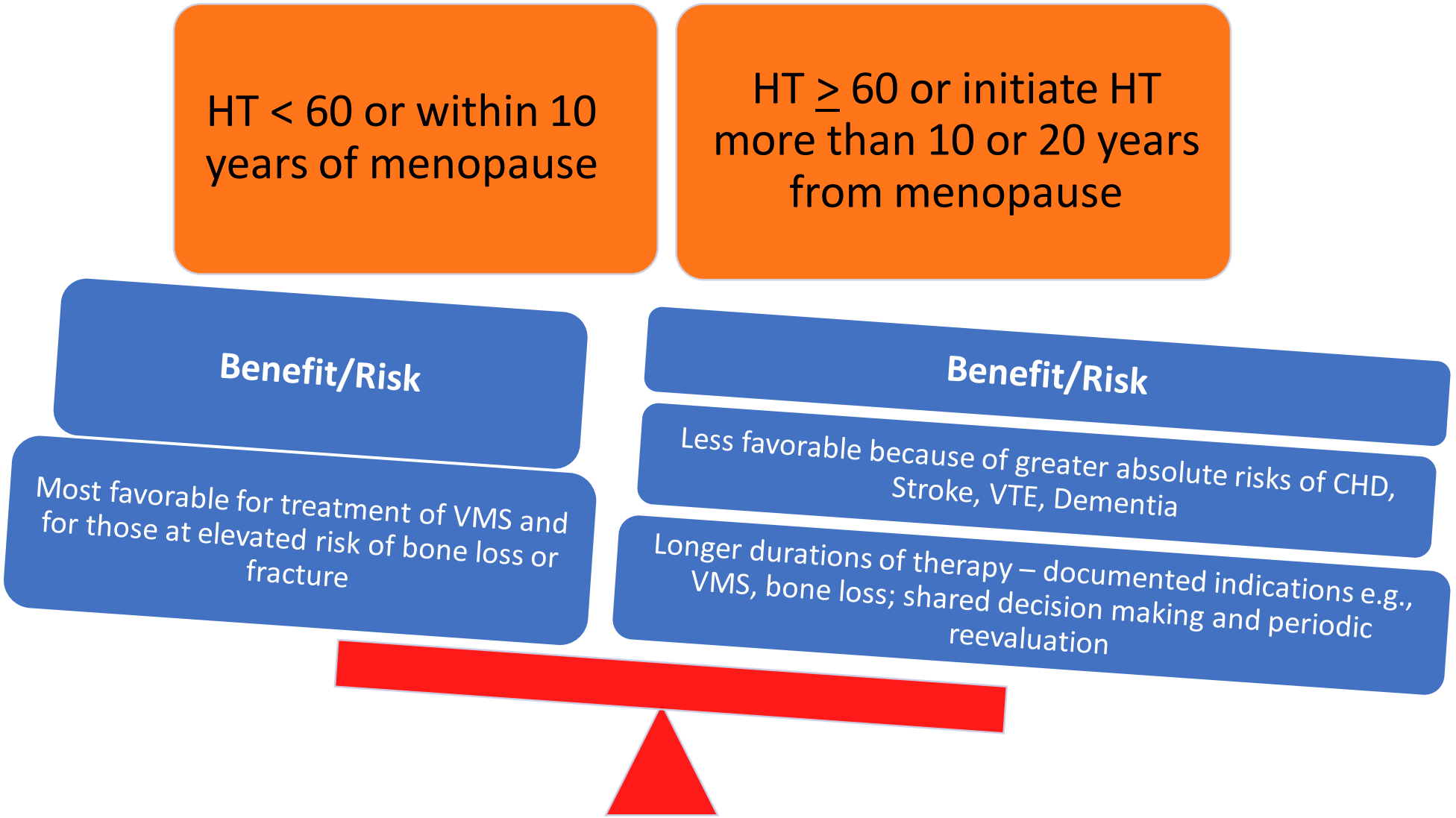
Individualize treatment: type, dose, formulation, route of administration, duration of use.

Use best available evidence to maximize benefits and minimize risks

Periodic reevaluation of benefits/risks of continuing or discontinuing

NAMS - 2022

NAMS Position Statement



Consensus Guidelines

Support offering hormone therapy to women who

- are younger than 60 years AND within 10 years of **symptom onset**
- do not have contraindications to HT
- desire it for the treatment of **moderate to severe vasomotor symptoms**

Common Side effects of Systemic HT

- Nausea
- Bloating
- Weight gain
- Fluid retention
- Breast tenderness
- Uterine bleeding
- Mood alterations

NAMS POSITION STATEMENT

No general rule for stopping at age 65

- HT does **not** need to be routinely discontinued in women aged older than 60 or 65 years
  - Considered for continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis/fracture after appropriate evaluation and counseling of benefits/risks.
  - **Ongoing use** of systemic HT by healthy women who initiated therapy **within** 10 years of menopause onset and without new health risks likely has a safety profile **more favorable** than that for women initiating HT when aged older than 65 years, although limited long-duration data are available
- **Annual reevaluation**, including reviewing comorbidities and periodic trials of lowering or discontinuing HT or changing to potentially safer low-dose transdermal routes, should be considered
- *ACOG recommends AGAINST routine discontinuation of systemic estrogen at age 65 years*

Discontinuation

- HT tapered vs. stopped abruptly – rates of vasomotor symptom recurrence are similar
- Recurrent vasomotor symptoms in approximately 50% of women regardless of age and duration of use.
- Decision to continue HT should be individualized based on each woman’s risk-benefit ratio, regardless of age

Summary

- Primary Goal of HT – Relieve vasomotor symptoms
- Other symptoms associated with perimenopause and menopause that respond to estrogen
  - sleep disturbances
  - depression/anxiety
  - in some cases, joint aches and pains
    - In the WHI, women with joint pain or stiffness at baseline were more likely to get relief with either combined estrogen-progestin therapy (EPT) or unopposed estrogen therapy (ET)

Nonhormonal Treatments for Vasomotor Symptoms

Medication	Dosage(mg)	Generic (Brand) 1m
Selective serotonin reuptake inhibitors Citalopram	10 to 20 po once daily	$5 (--)
Escitalopram	10 to 20 po once daily	$5 (--)
Paroxetine	10 to 25 po once daily	$5 (--)
Paroxetine mesylate (Brisdelle)†	7.5 po once daily hS	$5 ($230)
Serotonin-norepinephrine reuptake inhibitors Desvenlafxine (Pristiq)	100-150 po once daily	$10 ($415)
Venlafaxine	37.5-150 po once daily	$5 (--)
Alternatives Clonidine	0.1 po once daily	$10 (--)
Gabapentin	300-2400 po daily, in divided doses	$5 (--)
Oxybutynin	2.5-5 po twice daily	$15 (--) for 60 5-mg tablets
Pregabalin(Lyrica)	150-300 po daily, in divided doses	$15 ($600) for 60 150-mg capsules

†—*This is the only selective serotonin reuptake inhibitor approved by the U.S. Food and Drug Administration for the treatment of vasomotor symptoms of natural menopause.*

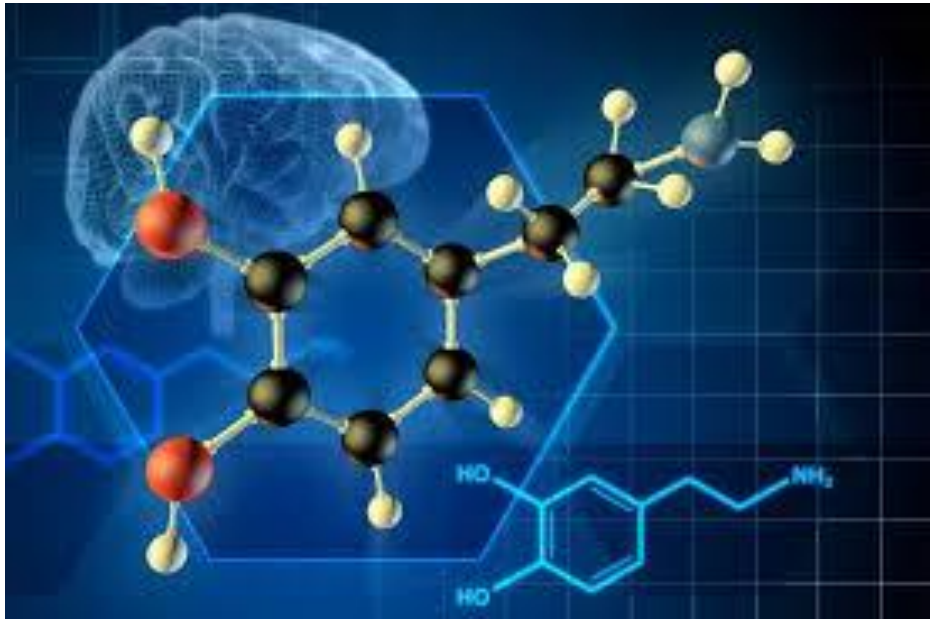
May 2023

FDA Approves New Treatment for Hot Flashes

The first-of-its-kind pill gives another option to women going through menopause

First-of-its-kind neurokinin 3 (NK_3) receptor antagonist – acts on part of the brain that helps regulate a person's body temperature. (Estrogen typically helps to keep that part of the brain properly balanced.)

Veozah



Indication: Moderate to Severe Hot Flashes (does NOT treat atrophic vaginitis)

Common side effects: abdominal pain, diarrhea, insomnia, back pain, hot flush and elevated hepatic transaminases

FDA Warning for Liver Injury: LFTs before starting

COST: **$550/month**

Testosterone?

- In **combination** with HT has been investigated for treatment of menopausal symptoms
  - No benefit
  - Potential adverse effects
    - Detrimental effects on lipid parameters
    - Clitoromegaly
    - Hirsutism
    - Acne
- In **combination** with HT for postmenopausal women
  - Improved sexual function scores
  - Improved number of satisfying sexual episodes
- **Alone**, NOT FDA-approved for use in women

Somboonporn W et al., Testosterone for peri and postmenopausal women. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No. CD004509.

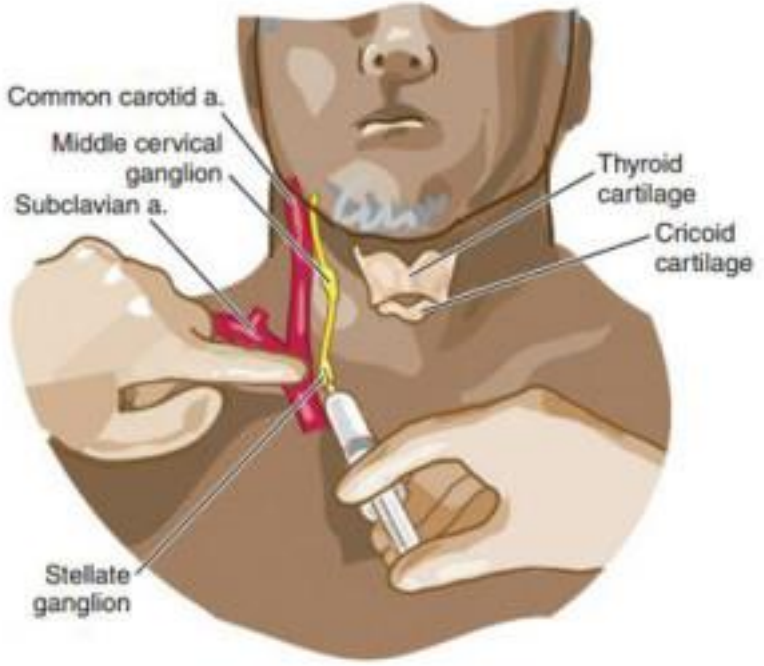
Nonpharmacologic Treatments for Vasomotor Symptoms

- Effective for short-term reduction of VMS and associated sleep disturbances.
  - Cognitive behavior therapy
    - Counseling may help deal with the changes of menopause as well, along with other underlying problems that come to the surface at this time
  - Clinical hypnosis
- **Black cohosh** and **isoflavones** are shown to be effective compared with placebo but not significantly more than hormonal preparations, and they lack standard formulations.

Treatment

- Counseling may help deal with the changes of menopause as well, along with other underlying problems that come to the surface at this time.
- Experts have found that **exercise, diet, getting enough sleep, and pursuing supportive friendships can all help** women with the emotional aspects of the transition into menopause.
  - Regular exercise is a great way to promote both mental and physical health. Being active helps relieve stress, improves mood, and makes it easier to put problems in perspective.
  - The Centers for Disease Control and Prevention (CDC) recommends 2.5 hours a week of moderately intense aerobic exercise, such as a fast walk, plus two days a week of muscle strengthening.
- **Diet** can also help individuals reduce menopausal mood swings, especially one rich in protein and omega-3 fatty acids.
- Practices such as tai chi, yoga, and meditation **can help you feel more grounded** - more straightforward to manage stress, irritability, and other symptoms of menopause.

Alternative Techniques



- Acupuncture
  - No benefit over placebo
- Reflexology
  - No benefit compared with non-specific foot massage
- Local injection of anesthetic (block) into the stellate ganglion (C6-T2 anterior cervical spine)[1]
  - May reduce VMS in women with contraindications to HT
  - More studies needed

[1]*Kontos M, et al. Climacteric 2010;13:4-21*

Transitioning from Hormonal Contraception to HT *(if the latter is needed)*

- ACOG – don't measure an FSH
  - Discontinue contraception when women are in mid-50s; spontaneous conception is rare
  - Checking follicle-stimulating hormone (FSH) levels to determine when OC users have become menopausal is not useful.
    - This approach is based on the following observations:
      - ✓in premenopausal women, FSH levels vary and a single elevated FSH level does not reliably document that contraception is no longer needed
      - ✓checking of FSH levels on the 5th-7th day of the pill-free interval is not useful, since sex steroids in OCs suppress FSH blood levels for far longer than 7 days; and
      - ✓about 50% of 52-year-old OC users are not yet menopausal, but by age 55 a great majority of women are menopausal.

Barriers to Practice

- Clinicians not discussing with patients the severity of vasomotor menopausal symptoms and therapeutic options.
- Patients are not discussing with clinicians about the severity of vasomotor menopausal symptoms and therapeutic options.
- Clinicians understand the benefits and risks of hormone therapy, non-hormonal prescription medications, and alternative treatments, familiarity with various delivery methods.

NIH

National Center for Complementary and Integrative Health

- What do we know about the **effectiveness** of complementary health approaches for menopause symptoms?
  - **Phytoestrogens**, **herbs**, and other natural products haven't been clearly shown to relieve menopause symptoms.
  - Research on **hypnotherapy** and **mindfulness meditation** is in its early stages, but some studies have had promising results
  - **Acupuncture** has **not** been shown to be more effective than simulated acupuncture for relieving hot flashes
  - **Yoga** has **not** been shown to relieve hot flashes but **may be helpful** for some symptoms associated with menopause.
  - The evidence doesn't support claims that custom-mixed (compounded) **bioidentical hormones** are more effective than conventional hormone therapy

https://www.nccih.nih.gov/health/menopausal-symptoms-in-depth

NIH

National Center for Complementary and Integrative Health

- What do we know about the **safety** of complementary health approaches for menopause symptoms?
  - **Natural products** may have side effects or interact with drugs, and little is known about their long-term safety.
  - **Mind and body practices** such as acupuncture, hypnosis, meditation, and yoga generally have good safety records.
  - Custom-mixed **bioidentical hormones** haven't been shown to be safer than other forms of hormone therapy, and their content may vary from batch to batch.

https://www.nccih.nih.gov/health/menopausal-symptoms-in-depth

Hot flashes

Night Sweats

Vaginal dryness

Anxiety

Changes in mood

Reduced sex drive

Children leaving the home

Aging parents

Retirement

Summary

Practice Recommendations

- Systemic HT, with estrogen alone or in combination with progestin, is the most effective therapy for vasomotor symptoms related to menopause. (SOR: A)
- Given the variable response to HT and the associated risks, it is recommended that healthcare providers individualize care and treat women with the lowest effective dose for the shortest duration that is needed to relieve symptoms. (SOR: C)
- The decision to continue HT should be individualized based on a woman's symptoms and the risk-benefit ratio, REGARDLESS OF AGE. (SOR: C)
- Combined estrogen/progesterone therapy, but NOT estrogen alone, increases the risk of breast cancer after three to five years of use. (SOR: B)
- Data do not support the use of progestin-only medications, testosterone, or compounded bioidentical hormones for the treatment of vasomotor.

Thank You

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