Menopause Magic: Learn Tricks for the Management of Women at Midlife and Beyond

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Objectives

At the end of this lecture, the attendee will:

1. List two common menopausal symptoms women experience
2. List one difference in oral versus transdermal estrogen therapy from the KEEPS trial
3. Discuss the current risks and benefits of hormone therapy for women in the early post menopause
4. Discuss treatment options for vasomotor symptoms including oral and transdermal estrogen

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Disclosures

Advisory Board:
Astellas
Speakers Bureau:
Astellas

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Reality Check

> 57 yo patient: presents with severe hot flashes.
  – Final menstrual period: age 55.
> PCP ordered a BMD in 2020 (though patient did not have risk factors for doing in early post-menopause). It showed mild and moderate osteopenia at femoral neck
> 5/18/22 Follow-up BMD
  – Femoral neck T-scores: -2.3 and -1.9
  – Loss from 2020: 6.3% and 4.3%
> FRAX 10 year risk: Major Osteoporotic Fracture: 4.2%
Hip: 1.9%

Work-up for secondary cause of bone loss: negative.

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Reality Check

> What is the best treatment for this patient?
> What did I recommend to the patient?
  – She has severe vasomotor symptoms and significant loss of bone.

What was the patient's response?

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An Historical Perspective on Hormone Therapy

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Hormone Therapy: Historical Perspective

> 1920's: Estrogen isolated from the urine of pregnant women and made available
> 1940's: Ayerst, a Canadian drug maker found a way to make it from pregnant mares and called it "Premarin"
> **1950's: Massive campaign to promote Premarin as a rejuvenating agent and mood stabilizer for postmenopausal women**
  – **Premarin ads frequent in medical journals**

Hormone-replacement therapy. Weighing the benefits and risks. *Harvard health letter / from Harvard Medical School.* Oct 1997;22(12):1-3.

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Hormone Therapy: Historical Perspective

> Mid 1960's: Approximately 12% of postmenopausal women were taking estrogen
> 1975: New England Journal of Medicine published 2 studies showing that women taking estrogen had as much as 14 times the risk of endometrial cancer as women not on the drug
> Progestogen was added when women had a uterus
> **1992: Conjugated estrogen (Premarin) was the most widely prescribed drug**

Hormone-replacement therapy. Weighing the benefits and risks. *Harvard health letter / from Harvard Medical School.* Oct 1997;22(12):1-3.

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Hormone Therapy: Historical Perspective

> 1998: Heart and Estrogen/Progestin Replacement study
  – Found that women who already had heart disease did not have prevention of MI's
> Women's Health Initiative (WHI)
  – Designed to answer the question of long term hormone therapy and prevention of heart disease
  – 2002: Prempro arm stopped early

Hormone-replacement therapy. Weighing the benefits and risks. *Harvard health letter / from Harvard Medical School.* Oct 1997;22(12):1-3.

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The Study That Changed Everything!
What Have We Learned in more than 20 Years?!

1998 and 2002: Results from 2 large randomized controlled trials:

>The Heart and Estrogen/Progestin Replacement Study (HERS): a secondary prevention study

>The Women's Health Initiative (WHI): a primary prevention study

Changed the widely accepted belief that hormone therapy was protective against cardiovascular disease!

Rossouw JE, Anderson GL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.
Anderson GL, Limacher M, Effects of conjugated equine estrogen in postmenopausal women with hysterectomy the Women's Health Initiative randomized controlled trial. JAMA. 2004:291(14):1701-1712.

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Panic ensued….

> Increased risk of breast cancer
> Increased risk of cardiovascular disease (CHD)
> Increased risk of stroke
> Increased risk of pulmonary embolism (PE)

Rossouw JE, Anderson GL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.
Anderson GL, Limacher M, Effects of conjugated equine estrogen in postmenopausal women with hysterectomy the Women's Health Initiative randomized controlled trial. JAMA. 2004:291(14):1701-1712.

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Change in Practice

> Women stopped taking hormone therapy
> Practitioners stopped prescribing hormone therapy
> Women who wanted hormone therapy couldn't always get prescriptions
> Confusion increased further with the marketing of so called, "safer" and "bioidentical" products in the marketplace

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What Data Has Led to Practice Change?

Providing evidence based information to patients for decision making: regarding management of vasomotor symptoms

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Kronos Early Estrogen Prevention Study (KEEPS)

Effects of Oral Conjugated Estrogens vs. Transdermal Estradiol on Common Carotid Artery Intima Media Thickness (CIMT) and Coronary Artery Calcium (CAC)

First data reported: October 3rd, 2012

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KEEPS

4-year randomized, double-blinded, placebo-controlled clinical trial of low-dose oral or transdermal estrogen and cyclic monthly progesterone

> **Inclusion**
  - **Healthy women ages 42 to 59 (mean age 52)**
  - **Within 3 years after menopause**

> **Excluded women with evidence of cardiovascular disease**

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Key Goal of KEEPS

> To compare two formulations of hormones
  - Low dose oral conjugated estrogens
  - Transdermal estradiol
  - Both with cyclical micronized progesterone
> Both studied over 4 years in relationship to:
  - Atherosclerosis progression by noninvasive imaging
  - Carotid intima-media thickness
  - Coronary artery calcium

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Main Differences in KEEPS From WHI

> WHI:
  - Mean age 65
  - More than 12 years past the onset of menopause
> KEEPS
  - Average age 52
  - Within 3 years of final menstrual period
> Doses, formulations and routes of delivery of hormones were different
> KEEPS trial much smaller with 727 women enrolled

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What Are Some Concerns About WHI?

> WHI did change the approach of recommending hormone therapy as a prevention of cardiovascular disease for older women… BUT…

> The results were often extrapolated to newly menopausal women who were considering hormone therapy for distressing symptoms

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Key Findings of KEEPS

> Favorable effects of estrogen in newly menopausal women
  – Reduction in vasomotor symptoms
  – Improvement in several parameters of sexual function
  – Improvement in bone mineral density
  – Oral estrogen: improvement in mood outcomes with decrease in depressive symptoms, anxiety and tension
> **No significant increase in adverse events!**

The Kronos Early Estrogen Study, Key Findings, Interview with JoAnn Manson, Women's Health, (2013) 9(1), 9-11
Clinton, D., et al. (2018). "Effects of oral versus transdermal menopausal hormone treatments on self-reported sleep domains and their association with vasomotor symptoms in recently menopausal women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS)." Menopause 25(2): 145-153.

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Key Differences Between Oral and Transdermal Therapy

> Oral
  – Benefits for mood, depressive symptoms, anxiety and tension
  – LDL lowering and HDL increase
  – Subset of women with low cardiovascular risk
    • Cognitive benefit in terms of memory and verbal learning
> Transdermal
  – Greater reduction in insulin resistance
  – Improvement in libido-related aspects of sexual function

The Kronos Early Estrogen Study, Key Findings, Interview with JoAnn Manson, Women's Health, (2013) 9(1), 9-11

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The Early VS Late Intervention Trial with Estradiol (ELITE)

> Included 643 Postmenopausal women
> Stratified according to time since menopause
  – < 6 years (Early postmenopause)
  – ≥ 10 years (Late postmenopause)
> Randomized to either 17 Beta Estradiol (1mg per day), plus progesterone (45mg) vaginal gel administered sequentially (for women with a uterus) and with placebo (for women without a uterus)

1. Hodis HN, Mack WJ, Henderson VW, et al; ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med. 2016;374:1221–1231.
2. Hodis HN, Mack WJ, Shoupe D, et al. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause. 2015;22:391–401.

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The Early Vs Late Intervention Trial with Estradiol (ELITE)

> Primary outcome
  – Rate of change in carotid-artery intima-media thickness (CIMT)
  – Measured every 6 months
> Secondary outcome
  – Assessment of coronary atherosclerosis by cardia computed tomography (CT)

1. Hodis HN, Mack WJ, Henderson VW, et al; ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med. 2016;374:1221–1231.
2. Hodis HN, Mack WJ, Shoupe D, et al. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause. 2015;22:391–401.

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The Early VS Late Intervention Trial with Estradiol (ELITE)

> Mean age of early: 55 years
> Mean age of late: 65 years
> Over 6 years:

Women in early menopause, had overall slower progression of atherosclerosis measured by carotid IMT than women in the later menopause

1. Hodis HN, Mack WJ, Henderson VW, et al; ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med. 2016;374:1221–1231.
2. Hodis HN, Mack WJ, Shoupe D, et al. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause. 2015;22:391–401.

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Women's Health Initiative and All-cause Mortality

Subgroup analyses in the Women's Health Initiative
> Showed that women in their 50's tended to do better for heart disease and all-cause mortality and global index than women who were older
> Reassuring news for women in early menopause who are are considering hormone therapy for vasomotor symptoms
  – Absolute risk of adverse cardiovascular events in women close to menopause are low
  – All cause mortality effects are neutral or even favorable for younger menopausal women

Chester RC, Kling JM, Manson JE. What the Women's Health Initiative has taught us about menopausal therapy. Clin Cardiol. 2018 Feb;41(2):247-252.

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Women's Health Initiative and All-cause Mortality

> Not a rationale for long-term use of hormone therapy for chronic disease prevention
  – Potential for increased risk for stroke, venous thrombosis and gall bladder disease
> This evidence does support the timing hypothesis

WINDOW OF OPPORTUNITY: AGE 50 TO 60

Chester RC, Kling JM, Manson JE. What the Women's Health Initiative has taught us about menopausal therapy. Clin Cardiol. 2018 Feb;41(2):247-252.

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It's Time to Rethink, Reboot and Review: Hormone Therapy

Advocacy for women to live with quality

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Different Approaches: Individualization of Care….

Disclaimer: Presenting an approach that supports evidence - based practice and position statements for practice:

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

"One goal of The North American Menopause Society (NAMS) is to develop position statements and other reports about clinical issues pertinent to women at midlife and beyond."

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KEY POINTS FROM

THE 2022 HORMONE THERAPY POSITION STATEMENT OF THE NORTH AMERICAN MENOPAUSE SOCIETY

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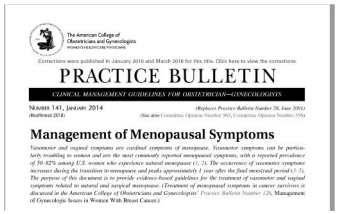
The American College of Obstetricians and Gynecologists (ACOG)


The American College of Obstetricians and Gynecologists

Corrections were published in January 2016 and March 2016 for this title. Click here to view the corrections.

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

Number 141, January 2014 (Replaces Practice Bulletin Number 70, June 2006)
(Reaffirmed 2018) (See also Committee Opinion Number 565, Committee Opinion Number 556)

Management of Menopausal Symptoms

Vasomotor and vaginal symptoms are cardinal symptoms of menopause. Vasomotor symptoms can be particularly troubling to women and are the most commonly reported menopausal symptoms, with a reported prevalence of 30–82% among U.S. women who experience natural menopause (1, 2). The occurrence of vasomotor symptoms increases during the transition to menopause and peaks approximately 1 year after the final menstrual period (3–5). The purpose of this document is to provide evidence-based guidelines for the treatment of vasomotor and vaginal symptoms related to natural and surgical menopause. (Treatment of menopausal symptoms in cancer survivors is discussed in the American College of Obstetricians and Gynecologists' Practice Bulletin Number 120, Management of Gynecologic Issues in Women With Breast Cancer.)

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Perimenopause

> The time around the FMP, also called "the menopause transition"
> Begins with variation in the menstrual cycle length
> Associated with a rise in follicle-stimulating hormone (FSH) and ends 1 year after the FMP
> **Often the most symptomatic phase for women**

Harlow SD *Menopause* 2012;19:387-95

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What is menopause?

> Menopause is a normal, natural event, **defined as the final menstrual period (FMP),** confirmed after 1 year of no menstrual bleeding
> Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually due to aging

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When Is Menopause?

> Naturally (spontaneously) average age 51
> Prematurely from medical intervention (eg, bilateral oophorectomy, chemotherapy, radiation)
> At any time from impaired ovarian function
> Premature menopause occurs before age 40

Manson JE In: *Harrison's Principles of Int Med*, 17th ed. NY: McGraw-Hill, 2008:2334-9

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Serum Hormone Levels At Menopause

⇩ Circulating estrogens

⇩ Ratio of estrogen to androgen

⇩ Sex hormone-binding globulin secretion

Peripheral aromatization of DHEA to estrone

Reversal of estradiol (E_2) to estrone (E_1) ratio

No significant change in testosterone levels

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What is the Problem?

Menopause Symptoms

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Menopausal symptoms & signs

Classic symptoms:

> Change in menstrual cycle pattern (during perimenopause)
> Vasomotor symptoms (hot flashes & night sweats)
> Vulvovaginal symptoms, dyspareunia
> Sleep disturbances

Other symptoms sometimes associated with menopause:

> Cognitive concerns (memory, concentration)
> Psychological symptoms (depression, anxiety, moodiness)

➢ There is no one universal menopausal syndrome

Avis et al *Am J Med* 2005;118 Suppl 12B:37-46; NIH *Ann Intern Med* 2005;142:1003-13

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Menopausal Concerns

Hot Flashes & Night Sweats
Sleep Disturbance
Cognition
Genitourinary Syndrome of Menopause

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MENOPAUSE SYMPTOMS
VASOMOTOR SYMPTOMS

- **Vasomotor symptoms (VMS) may begin during perimenopause, and frequent VMS may persist on average 7.4 years or longer. They affect quality of life and may be associated with cardiovascular, bone, and brain health.**
- **Hormone therapy remains the gold standard for relief of VMS.**
  - **Estrogen-alone therapy can be used for symptomatic women without a uterus.**
  - **For symptomatic women with a uterus, estrogen-progestogen therapy or a tissue-selective estrogen complex protects against endometrial neoplasia.**
- **Shared decision-making should be used when considering formulation, route of administration, and dose of hormone therapy for menopause symptom management, with adjustment tailored to symptom relief, adverse events, and patient preferences.**

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Frequency

> As many as 75% of perimenopausal women in US report hot flashes
> Number of episodes vary
> Few to multiple episodes daily
> Highest occurrence during perimenopause and first 2 years of postmenopause

Freeman EW *Climacteric* 2007;10:197-214

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Disparities: Racial and Ethnic

> Black and Latino women may experience the onset of hot flashes 1 to 2 years earlier than white women
  – Hot flashes may last longer
> Counseling and education should be tailored to the individual

Thurston, R. C. and H. Ioffe (2011). "Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation." Obstet Gynecol Clin North Am **38**(3): 489-501.
Harlow SD, Burnett-Bowie S-AM, Greendale GA, et al. Disparities in Reproductive Aging and Midlife Health between Black and White women: The Study of Women's Health Across the Nation (SWAN). *Women's Midlife Health*. 2022;8(1):3. doi:10.1186/s40695-022-00073-y

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Mechanism of Hot Flashes

> Estrogen levels are ***EQUAL*** in symptomatic and asymptomatic women
> Estrogen levels alone ***NOT*** predictive of hot flash frequency or severity
> ***NOT*** caused by pulses of LH
> Perimenopause often much worse than postmenopause
> FSH ↑'s 2 years prior to FMP = ↓ E_2

Freedman RF. *Semin Reprod Med.* 2005;23:117-25.

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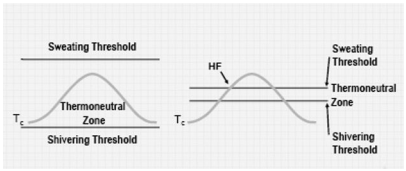
Thermoneutral Zone



Tc = core body temperature; HF = hot flash

Freedman RF. *Semin Reprod Med.* 2005;23:117-25.

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Hot Flash Hypothesis

> Women with no hot flashes have wider TNZ than women with hot flashes[1]
  – Includes women in peri and post menopause
> Tiny ↑ in Temp leads to hot flash
> A rise of 0.05 ° C leads to 70% of hot flashes in the lab[2]
> Lowered Estrogen levels narrow the TNZ

Freedman RF. *Semin Reprod Med.* 2005;23:117-25.

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Newest Science Regarding Etiology of VMS

> Hypothalamic KNDy neurons
  – Neuropeptides: kisspeptin, neurokinin B, and dynorphin
  – Estrogen-sensitive neurons in the hypothalamus
  – Become hypertrophied in menopausal women
> KNDy neurons innervate the thermoregulatory center
  – Stimulated by NKB via the NK3 receptor
  – Inhibited by estrogen
  – Estrogen decline disrupts the balance with NKB
  – Unopposed, NKB neurons can lead to altered activity in the thermoregulatory center

Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. Front Neuroendocrinol 2013;34(3):211-27.

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MENOPAUSE SYMPTOMS
SLEEP DISTURBANCES

- **During the menopause transition, women with vasomotor symptoms (VMS) are more likely to report disrupted sleep.**
- **Hormone therapy improves sleep in women with bothersome nighttime VMS by reducing nighttime awakenings.**
- **Estrogen may have some effect on sleep, independent of VMS.**

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Cognitive Changes

> There is evidence that psychomotor speed and to a lesser extent verbal memory can decline slightly in perimenopause
> Although depression and anxiety are related to cognitive decline, neither mood nor age account for these cognitive changes experienced by some women
> Any transient issue with cognition appears to resolve after menopause

Greendale GA *Neurology* 2009;26;72:1850-7

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HORMONE THERAPY AND COGNITION

- **Hormone therapy is not recommended at any age to prevent or treat a decline in cognitive function or dementia. (Level I)**
- **Initiating hormone therapy in women aged older than 65 years increased the risk for dementia, with an additional 23 cases per 10,000 person-years seen in women randomized to conjugated equine estrogens plus medroxyprogesterone acetate in the Women's Health Initiative Memory Study. (Level I)**
- **The effect of hormone therapy may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before hormone therapy initiation. (Level II)**
- **Estrogen therapy may have cognitive benefits when initiated immediately after hysterectomy with bilateral oophorectomy, but hormone therapy in the early natural postmenopause period has neutral effects on cognitive function. (Level II)**

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MENOPAUSE SYMPTOMS
SEXUAL FUNCTION

- **Both systemic hormone therapy and low-dose vaginal estrogen therapy (ET) increase lubrication, blood flow, and sensation of vaginal tissues.**
- **Systemic hormone therapy generally does not improve sexual function, sexual interest, arousal, or orgasmic response independent of its effect on genitourinary syndrome of menopause (GSM).**
- **If sexual function or libido are concerns in women with menopause symptoms, transdermal ET may be preferable over oral ET because of minimal effect on sex hormone-binding globulin and free testosterone levels.**
- **Low-dose vaginal ET improves sexual function in postmenopausal women with GSM.**
- **Nonestrogen FDA-approved alternatives for dyspareunia include ospemifene and intravaginal dehydroepiandrosterone.**

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Vulvovaginal symptoms: Genitourinary Syndrome of Menopause: GSM

> Symptoms such as vaginal dryness, vulvovaginal irritation/itching, and dyspareunia are experienced by ~10%-40% of postmenopausal women
> Unlike vasomotor symptoms, which abate over time, **vaginal atrophy can be progressive and is unlikely to resolve on its own**
> Treatments include: regular sexual activity, lubricants and moisturizers, and local vaginal estrogen

Stika CS *Dermatol Ther* 2010;23:514-522; Bachmann GA In: *Treatment of the Postmenopausal Woman* Philadelphia: Lippincott, Williams & Wilkins, 1999

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MENOPAUSAL HORMONE THERAPY

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Menopause Management

> There is no indication for hormone measurements for determining management
> Management is based on severity of symptoms
> Hormone therapy decisions are not based on levels of hormones from any measurement such as saliva testing
> There is no benefit in using potions and lotions of non FDA approved products!
> KEEPS addresses some differences in oral versus transdermal therapy

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Bioidentical hormones

> Many well-tested, government-approved HT products contain bioidentical hormones
> Usually refers to compounded formulations
> Compounded HT not tested for efficacy, safety, batch standardization, or purity
> Some compounders make unsubstantiated claims about safety and effectiveness

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

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COMPOUNDED BIOIDENTICAL HORMONES

- **Compounded bioidentical hormone therapy presents safety concerns**
  - **Minimal government regulation and monitoring**
  - **Overdosing and underdosing**
  - **Presence of impurities and lack of sterility**
  - **Lack of scientific efficacy and safety data**
  - **Lack of a label outlining risks (Level I)**
- **Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed. (Level II/III)**
- **Shared decision-making is important, but patient preference alone should not be used to justify the use of compounded bioidentical hormone preparations, particularly when government-regulated bioidentical hormone preparations are available. (Level III)**
- **Situations in which compounded bioidentical hormones could be considered include allergies to ingredients in a government-approved formulation or dosages not available in government-approved products. (Level III)**

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American College of Obstetricians and Gynecologists (ACOG)

> Because such preparations have not been rigorously tested, only FDA-approved HT formulations are recommended.

Practice Bulletin, No 141, Management of Menopausal Symptoms, January 2014, (Reaffirmed 2018), The American College of Obstetricians and Gynecologists

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Use of Hormone Therapy

Estrogen/Progestogen (EPT)
Estrogen (ET)

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Living Life is a Continuous Risk/ Benefit Analysis

This is no different in helping women make decisions regarding hormone therapy!

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Shared Decision Making

Advocacy for helping women make informed choices

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SAFETY

- **Overall, the increased absolute risks associated with estrogen-progestogen therapy (EPT) and estrogen alone (ET) are rare (<10/10,000/y) and include increased risk for venous thromboembolism and gallbladder disease.**
- **EPT carries a rare increased risk for stroke and breast cancer, and if estrogen is inadequately opposed, an increased risk of endometrial hyperplasia and endometrial cancer.**
- **Absolute risks are reduced for all-cause mortality, fracture, diabetes mellitus (EPT and ET), and breast cancer (ET) in women aged younger than 60 years (Figure 1).**

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DOSING: PROGESTOGEN THERAPY

- **Progestogen dosing-regimen options that provide for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose.**
- **Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous-combined) may have different associations with health outcomes.**
- **Patient preference can and should be considered because many women will opt for regimens that avoid periodic menstrual bleeding.**

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DOSING: ESTROGEN THERAPY

- **The therapeutic goal should be to use the most appropriate, often lowest, effective dose of systemic estrogen therapy consistent with treatment goals.**
- **The appropriate dose of progestogen is added to provide endometrial protection if a woman has a uterus, unless conjugated equine estrogens are combined with bazedoxifene.**

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FDA-APPROVED INDICATIONS

- **Hormone therapy is FDA approved for four indications:**
  - **Moderate to severe vasomotor symptoms**
  - **Prevention of osteoporosis in postmenopausal women**
  - **Treatment of hypoestrogenism caused by hypogonadism, bilateral oophorectomy, or primary ovarian insufficiency**
  - **Treatment of moderate to severe vulvovaginal symptoms**
- **FDA guidance for treatment of genitourinary symptoms related to menopause in the absence of indications for systemic estrogen therapy (ET) suggests the use of low-dose topical vaginal ET (Level I)**

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CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

- For healthy symptomatic women aged younger than 60 years or within 10 years of menopause onset, the favorable effects of hormone therapy on coronary heart disease (CHD) and all-cause mortality should be considered against potential rare increases in risks of breast cancer, venous thromboembolism (VTE), and stroke. (Level I)
- Hormone therapy is not government approved for primary or secondary cardioprotection. (Level I)
- Personal and familial risk of cardiovascular disease, stroke, VTE, and breast cancer should be considered when initiating hormone therapy. (Level III)
- The effects of hormone therapy on CHD may vary depending on when hormone therapy is initiated in relation to a woman's age and/or time since menopause onset. (Level I)

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CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY (CONT)

- Initiation of hormone therapy in recently postmenopausal women reduced or had no effect on subclinical atherosclerosis progression and coronary artery calcification in randomized, controlled trials. (Level I)
- Observational data and meta-analyses show reduced risk of coronary heart disease (CHD) in women who initiate hormone therapy aged younger than 60 years and/or within 10 years of menopause onset. Meta-analyses show a null effect of hormone therapy on CHD after excluding open-label trials. (Level II)
- Women who initiate hormone therapy aged older than 60 years or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, venous thromboembolism, and stroke than women initiating hormone therapy in early menopause. (Level I)

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BREAST CANCER

- The risk of breast cancer related to hormone therapy use is low, with estimates indicating a rare occurrence (less than one additional case per 1,000 women per year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with conjugated equine estrogens plus medroxyprogesterone acetate). (Level I)
- Women should be counseled about the risk of breast cancer with hormone therapy, putting the data into perspective, with risk similar to that of modifiable risk factors. (Level III)
- The effect of hormone therapy on breast cancer risk may depend on the type of hormone therapy, duration of use, regimen, prior exposure, and individual characteristics. (Level II)
- Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation. (Level II)

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BREAST CANCER (CONT)

- A preponderance of data does not show an additive effect of underlying breast cancer risk and hormone therapy use on breast cancer incidence. (Level II)
- Insufficient data are available to assess the risk of breast cancer with newer therapies such as tissue-selective estrogen complexes, including bazedoxifene plus conjugated equine estrogens. (Level II)
- Observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women at high risk because of a family history or after bilateral salpingo-oophorectomy for *BRCA 1* or *2* genetic variants. (Level II)

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BREAST CANCER (CONT)

- Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe vasomotor symptoms unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. (Level III)
- For survivors of breast cancer with the genitourinary syndrome of menopause, low-dose vaginal estrogen therapy (ET) or dehydroepiandrosterone may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal ET for women on aromatase inhibitors. (Level III)
- Regular breast cancer surveillance is advised for all postmenopausal women per current breast cancer screening guidelines, including those who use hormone therapy. (Level I)

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The Nuts and Bolts

Of Hormone Therapy

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Treatment of Hot Flashes

> **Treatment based on symptom severity, a woman's risk factors, and her personal preferences**
> **Serum estrogen levels are not predictive of hot flash frequency or severity**
> Many government-approved formulations of HT
> Off-label use of various non hormonal prescription therapies and various dietary supplements and complementary and alternative options

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Your Treatment Algorithm

> How bothersome are symptoms to her?
> Preference - non-hormonal, hormonal or step approach?
> Years since LMP (5 or more? No hormones)
> Risk factors? DVT, Migraine with Aura?
> Risks and benefits

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Considerations

> Clinician preference:
  – Start low and work up?
  – Mid-range? Titrate up or down
> Pt preference for frequency? Ease of use? Remembering to take/change
> Anticipatory Guidance for expected side effects, bleeding, when to call

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Practical Pearls for Prescribing HT

> Oral estrogen
  – Increases triglycerides by 15%
  – Increases HDL by 10%
  – Deceases LDL by 10%

LaRosa JC. Metabolic effects of estrogens and progestins. Fertil Steril. 1994; 62(6, suppl 2):140S-6S.

70

Practical Pearls for Prescribing HT

> If transdermal is used for hormone therapy, oral progesterone may be used at HS
> Combination estrogen/progestin patch available
> Start low and increase dose as necessary???
> Start average dose and decrease as symptoms come under control???
> Two products= two copays!!
> Generic products for transdermal patch, oral estrogen and combined estrogen/progestin

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Estrogen Therapy Estrogen/Progestogen Therapy

Primary indication for ET/EPT is to treat moderate to severe menopause symptoms (vasomotor)

> When symptoms are controlled or cease, may be continued though risks and benefits must be weighed
> Approved for prevention but not treatment of osteoporosis
> NAMS and ACOG recommend use of ET/ EPT at the lowest effective dose for the shortest time period consistent with treatment goals

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Practical Pearls for Prescribing HT

> Route of estrogen impacts risk of thromboembolic events, though data is not extensive
  – Oral estrogen has a first pass through the liver
    • May increase the risk of blood clot compared to transdermal
  – Transdermal estradiol had a 30% lower incidence of VTE than those who took oral estrogen only in a study reported in 2011.

Kahler KH, Nyirady J, Beresford E, et al. Does route of administration for estrogen hormone therapy and estradiol transdermal system dosage strength impact risk of venous thromboembolism. Washington, DC: North American Menopause Society (NAMS); September 23, 2011. Abstract S-4.

73

Protect the Endometrium

> Unopposed Estrogen causes an 8 fold increase in the risk of endometrial hyperplasia
> Add progestogens to the cycle
  – Daily
  – Cyclic
  – IUDs – haven't been studied as extensively

74

EPT Regimens

> Systemic progestogen required for endometrial protection
> Multiple approved dosing options available
> Current data support minimizing progestogen exposure
> Insufficient evidence regarding endometrial safety to recommend:
  – Off-label use of long-cycle regimens
  – Vaginal administration of progesterone
  – Levonorgestrel-releasing intrauterine system
  – Low-dose estrogen without progestogen

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Progestogen Regimens

> Progesterone can not be absorbed by the skin
> Can be absorbed in Vagina
  – Crinone – Micronized progesterone
  – 4% twice weekly
> Oral medications
  – Prometrium = Bio Identical
  – Provera = Medroxyprogesterone Acetate
  – Aygestin = Norethindrone

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Progestin Regimens

> Daily oral reduces BTB
> No need to cycle for menses
> Progestogen must be at least 12 days/month
> Little data to support q 3 month use
  – Is associated with more BTB

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Dosage of Hormone Therapy

> Improvement of vasomotor symptoms from low-dose and ultra-low dose preparations:
  – Not as well studied as standard-dose
  – May improve symptoms in many women, though not as effective as standard dose
> Recommended that health care providers individualize care
> Treat with lowest effective dose for the shortest duration

Practice Bulletin, No 141, Management of Menopausal Symptoms, January 2014, (Reaffirmed 2018), The American College of Obstetricians and Gynecologists

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Dosage of Hormone Therapy

> Standard Dose
  – Conjugated estrogen 0.625mg/d
  – Micronized estradiol-17 Beta 1 mg/d
  – Transdermal estradiol-17 Beta 0.0375-0.05
> Low Dose
  – Conjugated estrogen 0.3-0.45mg/d
  – Micronized estrogen-17Beta 0.5mg/d
  – Transdermal estradiol-17Beta 0.025mg/d

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Dosage of Hormone Therapy

> Ultra-Low Dose
  – Micronized estradiol-17Beta 0.25mg/d
  – Transdermal estradiol-17Beta 0.014mg/d
> Estrogen combined with estrogen agonist/antagonist
  – Conjugated estrogen 0.45mg/d and bazedoxifene 20mg/d
  – For post-menopausal women only. Do not add additional estrogens, progestogens, or estrogen agonists/antagonists.

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Dosage of Hormone Therapy

> Systemic HT, with estrogen alone or in combination with progestin, is the most effective therapy for vasomotor symptoms

> Low-dose and ultra-low dose systemic doses of estrogen are associated with a better adverse effect profile than standard dose and may reduce vasomotor symptoms in some women

Practice Bulletin, No 141, Management of Menopausal Symptoms, January 2014, (Reaffirmed 2018), The American College of Obstetricians and Gynecologists

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Duration of Use

> Some experts recommend keeping duration of treatment short
> For many women vasomotor symptoms are a long term concern
> Penn Ovarian Aging Study
  – Median duration of moderate to severe VMS was more than 10 years
> For many women, short-term use (3-5 years) will not be sufficient to control symptoms

Freeman EW, Sammel MD, t al, Duration of menopausal hot flushes and associated risk factors. Obstet Gynecol. 2011;117(5):1095-1104.

82

Duration of use

> With EPT, increased risk of breast cancer incidence and mortality with 3-5 years of use
> With ET, no increase of breast cancer with early postmenopausal use; a decrease was found after hiatus in estrogen exposure
> With ET, potential CAD and CHD benefits with early use
> Initial increase in CHD risk when EPT is initiated further from menopause

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

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Duration of use (continued)

> Extending EPT use is acceptable for:
  – Women who request it and are aware of its risks
  – Prevention of osteoporosis for women at high risk of osteoporotic fracture when alternate therapies are not appropriate

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

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DURATION OF USE

- **Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of cardiovascular disease and breast cancer with persistent vasomotor symptoms or at elevated risk of fracture for whom other therapies are not appropriate. (Level III)**
  - **Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone interventions, and underlying risk for osteoporosis, coronary heart disease, cerebrovascular accident, venous thromboembolism, and breast cancer. (Level III)**
- **Longer durations or extended use beyond age 65 should include periodic reevaluation of comorbidities with consideration of periodic trials of lowering or discontinuing hormone therapy. (Level III)**
- **In the absence of contraindications, a woman should determine her preferred hormone therapy formulation, dose, and duration of use, with ongoing assessment and shared decision-making with her healthcare professional. (Level III)**

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Use of HT to Treat Menopausal Symptoms: ACOG Guidance

"…ACOG recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of HT and estrogen therapy should be individualized based on each women's risk-benefit ratio and clinical presentation ."

Practice Bulletin, No 141, Management of Menopausal Symptoms, January 2014, (Reaffirmed 2018), The American College of Obstetricians and Gynecologists

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Continuation of Hormone Therapy

> Requires individualized assessment of HT benefits and risks
> Shared decision making

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Discontinuation of Systemic Therapy

> VMS may recur in as many as 50% of women
> Does not appear to vary between abrupt and tapered discontinuation
> Women may be reluctant to reduce their dose or to stop therapy
> Recommend a 3 month trial off with the understanding that therapy could be restarted

Kaunitz, A. When should a menopausal woman discontinue hormone therapy, OBG Management, Vol 26;14:59-65.

88

DISCONTINUATION OF HORMONE THERAPY

- **Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of cardiovascular disease and breast cancer with persistent vasomotor symptoms or at elevated risk of fracture for whom other therapies are not appropriate. (Level III)**
- **Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years. (Level III)**

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Age and Hormone Therapy

Is 65 too old to continue??

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INITIATION AFTER AGE 60 YEARS

- **The safety profile of hormone therapy is most favorable when initiated in healthy women aged younger than 60 years or within 10 years of menopause onset, so initiation of hormone therapy by menopausal women aged older than 60 years requires careful consideration of individual benefits and risks. (Level I)**
- **Mitigation of risk through use of the lowest effective dose and potentially with a nonoral route of administration becomes increasingly important as women age and with longer duration of therapy. (Level III)**
- **For women with the genitourinary syndrome of menopause, low-dose vaginal estrogen therapy may be considered for use at any age and for extended duration, if needed. (Level III)**

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American College of Obstetricians and Gynecologists (ACOG)

Because some women aged ≥65 might still need systemic HT for VMS, HT should not be routinely discontinued at age 65, but, as in younger women, should be individualized.

Practice Bulletin, No 141, Management of Menopausal Symptoms, January 2014. (Reaffirmed 2018). The American College of Obstetricians and Gynecologists

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HT summary

> HT formulation, route of administration, and timing of initiation produce different effects
> Individual benefit-risk profiles are essential
> Absolute risks in healthy women ages 50-59 are low
> Long-term use or HT initiation in older women, however, has greater risks
> Breast cancer risk increases with EPT beyond 3-5 years
> ET can be considered for longer duration of use due to its more favorable safety profile

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

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Genitourinary Syndrome of Menopause The Vulvovaginal symptoms

> Symptoms such as vaginal dryness, vulvovaginal irritation/itching, and dyspareunia are experienced by ~10%-40% of postmenopausal women
> Unlike vasomotor symptoms, which abate over time, vaginal atrophy can be progressive and is unlikely to resolve on its own
> Treatments include: regular sexual activity, lubricants and moisturizers, and local vaginal estrogen

1. Stika CS *Dermatol Ther* 2010.
2. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020;27(9):976-992. doi:10.1097/gme.0000

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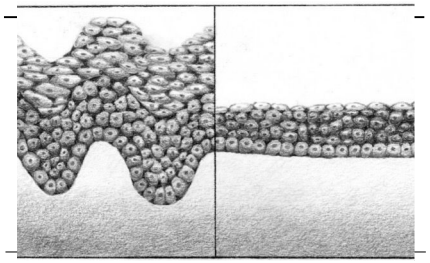
Well-estrogenized Premenopausal State

Low-estrogen Postmenopausal State



Courtesy of the Graphic Courtesy Dr. Diane Todd Pace NP from the North American Menopause Society

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Loss of Estrogen

– Vagina loses elasticity, shortens, narrows, easily traumatized and irritated
– Loss of rugae, fornices become obliterated, cervix flush with vaginal vault
– Petechiae may be present
– pH greater than 5.0, parabasal cells dominate
– Repopulation with diverse vaginal flora leads to frequent UTIs
– Worse for women on chemo (tamoxifen, aromatase Inhibitors)

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MENOPAUSE SYMPTOMS
GENITOURINARY SYMPTOMS

- **Low-dose vaginal estrogen therapy (ET) preparations are effective and generally safe for the treatment of genitourinary syndrome of menopause, with minimal systemic absorption, and are preferred over systemic therapies when ET is used only for genitourinary symptoms.**
- **For women with breast cancer, low-dose vaginal ET should be prescribed in consultation with their oncologists.**
- **Progestogen therapy is not required with low-dose vaginal estrogen, but randomized, controlled trial data are lacking beyond 1 year.**
- **Nonestrogen prescription FDA-approved therapies that improve vulvovaginal atrophy in postmenopausal women include ospemifene and intravaginaldehydroepiandrosterone.**

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MENOPAUSE SYMPTOMS
URINARY TRACT SYMPTOMS (INCLUDING PELVIC FLOOR DISORDERS)

- **Systemic hormone therapy does not improve urinary incontinence and may increase the incidence of stress urinary incontinence.**
- **Low-dose vaginal estrogen therapy may provide benefit for urinary symptoms, including prevention of recurrent urinary tract infections, overactive bladder, and urge incontinence.**
- **Hormone therapy does not have FDA approval for any urinary health indication.**

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Vaginal Estrogens

Low-dose, local, prescription vaginal ET products FDA-approved for vaginal atrophy

- > 17β Estradiol Vaginal cream (Estrace)
- > Conjugated EE vaginal cream (Premarin)
- > Estradiol vaginal ring (Estring)
- > Estradiol hemihydrate vaginal tablet (Vagifem)
  - – 10mcg
- > Estradiol vaginal insert (Imvexxy)
  - – 4mcg and 10mcg

Discuss the black box warning

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NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

Summary of Efforts to Encourage Product Labeling Changes for Low-Dose Vaginal Estrogen Published in *Menopause*

In a commentary published online in the journal *Menopause* on August 21, 2014, (and in print in the September 2014 issue), several clinicians and researchers summarize their activities this past year to encourage modifications to the product labeling of low-dose vaginal estrogen. Motivated by concerns of practicing clinicians that the boxed warning on the labels and package inserts for these products overstate potential risks and thus adversely affect patient care, leaders in the field have spearheaded an effort to encourage consideration of alternative labeling that actually *enhances* patient safety but does not include an alarming boxed warning. The authors of the report (Drs. JoAnn Manson, Steven Goldstein, Risa Kagan, Andrew Kaunitz, James Liu, JoAnn Pinkerton, Robert Rebar, Peter Schnatz, Jan Shifren, Cynthia Stuenkel, Margery Gass, and Wulf Utian) represent the Working Group on Women's Health and Well-Being in Menopause and have affiliations with a number of medical societies, including The North American Menopause Society (NAMS), the American College of Obstetricians and Gynecologists, the Endocrine Society, the American Society for Reproductive Medicine, the International Society for the Study of Women's Sexual Health, and other professional organizations. All of the authors are current or former members of the NAMS Board of Trustees, and this effort addresses a key concern of NAMS membership. The authors have held several conference calls this past year and shared their concerns, literature review, and proposal for alternative labeling with members of the U.S. Food and Drug Administration (FDA) in the Division of Bone, Reproductive and Urologic Products during a teleconference earlier this year. The authors encourage further consideration of their rationale and proposal by both the FDA and the pharmaceutical companies that own these products.

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Practical Pearls for Prescribing Vaginal Therapy

- > Vaginal estrogen: Cream, ring and tablet
  - – Cream may be less expensive
  - – Ring is convenient and left in for 3 months before changing
  - – Tablet is convenient and less messy
- > Opposition of vaginal estrogen by progestin is not required

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Treatment for Dyspareunia

Oral ospemifene 60mg

- > FDA approved for the treatment of dyspareunia associated with vulvovaginal atrophy
- > Estrogen agonist/antagonist (SERM)
- > NAMS
  - – The estrogen agonist/antagonist ospemifene is an oral agent for the treatment of moderate to severe dyspareunia due to GSM/VVA. (Level I)

(Level I based on good and consistent scientific evidence).

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Intrarosa (Prasterone)

Vaginal DHEA for moderate to severe dyspareunia
> FDA approved 11/16
> Once daily vaginal insert
> Two 12 week trials showed reduction in the severity of pain during sexual intercourse compared to placebo
> Most common adverse reactions were vaginal discharge and abnormal Pap tests
> The product was not studied in women with breast cancer

Intrarosa (package insert). Quebec City, Quebec, Canada: Endoceutics Inc, 2016.

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Intrarosa (Prasterone)

> Converted into estrogen and androgen locally
> Contraindicated:
  – Undiagnosed vaginal bleeding
  – History of breast cancer
> Administration
  – Administer 1 insert daily at bedtime intravaginally
  – Use applicator provided; each applicator is for one-time use only
  – Instruct patient to empty bladder and wash hands before handling the vaginal insert and applicator

Intrarosa (package insert). Quebec City, Quebec, Canada: Endoceutics Inc, 2016.

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Fractional Laser Treatment for Vulvovaginal Atrophy

The North American Menopause Society (NAMS) and the American Congress of Obstetricians and Gynecologists (ACOG) agree:
> Further research is needed before this procedure can be recommend for treatment of VVA
> Although the technology is marketed as being FDA approved for broad indications, it is not cleared by the FDA for the specific indication of treating VVA.

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7/30/18 FDA Safety Communication

The FDA stated that:
> "The safety and effectiveness of energy-based devices for treatment of these conditions has not been established"
> Warned that "the treatment of these symptoms or conditions by applying energy-based therapies to the vagina may lead to serious adverse events, including vaginal burns, scarring, pain during sexual intercourse, and recurring/chronic pain."

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Moisturizers & Lubricants

> Vaginal moisturizers – Non-hormonal, no prescription, attracts moisture to vagina, improves pH. Use 2-3 times/week for maintainence
> Lubricants – Water or silicon based, use with sex to help with gliding, also helps with arousal

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PRESCRIPTION NONHORMONAL REMEDIES

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Fezolinetant (Veozah)

> Neurokinin 3 (NK3) receptor antagonist indicted for the treatment of moderate to severe vasomotor symptoms due to menopause
> Contraindicated in women with any of the following: known cirrhosis, severe renal impairment or end-stage renal disease, concomitant use with CYP1A2 inhibitors
> Requires baseline liver enzymes and repeat at 3, 6 and 9 months after starting

Depypere, H., et al. (2021). "Fezolinetant in the treatment of vasomotor symptoms associated with menopause." Expert Opin Investig Drugs **30**(7): 681-694.

109

Fezolinetant (Veozah)

> Skylight 1 and 2 :Identical 12-week placebo-controlled, double-blind Phase 3 studies, followed by a 40-week extension for up to 52 weeks
> Demographics and baseline characteristics were balanced between fezolinetant and placebo with White, Black/African American, and Hispanic women
  – Average age: 54
  – Average BMI: 28
> Statistically significant decrease in VMS frequency and severity along study groups
  – Frequency decreased by week 4: 54% on drug with placebo decreased 33%
  – Frequency by week 12: 63% and 42%
  – Severity decreased from a top score of 3 to 1.0 in the daytime and 0.8 at night

Lederman S, et al. Lancet (Epub) 03-13-2023. 2. Johnson KA, et al. J Clin Endocr 2023 (Epub) 02-0202023.

110

Fezolinetant (Veozah)

> The improvement was reported in the study by women as meaningful
> Safety was evaluated in 1100 women in three 52-week studies
> Most common adverse reactions were abdominal pain, diarrhea, insomnia, back pain, hot flush, and hepatic transaminase elevation

Lederman S, et al. Lancet (Epub) 03-13-2023. 2. Johnson KA, et al. J Clin Endocr 2023 (Epub) 02-0202023.

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Nonhormonal prescription options

> Nonhormonal prescription drugs (off-label use):
  – Antidepressant
    • SSRIs: fluoxetine, paroxetine, escitalopram
    • SNRIs: venlafaxine and desvenlafaxine
  – Hypnotic
    • Eszopiclone
  – Anticonvulsant
    • Gabapentin
  – Antihypertensive
    • Clonidine
  – Neuropathic pain drug
    • Pregabalin

Thacker HL *J Womens Health* 2011;20:1007-16

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Antidepressants For Hot Flashes

> Selective serotonin reuptake inhibitors (SSRIs)
  – Fluoxetine
  – Paroxetine
  – Escitalopram
> Serotonin–norepinephrine reuptake inhibitors (SNRIs)
  – Venlafaxine
  – Desvenlafaxine
➢ None of the above are government approved for hot flashes, so use would be considered off-label

Thacker HL *J Womens Health* 2011;20:1007-16

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FDA Approved Non-Hormonal Treatment

Paroxetine 7.5 mg capsule
> Low dose SSRI
> Indication: Used to treat moderate to severe hot flashes of menopause
> Most common side effects
  – Headache, nausea, vomiting

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Anti-muscarinic (Oxybutynin)

- > Oxybutynin is an effective drug for treatment of hot flashes in patients who have relative or absolute contraindications to hormone-based therapy
- > Oxybutynin does not interfere with the metabolism of tamoxifen, which is an important consideration for breast cancer survivors
- > Women taking 5 mg of oxybutynin for the last 5 weeks of the study had 7.5 fewer hot flashes per day. Women taking 2.5 mg of oxybutynin for 6 weeks had 4.8 fewer hot flashes per day. Women taking the placebo had 2.6 fewer hot flashes per day.
- > Long term use of this drug class may increase risk of dementia

The study findings were presented at the 2018 San Antonio Breast Cancer Symposium.

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Non-Hormonal, Non-Estrogenic Supplement

Relizen

>Swedish flower pollen extract product

>Randomized, double–blind, placebo controlled trials show significant reduction in hot flashes and improved "quality of life" parameters

>No estrogenic effects

>Does not show inhibition of the CYP2D6 enzyme which is necessary for tamoxifen metabolization

Hellström A, Hein L, Hedman C., A herbal remedy made from pollen extracts, Climacteric. 2000; 3: 162-70

Hallström A, Munzing J, The pollen extract Femal+ a nonestrogenic alterative to hormone therapy in women with menopausal symptoms, Menopause. 2012; 7: 825-829

Goldstein SR, Espie M, Druckmann R. Does Relizen, a non-hormonal treatment for vasomotor symptoms, inhibit the CYP2D6 enzyme system, Abstract, Menopause, 12/2014

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Non-Hormonal, Non-Estrogenic Supplement

Equelle

- > Equelle's active ingredient, S-equol, shares a similar molecular structure to estrogen.
- > Is a plant-based compound, derived from soy
- > Allows it to bind to some estrogen receptors and mimic the effects and actions of estrogen.
  - – Alpha receptors: breast, ovary, and uterine tissues
  - – Beta receptors: line blood vessels and some parts of brain
- > Estrogen including hormone replacement binds to both alpha and beta receptors
- > Equelle mostly binds to beta receptors

1. Jenks BH, Iwashita S, Nakagawa Y, et al. A pilot study on the effects of S-equol compared to soy isoflavones on menopausal hot flash frequency. *J Womens Health*. 2012;21(6):674-682. **2.** Aso T, Uchiyama S, Matsumura Y, et al. A natural S-equol supplement alleviates hot flushes and other menopausal symptoms in equol-nonproducing postmenopausal Japanese women. *J Womens Health*. 2012;21(6):635-643. **3.** Data on File. SPI Study Report; Pharmavite LLC. **4.** Tousen Y, Ezaki J, Fujii Y, Ueno T, Nishimuta M, Ishimi Y. Natural S-equol decreases bone resorption in postmenopausal, non-equol-producing Japanese women: a pilot randomized, placebo-controlled trial. *Menopause*. 2011;18(5):563-574. **5.** Muthyala RS, Ju YH, Sheng S, et al. Equol, a natural estrogenic metabolite from soy isoflavones: convenient preparation and resolution of R- and S-equols and their differing binding and biological activity through estrogen receptors alpha and beta. *Bioorg Med Chem*. 2004;12(6):1559-1567.

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Yoga

- > Regular yoga practice did not show any improvement in HF or NS
  - – No difference at baseline, 3, 6 and 12 weeks
- > 249 women randomized
- > Did show improvement for insomnia
- > Other studies have shown about a 36% reduction about the same as placebo

Newton, KM, *Menopause*, 2014.

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Acupuncture

- > Multiple RCTs with various study designs have shown efficacy in reduction of HF and NS of 35-70%
- > Is it possible that Acupuncture reduces neural activity in the hypothalamus and helps regulate temperature
- > A systematic review did not show any benefit over sham acupuncture
  - – 6 trials reviewed did not show any benefit

Lee, MS et al. Climacteric, 2009

119

Case #1

45 yo non-smoker, healthy, normal weight, normal blood pressure, normal lipid profile, has been on birth control pills for twenty years. She is sexually active and requires birth control. She sees you for her annual well woman visit.

Will you continue her birth control pill?

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Case #1

She returns yearly and comes in for her visit at age 51. She asks you if she should continue the pill.

What do you tell her?

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Case #2

54 yo c/o severe hot flashes both day and night. She is a non-smoker, BMI 28, F.H. Mother: osteoporosis, on Benicar 40 mg a day for HTN. Lipids: Mild elevated LDL, Low HDL

Is she a candidate for HT?
Would you suggest oral or transdermal?
What about endometrial protection?
Would you start at the average, middle or lowest dose of therapy?
What is the patient's desire?

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Case #3

63 yo smoker, has HTN, obesity, and type 2 diabetes. c/o trouble sleeping, mood concerns and a few hot flashes a day.

Is she a candidate for hormone therapy?
Would you offer other therapy for her menopausal symptoms?
What is her risk for endometrial cancer, osteoporosis?

123

Case #4

58 yo with severe day and night time hot flashes. She has a BMI of 32, exercises regularly, has normal blood pressure. She had a hysterectomy for fibroids and excessive bleeding at age 45. History of metabolic syndrome with insulin resistance.

Is she a candidate for hormone therapy?
What route of therapy would you recommend?
Would you start with an average, middle or low dose of estrogen?

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Case #5

59 yo woman with c/o severe vaginal dryness and dyspareunia. She has occasional hot flashes, but does consider them manageable.
What therapy would you recommend?
Would you offer vaginal cream, ring or tablet insert?
Would you prescribe progesterone?

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Case #6

69 yo patient is new to your practice. She has been on estrogen and progestin therapy for 20 years. She is on a statin and one medication for HTN. She states that she has tried stopping the hormones, but she is not willing to tolerate the severity of her hot flashes.
Will you continue to prescribe her HT?
What will you tell her about risk and benefit?
What about long term use?

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Menopause Management

> Hormone therapy appears to have favorable effects on symptom management and quality of life in newly menopausal women
> Individualization of care is important
> There may be some advantages of transdermal therapy for some women and advantages of oral therapy for others
> Clinical decisions should be based on:
  – The woman's symptoms
  – Underling risk factors
  – Personal preferences
  – Priorities for treatment

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CONCLUSIONS

- **Hormone therapy is the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and and has been shown to prevent bone loss and fracture.**
- **Risks of hormone therapy differ for women, depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation.**
- **For women aged younger than 60 years or within 10 years of menopause onset and without contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and for the prevention of bone loss and reduction of fracture. Based on the Women's Health Initiative randomized, controlled trials, longer duration may be more favorable for estrogen therapy than for estrogen-progestogen therapy.**

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CONCLUSIONS (CONT)

- **For women who initiate hormone therapy more than 10 or 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable than for younger women because of greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.**
- **For genitourinary syndrome of menopause symptoms not relieved with nonhormone therapies, low-dose vaginal estrogen therapy or other government-approved therapies (eg, vaginal dehydroepiandrosterone or oral ospemifene) are recommended.**

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Conclusion

"Decisions about duration of HT require individualization, including consideration of personal preferences, balancing potential ongoing benefits and risks, and decisions to continue HT for preventative and/or quality of life purposes"

Shared decision making helps our patients make sound choices

Nams. 2016. Kanuitz AM. Menopause June 2014

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QUESTIONS?

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