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OHSU Center for Women's Health

Menopause & Sexual Medicine Program





Disclosures:

- I have no commercial interest in any of the products
 I will discuss today
- I will discuss both on- and off-label uses of drugs
- My perspective is solely that of a clinician and educator



Learning Objective:

 After this talk, you will know important guidelines regarding hormone therapy use in various clinical settings





NOT...





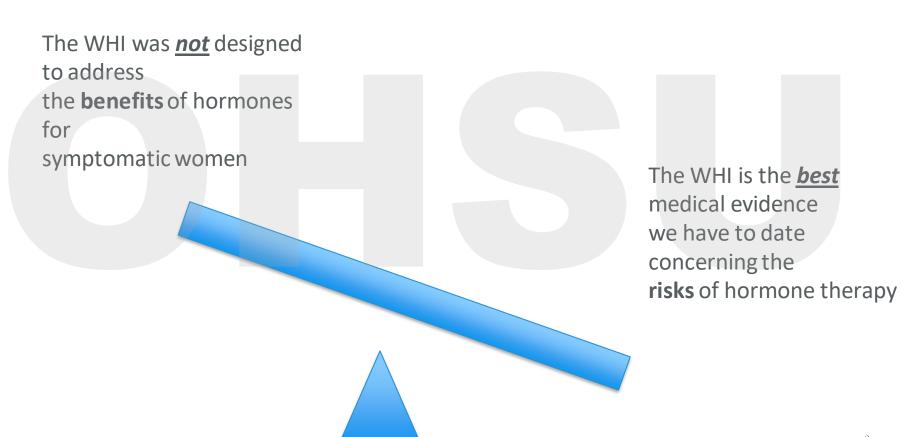
BUT...







Balancing Benefits and Risks





Individualizing:

- Risks differ for different women depending on
 - Dose
 - Duration
 - Route of administration
 - Timing of initiation
 - Progestin or not?
- Periodic reevaluation



The Seven Dwarves of Menopause

Which are caused by menopause? Which can be relieved by hormones?

- Sweaty
- Sleepless
- Bone-dry
- Grumpy
- Anxious
- Dopey
- Sexless





Benefits of Hormone Therapy for **Symptoms**

Unequivocal

- Hot flashes and night sweats
- Vaginal dryness

Probably Beneficial

- Poor sleep
- Adverse mood

Conflicting/ Inadequate Data

- Sexual function
- Urinary incontinence
- Joint pains
- 'Brain fog'
- Changes in body composition
- Skin dryness/wrinkling



It's not just symptoms, it's long term health too!





Essential to know:

Menopause: The Journal of The North American Menopause Society

Vol. 24, No. 7, pp. 728-753

DOI: 10.1097/GME.00000000000000921

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Position Statement

The 2017 hormone therapy position statement of The North American Menopause Society

Abstract

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach



July 13, 2021

Annals of Internal Medicine®

In the Clinic®

Menopause

his review focuses on the diagnosis and management of menopause, highlighting both hormonal and nonhormonal treatment options. In particular, the article focuses on recent data on the risks and benefits of hormone therapy to help clinicians better counsel their patients about decision making with regard to understanding and treating menopause symptoms.

CME/MOC activity available at Annals.org.

Diagnosis

Treatment

Practice Improvement



Practice Improvement

What do professional organizations recommend with regard to management of menopausal patients?

Several professional organizations have released recommendations on management of menopause, including the American College of Obstetricians and Gynecologists in 2014 (68), the North American Menopause Society in 2017 and 2020 (56, 60), the U.S. Preventive Services Task Force in 2017 (51), and the Endocrine Society in 2015 (69). Although the scope of professional guidelines varies, the main areas of disagreement are

related to the effect of HT on specific disease end points, reflecting a rapidly evolving knowledge base and different ways of interpreting conflicting studies.

Most professional organizations agree on 5 principles. First, women should not use HT for prevention of chronic diseases because the risks are likely to outweigh the benefits in the absence of an indication for treatment (such as moderate to severe vasomotor symptoms) and quality-of-life benefits. Second, HT is the most effective treatment for vasomotor symptoms and may be

appropriate for treating moderate to severe vasomotor or urogenital symptoms that do not respond to nonhormonal interventions. Third, women considering HT should discuss with their clinicians their individual risks and balance the benefits and risks of treatment as well as their personal preferences. Fourth, women who choose to use HT should use the lowest dose and the shortest duration necessary to achieve treatment goals. Finally, women with a uterus who choose HT should use therapy that includes a progestogen.



Contraindications to Hormone Therapy

Absolute contraindications:

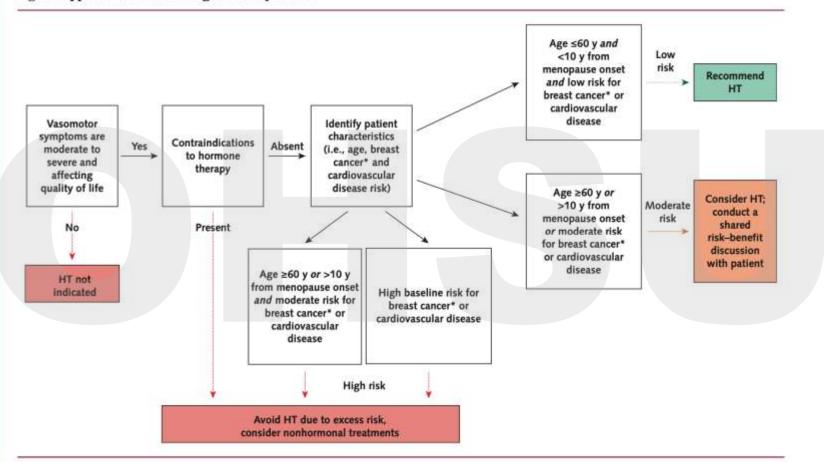
- Pregnancy
- Unexplained vaginal bleeding
- Active liver disease
- Acute cardiovascular disease
- Immobilization
- History of breast or endometrial cancer
- History of coronary artery disease or stroke
- History of thromboembolic disease
- Hypertriglyceridemia (oral estrogen)

Relative contraindications:

- Increased risk for breast cancer
- Increased risk for cardiovascular disease
- Active gallbladder disease
- Hypertriglyceridemia (transdermal estrogen)
- Migraine with aura



Figure. Approach to determining candidacy for HT.



HT = hormone therapy. (Adapted from reference 67.)



^{*} HT increases breast cancer risk only in women with a uterus treated with combined estrogen and progestin.

How We're Going to Think About This Today:

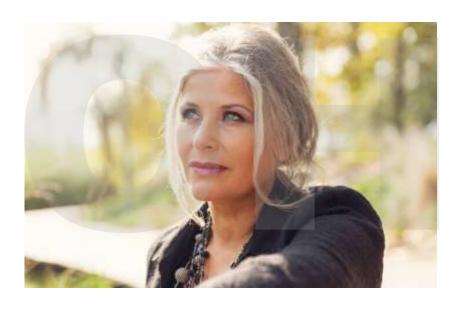


CASES

then POSITION STATEMENT



Patient #1



- 45 yo woman
- Periods are heavier and more unpredictable, skips a period now and then
- 10 hot flashes per day
- 3 night sweats per night
- Using dong quai and evening primrose oil



Cycle Control in Perimenopause

 HT not usually effective for perimenopausal irregular bleeding because these women need CYCLE CONTROL

 HT dosages are about ¼ the strength of the lowest dose oral contraceptive (not enough to control irregular bleeding)



Is it weird that she's hot flashing so much at such a young age?



Natural History of Hot Flashes

Transition Stage	% affected*	Age
Premenopause	20-45%	<45
Pre- to-Early Perimenopause	25-55%	45-47
Early-to-Late Perimenopause	50-80%	47-49
Late Peri-to-Postmenopause	35-75%	49-55
Late Postmenopause (>5yr)	16-44%	56+

References:

Barnabei V et al. Obstet Gynecol 2002; 100:1209-18 Gold EB, et al, Am J Pub Health 2006; 96:1226-35 Politi MC, et al. J Gen Intern Med 2008;23:1507–13.



Patient #1 how to manage?



- Consider endometrial sampling
- Stop the dong quai and evening primrose oil
- Low dose monophasic OCP
- When to stop?





Patient #2

- 54 yo woman
- LMP 2 years ago
- 10 hot flashes per day
- 3 night sweats per night
- Waking more than she used to





Patient #2 How to manage?

- She is fully menopausal and incredibly symptomatic
- Start E + P
- Vivelle 0.5 mg/day biweekly patch
- prometrium 100 (200) mg at night
 - Could also consider LNS IUD
- Give her sleep hygiene recs
- See her back in 6-8 weeks





Vasomotor Symptoms

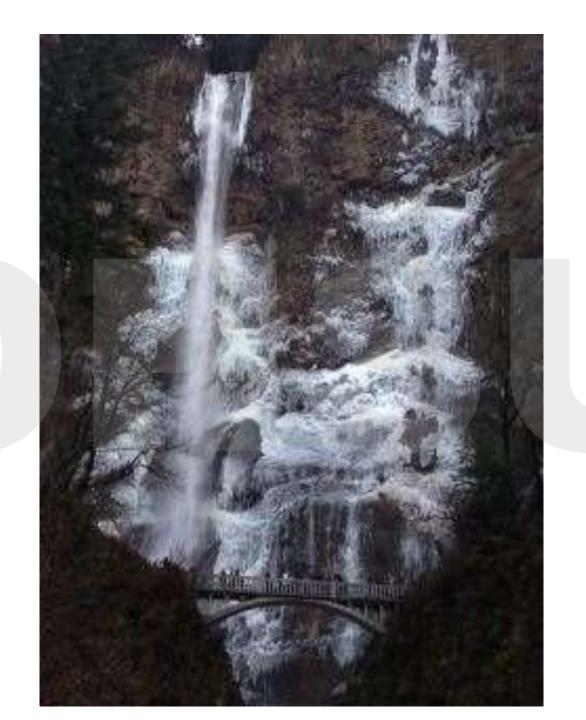




NAMS Position Statement

- HT is the gold standard for relief of vasomotor symptoms
 - ET
 - -E+PT
 - PT
- Use the lowest dose that gives relief and periodically reevaluate
- SSRIs/SNRIs best alternative; gabapentin thirdline







Type, dose, regimen, duration

- Women with a uterus need P
 - Prometrium 100 mg q hs (200)
 - Mirena or Skyla IUD
- Transdermal may decrease some risks
 - No RCT data, observational only
- Decisions about continuation must be individualized



Oral vs. transdermal estrogen therapy and thromboembolic complications

Study Publication	Oral Estrogen	Transdermal Estrogen
	Odds Ratios (95% Confid	ence Intervals)
Scarabin, et al. <u>Lancet</u> , 2003, 362(9382): p. 428-32.	3.5 (1.8-6.8)	0.9 (0.5-1.6)
Canonico, et al. <u>Circulation</u> , 2007,115: 840-845	4.2 (1.5-11.6)	0.9 (0.4-2.1)





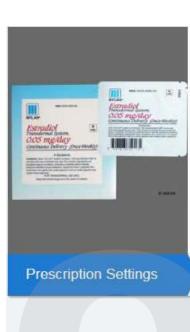
Combipatch

ESTRADIOL; NORETHINDRONE contains a mixture of female hormones. This medicine helps to relieve the symptoms of menopause like hot flashes, night sweats, mood changes, and vaginal dryness and irritation. It is also used to treat women with low estrogen levels or those who have had their ovaries removed. Compare estrogen / progestin combinations.

with free coupon

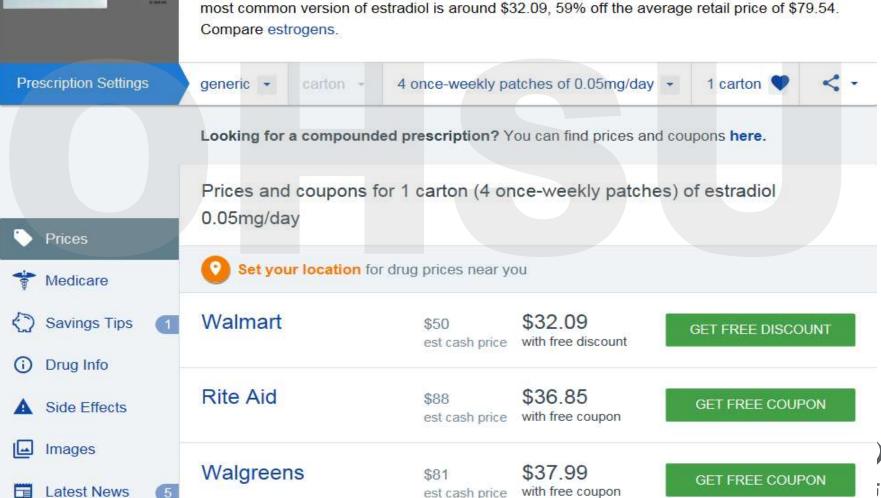
GET FREE COUPON

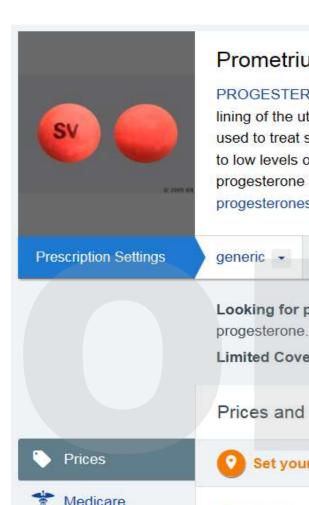
brand + package -8 patches of 0.05mg/0.14mg -1 package Prices and coupons for 1 package (8 patches) of Combipatch 0.05mg/0.14mg Set your location for drug prices near you Costco \$181.68 GET FREE COUPON with free coupon Shopko \$181.68 **GET FREE COUPON** with free coupon Walmart \$185.07 GET FREE DISCOUNT with free discount Fred Meyer Pharmacy \$186.71



Climara Estradiol

Estradiol (Estrace, Vivelle-Dot, Climara) is a moderately priced drug used to treat hot flashes and osteoporosis. It is also used to treat women with low estrogen levels or those who have had their ovaries removed. This drug is more popular than comparable drugs. It is available in multiple generic and brand versions. It is covered by some Medicare and insurance plans, but manufacturer and pharmacy coupons can help offset the cost. The lowest GoodRx price for the most common version of estradiol is around \$32.09, 59% off the average retail price of \$79.54. Compare estrogens.





Prometrium Progesterone

PROGESTERONE is a female hormone. This medicine is used to prevent the overgrowth of the lining of the uterus in women who are taking estrogens for the symptoms of menopause. It is also used to treat secondary amenorrhea. This is when a woman stops getting menstrual periods due to low levels of progesterone. The lowest GoodRx price for the most common version of progesterone is around \$20.60, 62% off the average retail price of \$54.96. Compare progesterones.

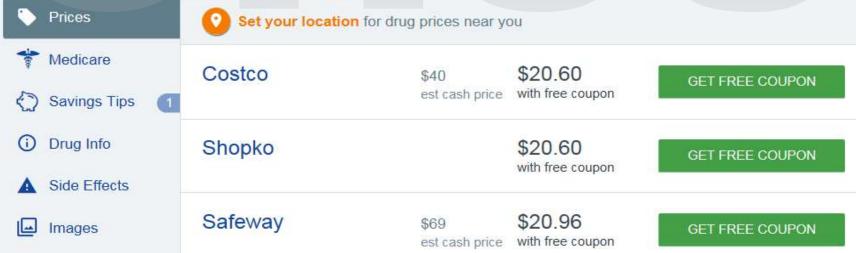
30 capsules -

Looking for progesterone in oil? Select "vial" as your form to see prices for injectable

Limited Coverage: Most insurance plans will not cover progesterone for fertility treatments.

Prices and coupons for 30 capsules of progesterone 100mg

100mg -



Practice Pearl: dosing gabapentin for vasomotor symptoms

	Morning	Afternoon	Evening
First 7 days			100 mg
Next 7 days	100 mg		100 mg
Next 7 days	100 mg	100 mg	100 mg
Next 7 days	100 mg	100 mg	200 mg
Next 7 days	200 mg	100 mg	200 mg
etc	Etc up to 300 mg	Etc up to 300 mg	Etc up to 300 mg



What about herbs/botanicals?

- Soy and maca a little more effective than placebo
- Not more effective than placebo:
 - Red clover
 - Dong quai
 - Women's botanical formulas
 - Evening primrose oil
 - Black cohosh











Patient #3 how to evaluate?



- 35 year old woman
- No period for 10 months



Patient #3 how to manage?



- 35 year old woman
- No period for 10 months
- HCG neg
- TSH, PRL normal
- FSH 59, Estradiol 12
- Neg P withdrawal bleed



Early menopause/POI

- Benefits outweigh risks
 - Bone
 - Heart
 - Cognition
 - VVA/GSM
 - Sexual function
 - Mood
- HT recommended at least until age of menopause
- Younger women require higher doses



"lowest effective dose"

- Treats vasomotor symptoms
 - 30 pg/mL
- Protects bone health
 - 40 pg/mL
- Cardioprotection
 - 50-80 pg/mL
- POI patients
 - 100 pg/mL
- Serum assays are an advantage of estradiol over conjugated estrogens
- Stop all biotin-containing vitamins 48 h prior to draw



When to follow estradiol levels?

- NOT routinely
- For a particular therapeutic goal
- If patient is not responding clinically
- Progesterone levels not clinically relevant





Patient #4 how to manage?

- 40 year old woman
- BRCA+
- Planning RRBSO



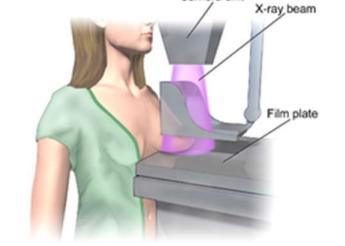


Family history of breast cancer

- Limited data from observational trials indicates that HT doesn't alter risk for breast cancer in women with a family history
- This risk should be assessed when counseling women
- BRCA+ women who have undergone RRSO should be given HT until at least the age of menopause



Breast cancer



Mammogram

- HT's effect on risk of breast cancer is complex and conflicting
- May depend on
 - Type of HT, dose, duration of use
 - Regimen, route of administration
 - Individual characteristics



Breast cancer and WHI

- Increased risk of invasive breast cancer after 3-5 years of CEE + MPA
- No increased risk of breast cancer seen with 7 years of CEE alone
- Allows more flexibility in use of HT in women without a uterus
- Risk is greater from sedentary lifestyle, obesity, or alcohol intake than from estrogen





Survivors of endometrial cancer

- YES if early stage
 - Especially if younger than age 51
- Non-hormonal therapies recommended for more advanced stages
- Low dose vaginal ET works for GSM/VVA



Survivors of breast cancer



Survivors of breast cancer

- Generally contraindicated
- Selected cases with compelling reasons may be discussed with medical oncologist
- After nonhormonal options have failed
- Local ET for GSM/VVA is OK
 - Try nonhormonal options first
- NOT if on aromatase inhibitors without consultation



Contraindications to Hormone Therapy

Absolute contraindications:

- Pregnancy
- Unexplained vaginal bleeding
- Active liver disease
- Acute cardiovascular disease
- Immobilization
- History of breast or endometrial cancer
- History of coronary artery disease or stroke
- History of thromboembolic disease
- Hypertriglyceridemia (oral estrogen)

Relative contraindications:

- Increased risk for breast cancer
- Increased risk for cardiovascular disease
- Active gallbladder disease
- Hypertriglyceridemia (transdermal estrogen)
- Migraine with aura

The Annals



Duration

- Risk/benefit balance (vasomotor sx, bone loss)
- Absolute risks that increase with age
 - CHD
 - Stroke
 - VTE
 - PE
 - Breast cancer
- No recommendation to automatically stop at age 65



Patient #5

- 59 yo African
 American woman
- Has been struggling with hot flashes for years
- T2DM
- On a statin and a BP med





NAMS MenoPro App incorporates the ASCVD risk calculator





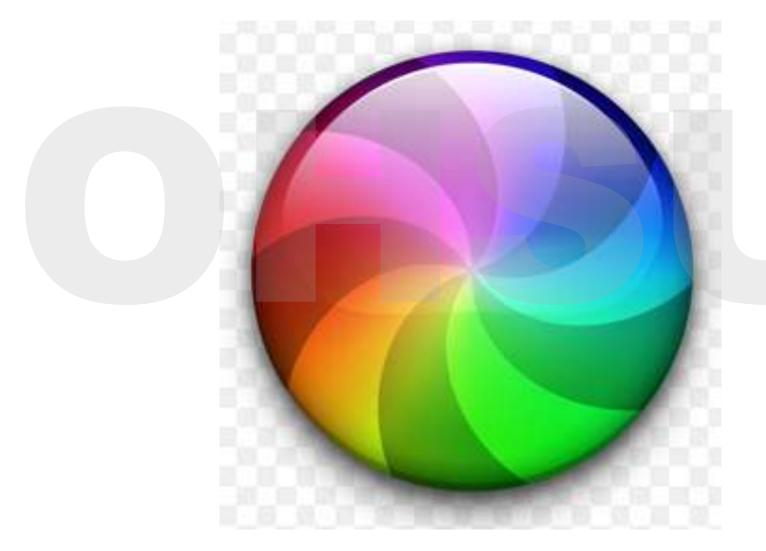
The app asks you

- Age?
- Less than 10 years past the onset of menopause?
- Hysterectomy?
- Ethnicity?
- Smoker?
- Treatment for HTN?
- Systolic BP?

- Diabetes?
- On cholesterol-lowering medication?
- Total cholesterol level?
- HDL?

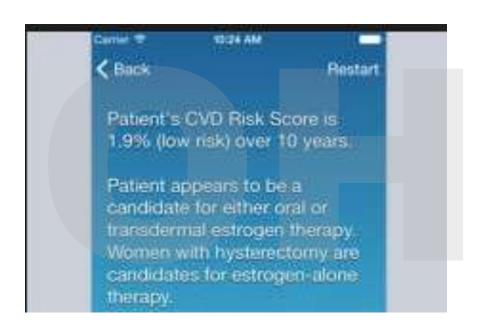


Then you wait...





Results Page



- Gives the patient's CVD Risk Score over 10 years
- Gives you a list of every appropriate treatment option and dosages



Patient #5

- "The CVD Risk Score is 13.9% (high risk) over 10 years"
- "Patients with CVD risk scores above 10% should avoid initiation of systemic hormone therapy but may be candidates for nonhormonal therapy"





Patient #6

- 56 yo woman
- BMI 19.6
- Smoker
- Mother had a hip fracture





BMD testing recommendations

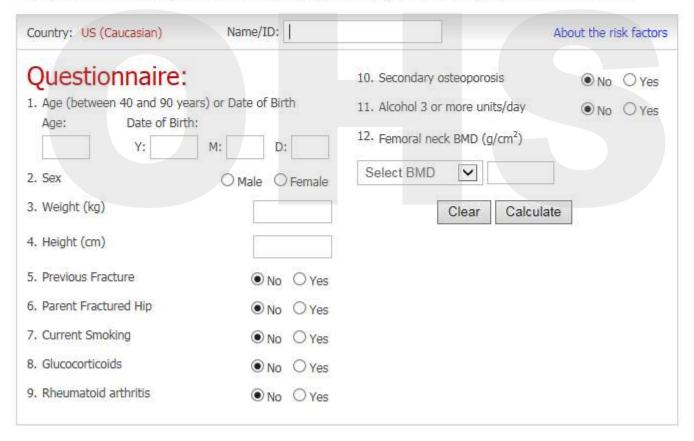
- All women age 65 and older
- Postmenopausal women younger than age 65
 if FRAX score for 10-year risk of major fracture
 is
 ≥9% (average fracture risk for healthy women)
- Postmenopausal women with medical causes of bone loss
- Postmenopausal women with history of fragility fracture



Home Calculation Tool ▼ Paper Charts FAQ References English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.





Individuals with fracture risk assessed since 1st June 2011

Osteoporosis risk assessment

- Identify postmenopausal women at risk for fracture using FRAX
- Reduce modifiable risk factors through dietary and lifestyle changes
- If indicated, prescribe pharmacologic therapy or refer for this treatment



HT and Fracture Prevention

- WHI showed that HT reduced risk of fractures even in low risk women
- Average T scores of women in WHI
 - hip -0.94
 - spine -1.3
- Vertebral and radiologically-detected not included in global index



Patient #6

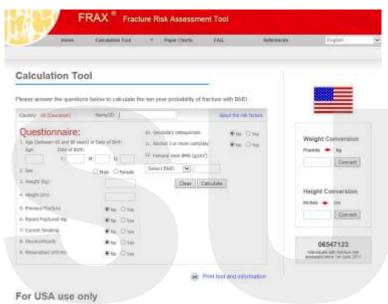
- 10 year risk of osteoporotic fracture = 11%
- 10 year risk of hip fracture = 1.2%
- Can consider HT because she is higher than average risk for healthy women

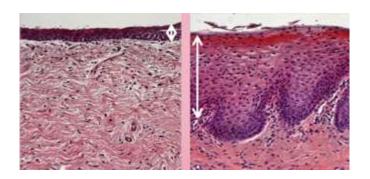




FDA-approved indications for HT









FDA-approved indications for HT

Vasomotor symptoms

Surgically or medically menopausal women

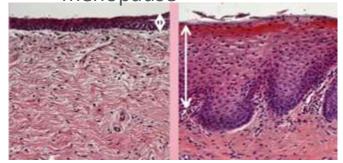


Treatment of women at high risk for osteoporosis



For USA use only

Genitourinary syndrome of menopause





US Preventative Services Task Force 2017

Final Recommendation Statement

Hormone Therapy in Postmenopausal Women: Primary Prevention of Chronic Conditions

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Population Recommendation Grade (What's This?) Postmenopausal women The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women. Postmenopausal women who have had a hysterectomy The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal women who have had a hysterectomy.

Grade D = evidence of no net benefit or harms outweigh benefits



A Word about GSM and local estrogens...



FDA-approved estradiol treatments

- Topical vaginal cream (Estrace)
 - 1 gm on fingertip nightly x 2 weeks then 2x week
- Vagifem tablets or Estring inserted in the vagina
- Estrogen softgel approved June 2018 ("more elegant delivery system")







Safety of local E therapy

- Reassuring when serum levels are measured
 Serum levels: E cream > E tablet > E ring
 All within menopause levels
- Reassuring when endometrial stripes are ck'd
- We now have 7-year follow up
- Breast cancer survivors need to know what is safe!





SCARY PACKAGE LABELLING!

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VAGIFEM® safely and effectively. See full prescribing information for VAGIFEM®.

Vagifem® (estradiol vaginal inserts)

Initial U.S. Approval: 1999

WARNING: ENDOMETRIAL CANCER, Cardio Vascular disorders, breast cancer and probable dementia

See full prescribing information for complete boxed warning

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The Women's Health Initiative (WHI) estrogenalone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.2)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

—— RECENT MAJOR CHANGES ——

- Warnings and Precautions, Malignant Neoplasms (5.3) 11/2017
 - INDICATIONS AND USAGE ———
- Vagifem® is an estrogen (estradiol) indicated for the treatment of atrophic vaginitis due to menopause (1.1).

— DOSAGE AND ADMINISTRATION ——

Vagifem® should be administered intravaginally:

 1 insert daily for 2 weeks, followed by 1 insert twice weekly (for example, Tuesday and Friday) (2.1)

DOSAGE FORMS AND STRENGTHS

- Vagifem® 10 mcg insert: One vaginal insert contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol (3)
- Vagifem® 25 mcg insert: One vaginal insert contains 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol (3)

——— CONTRAINDICATIONS —

- Undiagnosed abnormal genital bleeding (4)
- . Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active DVT, PE, or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.2)
- Known anaphylactic reaction or angioedema to Vagifem®
- Known liver impairment or disease (4, 5.11)
- Known protein C, protein S, or antithrombin deficient, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

— WARNINGS AND PRECAUTIONS ———

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- The Vagifem® applicator may cause vaginal abrasion (5.17)
- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

—— ADVERSE REACTIONS ——

In prospective, randomized, placebo-controlled, double-blind studies the most common adverse reactions (incidence ≥5 percent)

were upper respiratory tract infection, headache, abdominal pain, back pain, genital pruritus, moniliasis, vulvovaginal mycotic infection and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-824-4336 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---- DRUG INTERACTIONS ----

 Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

— USE IN SPECIFIC POPULATIONS —

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

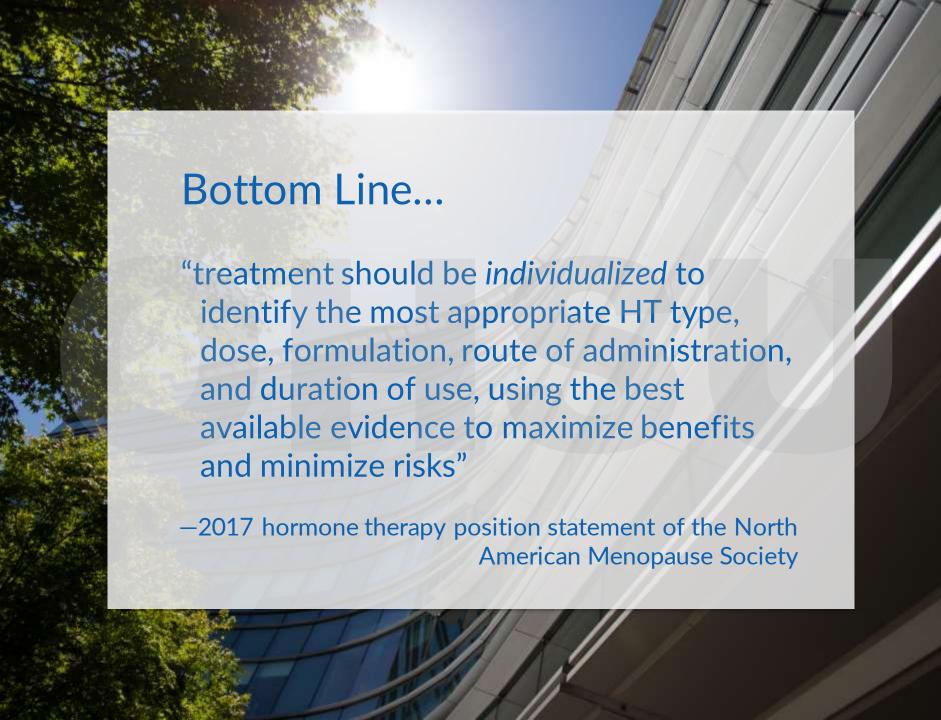
Revised: 11/2017



Choices of local therapy

- User abuse less likely with vaginal tablets or vaginal ring – temptation to use lots of cream
 - Med oncs are happier with tablet or ring than cream
 - OK if you take time to explain to your patient!





Menopausal Zest



- In a Gallup survey of 752 women, in the majority of women these areas were better or stable:
 - role at work
 - family life
 - partner/sexual relationship
 - friendships
 - self-fulfillment
 - and physical health.

Utian WH Menopause 1999;6:122-8





