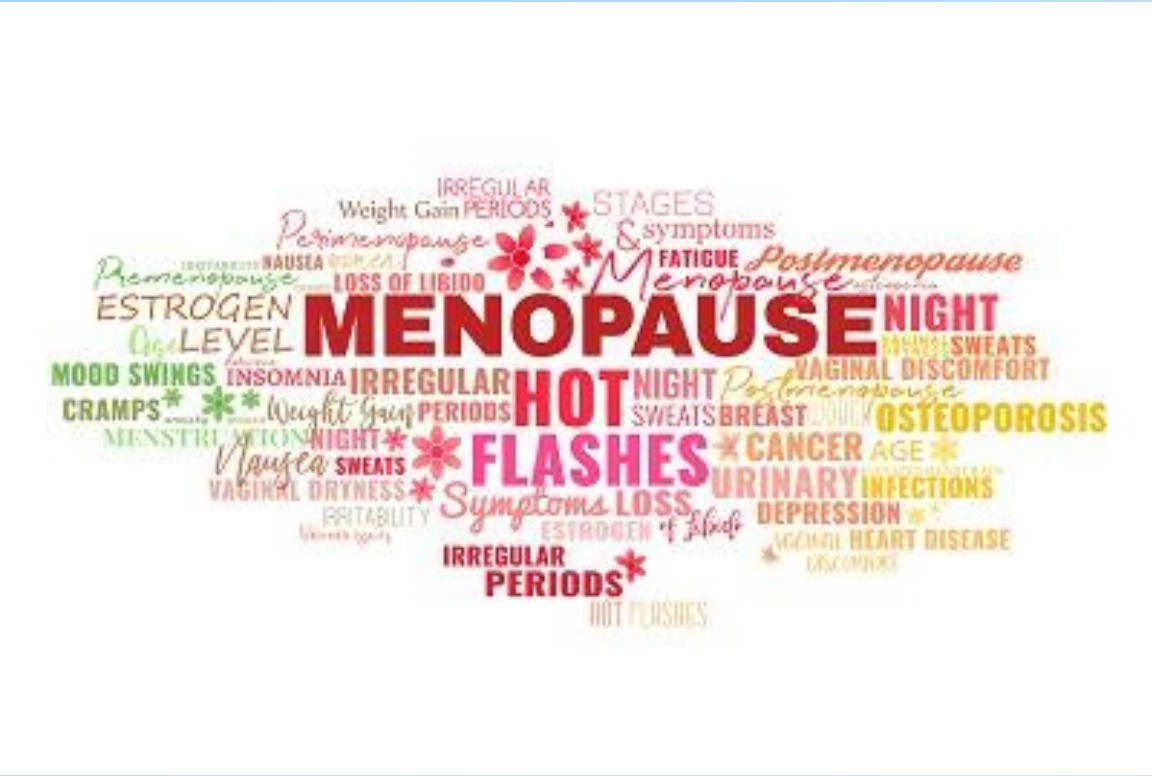

Menopause

Lisa J. Wastila, MD, FACP, NCMP

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Educational Objectives

- Define menopause and describe associated symptoms
- Define and understand treatment rationale for vasomotor, genitourinary, and neuropsychiatric symptoms of menopause
- Identify safety and efficacy of common treatment options
- Gain comfort in treatment of menopausal symptoms

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Case:

Ms. MP is a 52-year-old healthy woman who takes no medications. She presents with episodic symptoms of an intense sense of heat of her upper chest and face associated with flushing and profuse diaphoresis. The episodes started two years ago and have increased in frequency and severity. They now occur 3-4 times a week and can wake her at night. Her last period was 20 months ago. She is distressed that her sexual desire is diminished and that intercourse has become increasingly uncomfortable due to vaginal dryness. She is also concerned that she can be forgetful and, at times, has trouble remembering people's names. She asks you if these symptoms are related to menopause and what you can prescribe to treat them. A good friend of hers, who was taking hormone therapy for similar symptoms, was recently diagnosed with breast cancer, and Ms. MP does not wish to use hormones. On pelvic exam, the vaginal mucosa is pale and dry with some loss of rugae.

The Real Challenge:

Average length of menopausal symptoms is felt to be 7.5 years!

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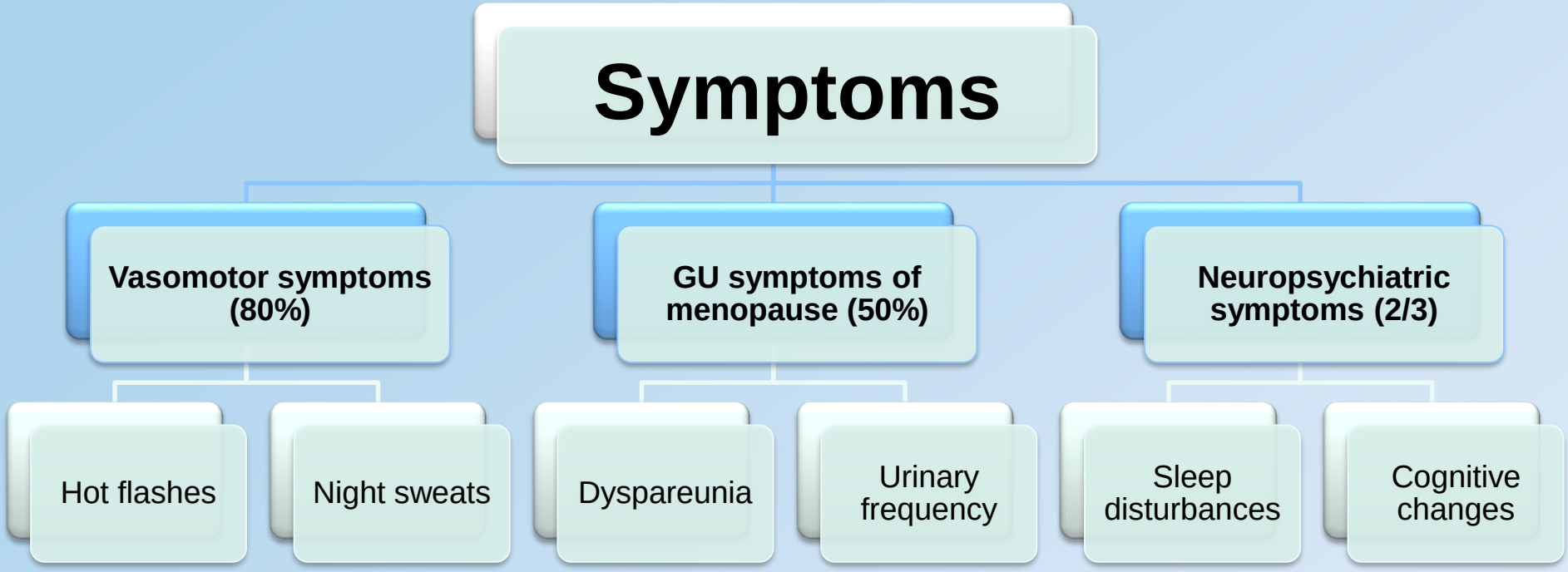
Definition of Menopause

- **Natural menopause:** Retrospective diagnosis made after 12 months of amenorrhea due to natural causes in an age-appropriate woman (median age 51 years in the US)

- Symptoms are related to the marked reduction in estrogen production and can start any time after the onset of menstrual irregularities (but as late as 1 year after the final period).



For our patient, you can attribute her hot flashes, night sweats, vaginal dryness, and cognitive symptoms to menopause. You can reassure her that the vasomotor symptoms will diminish and that memory problems are common during the perimenopause and may improve now that she is postmenopausal. Her lower libido may be related to dyspareunia and will likely improve with treatment of the GU symptoms of menopause.

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Nonhormonal Medications

SSRI/SNRIs*	•Paroxetine 10-25 mg daily, citalopram 10-20 mg daily, fluoxetine 20 mg daily, venlafaxine 37.5-75 mg daily, desvenlafaxine 75 mg 1-2 times daily
Gabapentinoids†	•Pregabalin 75-150 mg twice daily, gabapentin up to 900 mg total daily
Clonidine‡	• Clonidine 0.1-0.3 mg/day (via weekly patch)
NK-B Antagonists	• Fezolinetant 30-45 mg daily (awaiting FDA approval)

*HA, insomnia, sexual dysfunction, anxiety, SI †HA, fatigue, dizziness, somnolence, wt gain, edema ‡Dry mouth, hypotension

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A new nonhormonal option for vasomotor symptoms: NK3RA

- Fezolinetant: neurokinin-3 receptor antagonist
- Oral medication taken once daily
- Phase 3 clinical trials completed 6/2022, awaiting FDA approval
- Studied in women aged 40-62
- Reduced hot flashes significantly after 4 weeks
- May provide a nonhormonal option for women who cannot take hormone therapy due to risks

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Complementary and Alternative Therapies

- Isoflavones (phytoestrogens from soy or red clover) and botanicals (e.g., black cohosh, dong quai, evening primrose, ginseng): Inconsistent or no benefits (Nelson, 2006; Stuenkel, 2015; Franco, 2016)
- Weight loss, mindfulness, hypnosis, and CBT: Randomized studies support effectiveness of these therapies (Franco, 2016)
- Acupuncture, exercise, and yoga: Inconsistent or no effect, but individual women may benefit (Franco, 2016)

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Treatment of GU Symptoms

- Moisturizers (daily) and lubricants (during intercourse)
- Regular stretching of the vagina by intercourse or stimulation/vaginal dilators, pelvic floor PT
- Topical vaginal estrogens: Some systemic absorption expected from cream (not tablet, insert, or ring)
- Ospemifene: SERM with agonists effects on vaginal epithelium and bone; increases hot flashes, VTE risk, and stroke risk
- DHEA vaginal suppositories: Converted into androgens and estrogens, so may have small systemic effects

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SERMs in Menopause

Table Effects of SERMs vary in target tissues[3–21, 23–26]

SERM	Bone	Brain	Breast	Endometrium-uterus	Vagina	Cardiovascular	FDA indication
Tamoxifen[3–7]	Agonist	Antagonist	Antagonist	Agonist	Agonist, variably	Agonist	Prevention of breast cancer in high-risk women
Raloxifene[8–14]	Agonist	Antagonist	Antagonist	Neutral	Neutral	Agonist	Treat and prevent osteoporosis; prevention of breast cancer in high-risk postmenopausal women
Bazedoxifene[15,16]	Agonist	Weak antagonist	Antagonist	Antagonist	Antagonist	Neutral	None as monotherapy
Ospemifene[17–21]	Agonist	Antagonist	Neutral	Partial agonist	Agonist	Agonist	Moderate-to-severe dyspareunia in VVA
Lasofoxifene[23,24]	Agonist	Weak antagonist	Antagonist	Neutral	Agonist	Agonist	None; in development
BZA/CE[25,26]	Agonist	Agonist	Neutral	Neutral	Agonist	Agonist	Vasomotor symptoms and prevention of osteoporosis

Abbreviations: BZA/CE, bazedoxifene/conjugated estrogen; FDA, US Food and Drug Administration; SERM, selective estrogen receptor modulator; VVA, vulvovaginal atrophy.

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Case continued

- You prescribe venlafaxine for hot flashes and a vaginal moisturizer and lubricant. Our patient returns six months later with an increase in vasomotor symptoms and with drenching night sweats that interfere with her sleep and ability to function at work. Her vaginal symptoms have improved to a tolerable level with the use of moisturizers and lubricants. Her low libido and memory problems persist, though they are not worse. She is ready to consider hormone therapy and asks if hormones are a safe option.
- Ms. MP's calculated 10-year ASCVD risk is less than 5%, and she is 8 months post-menopause.

Would you prescribe hormone therapy?

- **Menopause hormone therapy (MHT):** Most effective therapy for hot flashes (75% ↓ in frequency and 87% ↓ in severity)

Does the patient have moderate to severe vasomotor symptoms?

If yes, and no contraindications (unexplained vaginal bleeding, CVD, CVA/TIA, history of breast/endometrial cancer, VTE, liver disease), assess time from menopause (TFP) and 10-yr. ASCVD risk.

If ASCVD risk <5% and TFP <10 years, consider MHT.

If ASCVD risk 5-10% and TFP <10 years, consider MHT (esp. transdermal estrogen).

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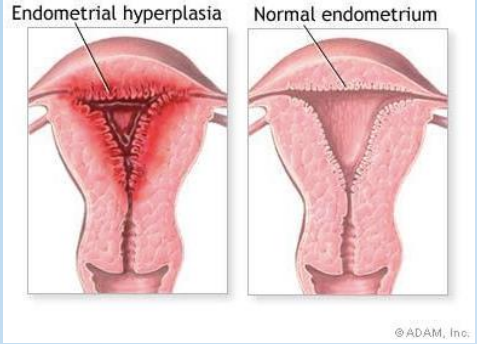
Some basics about HT



- If a patient has a uterus, she needs to take a progestogen (progesterone) along with estrogen in order to prevent endometrial hyperplasia
- If a patient has had a hysterectomy, she may take estrogen alone
- Risk profile is slightly different for these two types of HT

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Endometrial Protection

- For systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen (or use of the combination conjugated equine estrogen and ther SERM bazedoxifene: Duavee) (Level 1)
- Progestogen is **not** recommended with low dose vaginal estrogen (Level 1) – FDA labeling to be changed
- Appropriate evaluation of the endometrium should be performed if vaginal bleeding occurs (Level 1)

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“Bioidentical”: What Does it Mean?

- Bioidentical: The same form of hormone that would be endogenously secreted by the body
  - The bioidentical estrogen is estradiol
  - The bioidentical progesterone is micronized progesterone (Prometrium)

❖There is no need to have custom compounded hormonal products in order for them to be bioidentical. There are plenty of FDA approved preparations, the concentrations of which are regulated.

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Women's Health Initiative

- Landmark RCTs started in 1991
- Randomized women to either oral CEE 0.625 mg-MPA 2.5 mg or CEE 0.625 mg daily alone (for women with hysterectomy) for primary prevention of CHD, stroke, cancer, osteoporosis
- CEE-MPA group: small increased risk for breast cancer, heart attack, and stroke
- CEE alone group: small increased risk for stroke
- Both groups: small increased thrombosis risk

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Women's Health Initiative cont'd

- Stopped CEE-MPA arm in 2002 due to concerns about risk for CV disease, stroke, breast cancer
- Stopped CEE arm in 2004 due to concerns about risk for stroke
- Caused many women to be taken off HT abruptly
- Initial findings did not separate groups by age, confidence intervals very close to 1.0

Posthoc analysis of WHI

- WHI: women aged 50-59 or within 10 years of menopause
  - No increased risk of stroke or CVD in either group (CEE alone or CEE-MPA)
  - most risks of HT, except for breast cancer in the EPT trial, dissipated over time
  - Suggestion of increased risks beginning at age 60, >10 years after menopause
  - Increased thrombosis risk still present (more with oral therapy)

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Continuation Data from WHI

- WHI has been continued and in 2017 reported new data including up to 18 years of follow up
- Conclusion: continuation (not “new start”) for patients even now well above age 60 and up to 18 years of follow up did not affect mortality
- HT not recommended for primary cardiovascular disease prevention, but can be considered for lower risk women for symptom control

Safer treatment options

- WHI was conducted with oral CEE/MPA only
- Transdermal estrogen found to be safer than oral
  - Lower thrombosis risk (avoidance of first pass effect and hepatic metabolism which leads to increase in clotting factors), less lipid effects
  - Some studies show transdermal estrogen alone causes no increase or even slightly reduced risk of stroke (i.e. BMJ, 2010)

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HT and Premature Menopause/POI

- Data regarding HT in women over age 50 should not be extrapolated to younger postmenopausal women
- Observational studies suggest that benefits of HT outweigh the risks for effects on bone, heart, cognition, GSM, sexual function, and mood
- HT recommended until at least the median age of menopause (51.4)
- HT at higher doses of estrogen with adequate endometrial protection may be needed to protect bone

HT and Coronary/Heart Disease

- The effects of HT on CHD may vary depending upon a woman's age and time since menopause
- There are data that show reduced CHD in women who initiate HT before age 60 and/or within 10 years of menopause (11 fewer cases of CHD per 10,000 in WHI, Finnish studies)
- There is concern for increased risk of CHD in women who initiate HT above age 60 or more than 10 years from menopause, "new start" phenomenon

HT and Stroke

- Meta-analyses of RCTs: no increased risk of stroke if HT initiated within 10 years of menopause
- WHI: Initiating oral HT >age 60 led to a rare attributable risk of stroke
- WHI: Increased risk of stroke with both CEE/MPA and CEE alone in overall study cohort
- Meta-analysis of RCTs shows increased risk of stroke in women >10 years from menopause
- Risk of stroke may not be present or as significant with transdermal HT (particularly ET alone)

HT and Cognition

- HT is not recommended at any age for preventing or treating cognitive problems or dementia
- CEE/MPA initiated at age >65 showed a small increase in risk for dementia (WHI)
- ET may have positive cognitive benefits if initiated immediately after early surgical menopause
- HT in the early postmenopausal period has neutral effects on current cognitive function
- Only tentative support (observational studies) for critical window hypothesis of HT in Alzheimer's disease prevention

HT and Mood

- Mood disorders can be unmasked by menopause
- Evidence is insufficient to support hormone therapy use in the treatment of clinical depression
  - In small RCTs, ET improved clinical depression in perimenopausal, but not postmenopausal, women. Indicated if vasomotor symptoms present.
- Progestins may contribute to mood disturbance
- Subset of women whose depression improves with HT are likely to experience a worsening of mood after estrogen withdrawal

FDA Approved Indications for Hormonal Treatment

- First line therapy for bothersome VMS in PM women without contraindications (Level 1)
- Primary therapy for prevention of bone loss and fracture in PM women at elevated risk of osteoporosis or fractures (Level 1)

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FDA Approved Indications for Hormonal Treatment cont'd

- For hypogonadism, POI, or premature surgical menopause, HT is recommended until the average age of menopause (51.4) (Level 1)

- Low dose vaginal ET is recommended first line for isolated GSM (Level 1)
  - No progestogen necessary with vaginal ET only

Discontinuation of HT >60-65

- The recommendation using the Beers criteria to routinely discontinue systemic HT after age 65 is not supported by data
- Decisions regarding whether to continue HT beyond the age of 60 should be made on an individual basis
  - After appropriate evaluation
  - Counseling about potential benefits and risks
  - Ongoing surveillance

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Appropriate Type, Dose, Formulation, Route of Adminstration and Duration

- Movement in menopause health community to change “lowest dose for shortest period of time”
- Use an “appropriate HT type, dose, formulation, route of administration, and duration”
  - To meet treatment objectives
  - Periodic reassessment of changes in benefits, risks, and treatment goals over time

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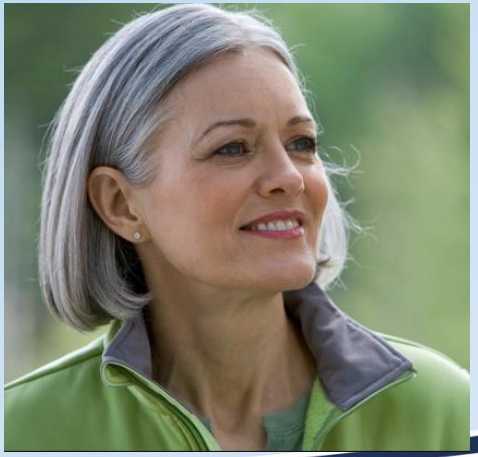
Key Message: Overall Risk-Benefit (NAMS)

- HT represents a safe and effective option for treatment of menopausal symptoms (VMS and GSM) and prevention of bone loss in healthy younger postmenopausal women, despite concerns about adverse CV effects in older women



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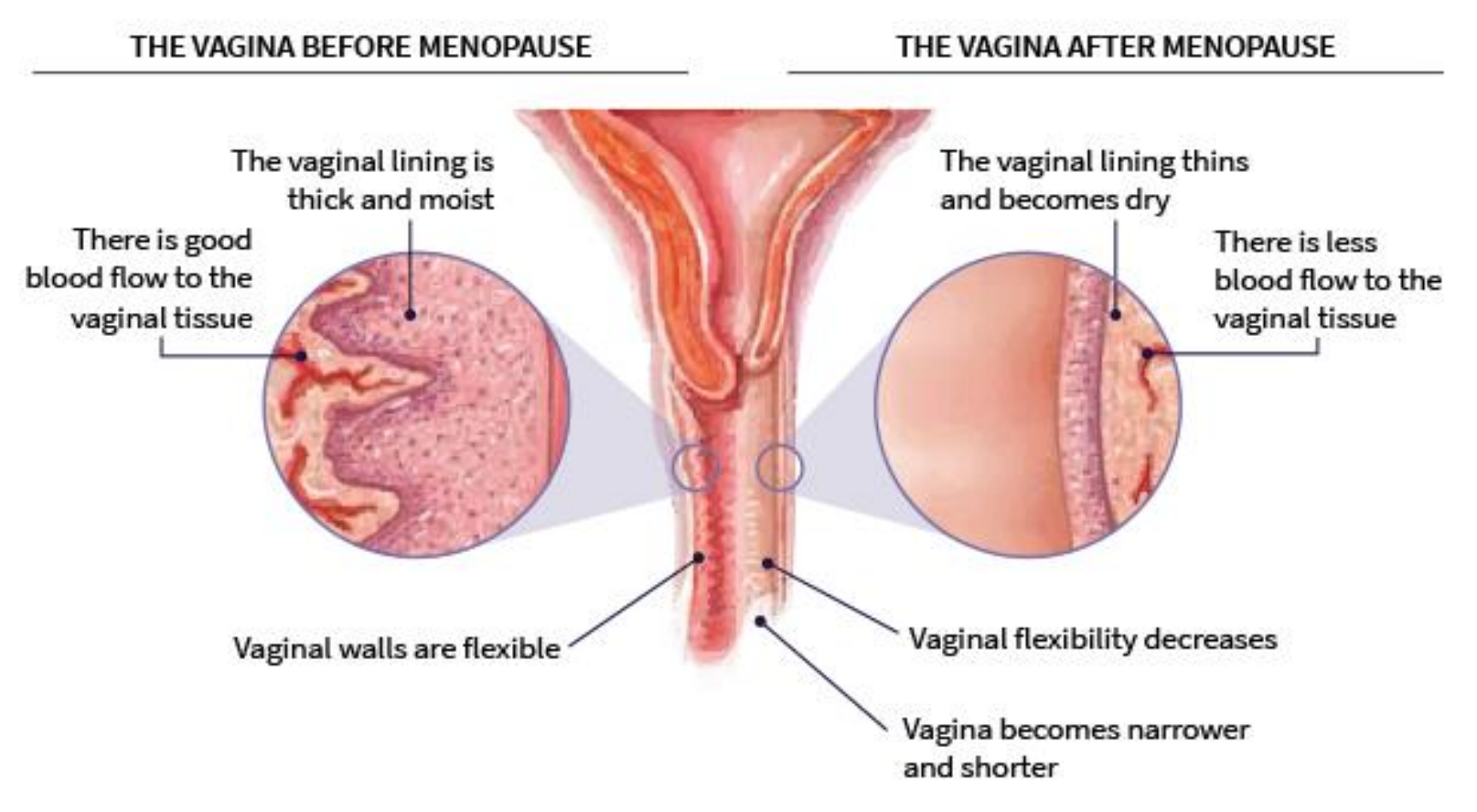
Case continued

You prescribe a 0.025 mg transdermal estradiol patch and micronized progesterone 100 mg nightly. She comes back for follow up 6 months later reporting that her hot flashes and night sweats have mostly resolved, but now she notices dryness and pain with intercourse which is no longer relieved by vaginal moisturizers and lubricants. She also complains of low libido.

Genitourinary Syndrome of Menopause (GSM)



In contrast to vasomotor symptoms, genitourinary symptoms typically worsen over time

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Low Dose Vaginal ET Safe and Effective

- Available as tablet, insert, cream (maintenance dose is twice weekly), and ring (changed every 3 months)
- Very low systemic absorption for tablet, insert, and ring (higher for cream)
- Progesterone not necessary at usual doses
- FDA boxed warning: based on systemic HT, not accurate for vaginal ET (to be changed)

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Breast Cancer Survivors with GSM

- Low dose vaginal ET has minimal systemic absorption (blood levels in postmenopausal range) particularly for tablet/insert and ring
- Based on limited data, minimal risk for recurrence of breast cancer (Level 2)
- Decisions should involve the woman's oncologist

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Use It or Lose It?

- Vaginal dryness is a predictable symptom of menopause at some point; may also develop other urinary symptoms of GSM
- Vaginal estrogen treatment is safe and effective
- The use of lubricants should be routinely recommended (slippery liquids, not gels) with regular intercourse
- Laser treatment : a less common option ($$$)

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Estradiol vaginal inserts

- 4 mcg or 10 mcg doses
- Negligible systemic absorption, especially 4 mcg

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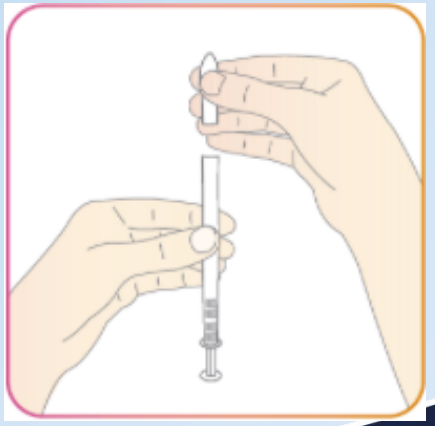
Vaginal DHEA

- Prasterone is a new vaginal insert which is metabolized to active androgens and estrogens
- Low levels of systemic absorption
- 6.5 mg insert used nightly

Intrarosa® Prasterone VAGINAL INSERTS 6.5 mg



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What About Testosterone?

- Since testosterone is produced by the ovaries, at the time of menopause the levels of testosterone decrease significantly
- Low libido (sex drive) is multifactorial, but sometimes testosterone treatment can be beneficial for women
- There is currently no FDA approved preparation of testosterone for women, but there are some recipes for compounded testosterone recommended by NAMS

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Case concluded

You prescribe vaginal estradiol tablets (Vagifem 10 mcg) inserted twice weekly and continue the use of a lubricant with intercourse. She sends you a message a few months later letting you know that her vaginal dryness is much better with this treatment, and her libido has improved as a result. She thanks you for your expertise in helping her navigate her menopause transition.

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Resources/Contact Information

- North American Menopause Society (NAMS): menopause.org
- Refer to Internal Medicine with request for Wastila/Menopause Clinic
- Epic message or email with questions: lwastila@health.ucsd.edu

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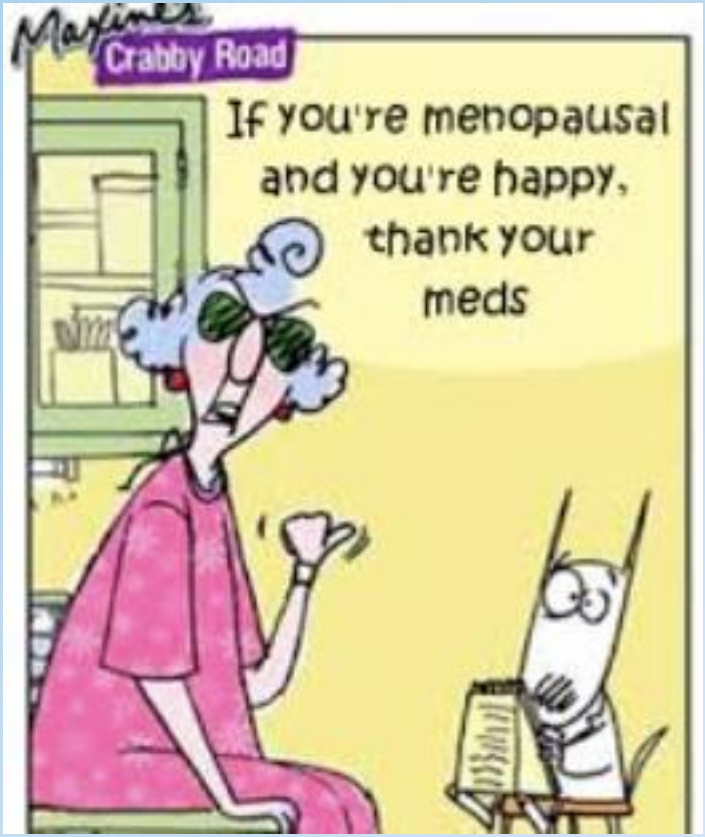

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