Brigham and Women's Hospital
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# Clinical Updates and Practical Considerations in Menopause Care

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- Clinical and research foci: Perimenopause and Menopause, Obesity Medicine

# Disclosures summary of relevant financial relationships

Financial Disclosures:  While not pertinent to the content of this lecture, I have in the past 24 months or am currently serving as a consultant for Bayer and Astellas.

In compliance with the ACCME, when I discuss specific healthcare products or services, I will use generic names to the extent possible.  If I need to use trade names, I will use trade names from several companies when available, and not just trade names from any single company.

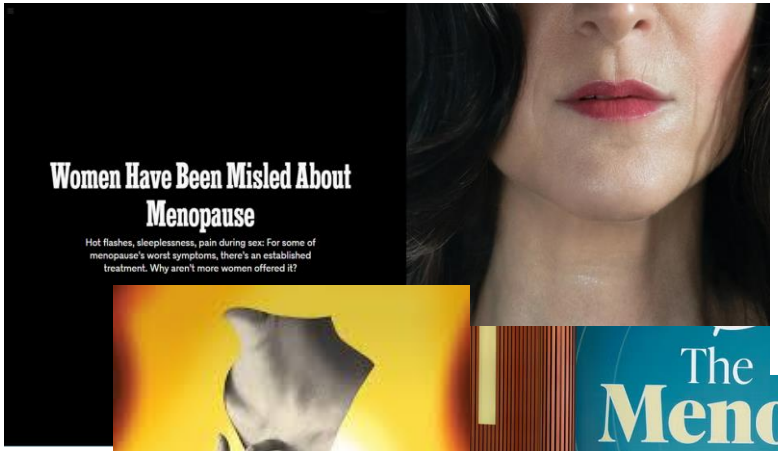
I value and respect each individual's gender identity and aim to be inclusive of all patients in need of our care. I recognize the limitations of applying inclusive language when source materials use gender-binary terms and descriptors, and thus I primarily use the terms female and woman when discussing perimenopause, menopause, and the genitourinary syndrome of menopause.

# Learning Objectives:

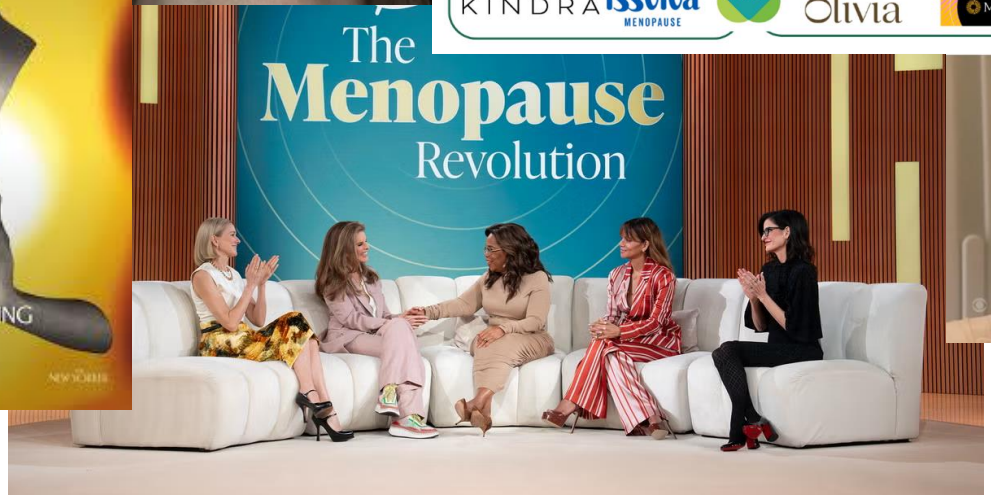
*Upon completion of this activity, participants will be able to…*

- Identify the significance of menopause as a health risk factor in women and discuss the clinical evaluation of perimenopausal and menopausal patients
- Demonstrate knowledge of the appropriate use of hormone therapy and non-hormone medications in the treatment of perimenopausal and menopausal symptoms and health consequences
- Discuss the most up to date literature surrounding menopausal hormone therapy

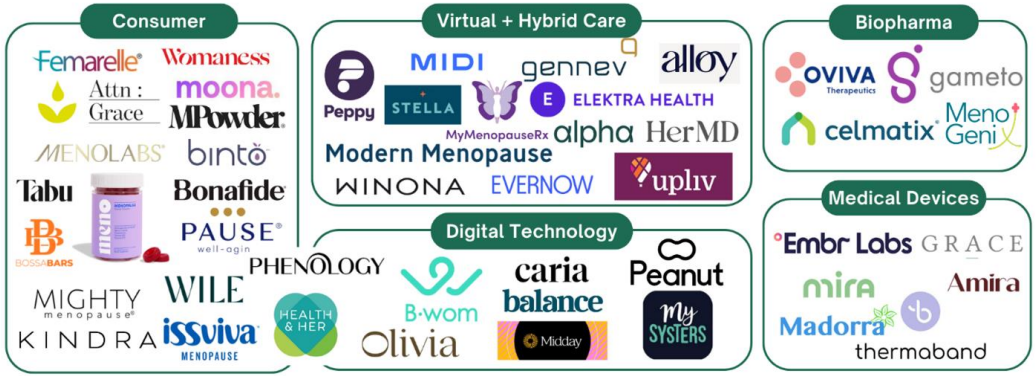
# Menopause is having a moment!











# Terminology

- **Perimenopause:** The highly symptomatic time frame that exists from the first occurrence of menopause-related symptoms to one full year after the final menstrual period (FMP)
- **Natural Menopause:** Cessation of menses for 12 consecutive months after (FMP) due to loss of ovarian follicular activity
  - Early Menopause: < 45 yo
  - Late Menopause: > 55 yo
- **Induced Menopause:** Cessation of menses due to surgical or iatrogenic causes
- **Premature Ovarian Insufficiency (POI):** Menopause occurring < 40 yo

# STRAW+10 Classification

Menarche — FMP (0)

| Stage | -5 | -4 | -3b | -3a | -2 | -1 | +1 a | +1b | +1c | +2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Terminology | REPRODUCTIVE | | | | MENOPAUSAL TRANSITION | | POSTMENOPAUSE | | | |
| | Early | Peak | Late | | Early | Late | Early | | | Late |
| | | | | | *Perimenopause* | | | | | |
| Duration | *variable* | | | | *variable* | 1-3 years | 2 years (1+1) | | 3-6 years | *Remaining lifespan* |
| **PRINCIPAL CRITERIA** | | | | | | | | | | |
| Menstrual Cycle | Variable to regular | Regular | Regular | Subtle changes in Flow/ Length | *Variable Length* Persistent ≥7- day difference in length of consecutive cycles | Interval of amenorrhea of >=60 days | | | | |
| **SUPPORTIVE CRITERIA** | | | | | | | | | | |
| *Endocrine* FSH<br>AMH<br>Inhibin B | | | Low<br>Low | Variable<br>Low<br>Low | ↑ Variable<br>Low<br>Low | ↑ >25 IU/L**<br>Low<br>Low | ↑ Variable<br>Low<br>Low | | Stabilizes<br>Very Low<br>Very Low | |
| *Antral Follicle Count* | | | Low | Low | Low | **Low** | Very Low | | Very Low | |
| **DESCRIPTIVE CHARACTERISTICS** | | | | | | | | | | |
| Symptoms | | | | | | Vasomotor symptoms *Likely* | Vasomotor symptoms *Most Likely* | | | *Increasing* symptoms of urogenital atrophy |

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

FIG. 2. The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.



Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW+10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. Climacteric. 2012 Apr;15(2):105-14.

# The Importance of Identifying Age at Menopause in Women

- Age at menopause is a significant marker of health in midlife women
  - Early menopause is associated with increased all-cause mortality and increased risk of cardiovascular disease (CVD), osteoporosis, and dementia
  - Late menopause may increase risk for breast, endometrial, and ovarian cancer
    - Late menopause has also been associated with increased longevity of life

# Cardiometabolic changes during the menopausal transition independent of aging

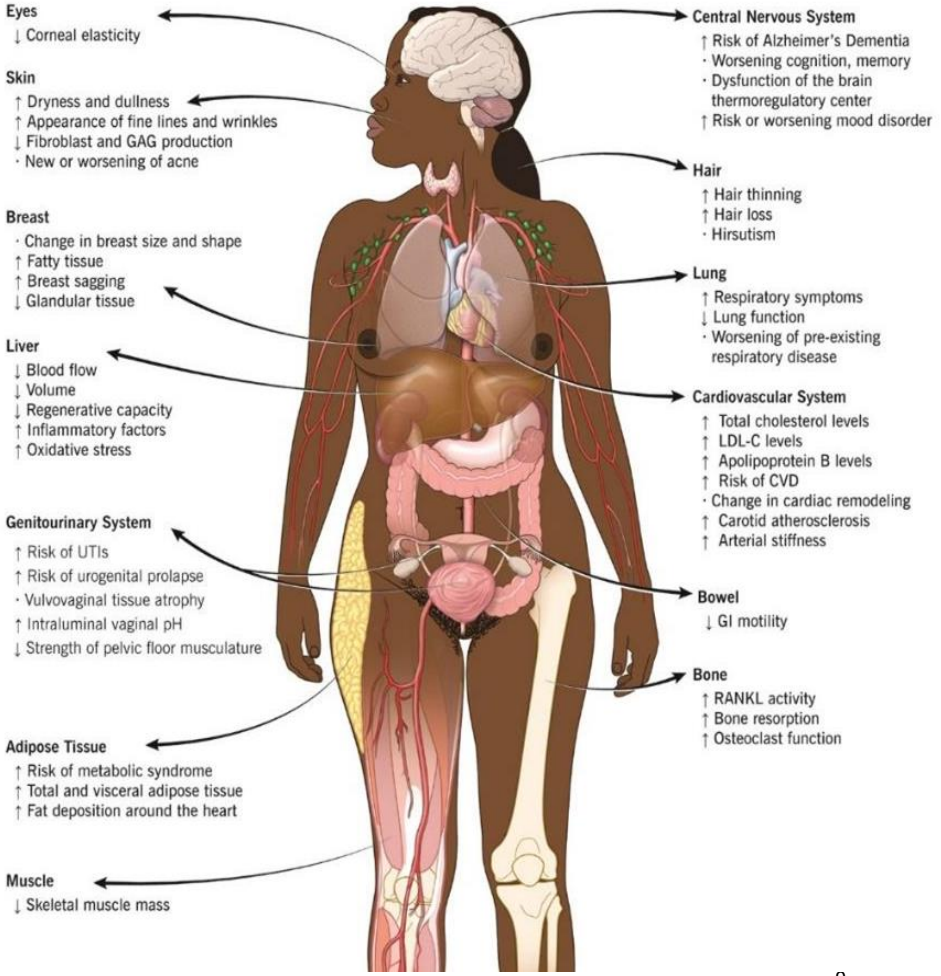
- Given the established accelerating CVD risk in women undergoing the menopausal transition, there is a key role for clinicians to monitor and intervene on the cardiovascular health of their patients that is often overlooked
  - Increased carotid atherosclerosis and arterial stiffness
  - Adverse changes in body composition
    - Increased total and visceral adipose tissue
    - Reduction in lean muscle mass
  - Increased prevalence of metabolic syndrome
  - Worsening lipid profile
    - Increased total cholesterol
    - Increased LDL-C
    - Increased Apolipoprotein B



El Khoudary SR, Aggarwal B, Beckie TM, et al. American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. Circulation. 2020 Dec 22;142(25):e506-e532.

# Perimenopausal and menopausal symptoms

- Estrogen affects every organ system in the body leading to a vast possible symptom profile
- Classic symptoms of the menopause transition
  - Change in bleeding patterns, vasomotor symptoms (VMS), genitourinary syndrome of menopause (GSM)
- Other symptoms associated with the menopause transition
  - Sleep disturbances
  - Cognitive concerns (brain fog, memory, concentration, word-finding difficulty)
  - Psychological symptoms
  - Musculoskeletal pain
  - Weight gain (esp. visceral distribution)
  - Headaches
  - Changes to skin, hair




Iyer TK, Thacker HL. "Menopause" In: Falcone T, Hurd WW. Editors. Clinical Reproductive Medicine and Surgery: A Practical Guide, 4th Edition Springer Nature; 2022.

# Weight changes in peri- and menopausal women

- Higher prevalence of women with obesity in the postmenopausal population compared to premenopausal population
    - Data is mixed regarding weight gain and basal metabolic rate decreases throughout the menopause transition, though changes in body composition are consistently demonstrated in literature
        - Many studies suggest environmental/psychosocial factors and aging may play more of a role in weight changes at midlife than hormonal changes
    - SWAN study: Women aged 40–55 years had an average 3-year increase in body weight of 4.5 pounds
    - Healthy Women's Study: Women gain approx. 1.5 pounds/year during their 5th and 6th decades of life
- Multiple studies have demonstrated that perimenopause is associated with a rapid increase in fat mass and visceral adiposity
    - Loss of lean muscle mass and redistribution of fat mass, with an increase in the waist-to-hip ratio (increase of central adiposity, visceral fat)
        - Loss of lean mass starts ~40 years old at a rate of 1-2%/year and slows after menopause to ~0.6%/year
        - Increased inflammation and adipokines associated with insulin resistance, DM2, metabolic syndrome

Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, Cauley JA, Finkelstein JS, Jiang SF, Karlamangla AS. Changes in body composition and weight during the menopause transition. JCI Insight. 2019 Mar 7;4(5):e124865. doi: 10.1172/jci.insight.124865. PMID: 30843880; PMCID: PMC6483504.

Wing R.R., Matthews K.A., Kuller L.H., Meilahn E.N., Plantinga P.L. Weight gain at the time of menopause. Arch. Intern. Med. 1991;151:97–102. doi: 10.1001/archinte.1991.00400010111016.

## Direct Effects of Aging

- Decrease in lean muscle mass
- Decrease in total energy expenditure


## Direct Effects of Hormonal Changes

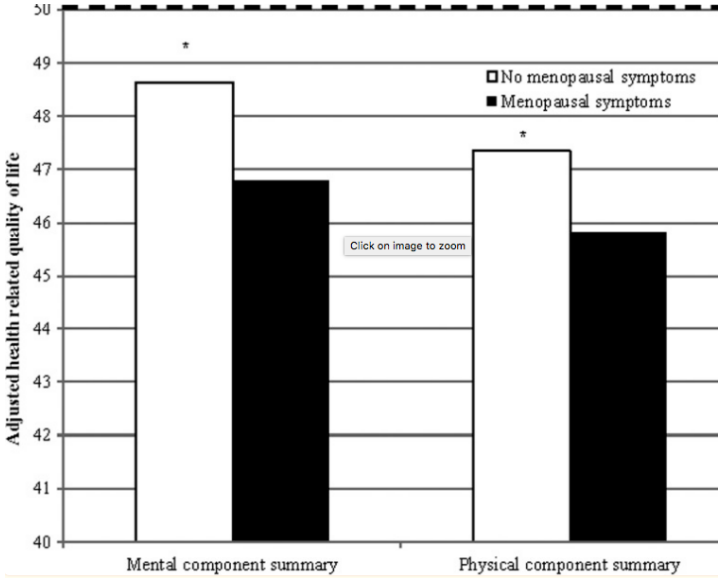
- Increase in visceral adiposity
- Decrease in lean muscle mass
- Decrease in fat oxidation
- Increase in appetite

## Indirect Effects of Aging and Hormonal Changes

- Increased environmental stressors/factors and disruptive menopausal symptoms (hot flashes/night sweats, sleep disruption, etc.) may negatively impact lifestyle and behaviors

# Psychosocial and economic considerations

- 2023 Study out of Mayo Clinic estimated $1.8 billion in lost work time per year, and $26.6 billion annually when medical expenses are added, in the U.S. alone
- 2005 United States National Health and Wellness Survey: menopause may cause significant "humanistic and economic burden"
  - Lower mental and physical health-related quality of life (QOL)
  - Symptomatic women experience significantly higher overall work impairment, impairment in daily activities, and more physician visits
- Personal and global financial impact
- Possible relationship issues
- Impact on sexuality
- Impact on physical appearance/confidence




Faubion SS, Enders F, Hedges MS, Chaudhry R, Kling JM, Shufelt CL, Saadedine M, Mara K, Griffin JM, Kapoor E. Impact of menopause symptoms on women in the workplace. InMayo Clinic Proceedings 2023 Jun 1 (Vol. 98, No. 6, pp. 833-845). Elsevier.

Whiteley J, DiBonaventura Md, Wagner JS, Alvir J, Shah S. The impact of menopausal symptoms on quality of life, productivity, and economic outcomes. J Womens Health (Larchmt). 2013 Nov;22(11):983-90. doi: 10.1089/jwh.2012.3719. Epub 2013 Oct 1. PMID: 24083674; PMCID: PMC3820128.

# Evaluation: perimenopause and menopause are both a clinical diagnosis!

- Clinical diagnosis
  - Perimenopause vs Menopause
- Utility of labs
  - FSH
  - 17-B-Estradiol
  - TSH
- Special considerations
  - Hysterectomy, endometrial ablation
  - Certain forms of contraception
  - Underlying menstrual disorders

Summary of hormones of reproductive aging by STRAW criteria

| | Peak Reproductive | Late Reproductive | Early MT | Late MT | | Postmenopause |
|---|---|---|---|---|---|---|
| **FSH** | Normal | ↑ | ↑ | ↑ | | ↑ |
| **AMH** | Normal/↓ | ↓ | ↓ | Undetectable | **FMP** | Undetectable |
| **Inhibin B** | Normal | ↓ | ↓ | Undetectable | | Undetectable |
| **Estradiol** | Normal | Normal | Normal | ↓ | | ↓ |



Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW+10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. Climacteric. 2012 Apr;15(2):105-14.

# CASE #1

52 yo woman presenting with hot flashes, night sweats, mood swings, sleep disturbance, hair thinning and joint pain. It has been 14 months since her last menstrual period.

- PMHx: hypertension, overweight (BMI 29.7), hypothyroidism
- PSHx: none
- Medications: losartan, levothyroxine

## What therapy is most effective to treat her symptoms?



Image from: https://www.health.harvard.edu/blog/menopause-related-hot-flashes-night-sweats-can-last-years-201502237745

# Management of menopausal symptoms

- Gold standard of treatment: menopausal hormone therapy (MHT)
- FDA-approved for:
  - Vasomotor symptoms
  - Genitourinary syndrome of menopause
  - Prevention of bone loss/ fracture reduction in postmenopausal women
  - Mitigation of early estrogen loss in surgical menopause/ POI




Image from: https://news.cancerconnect.com/treatment-care/hormonal-therapy

# Prescribing hormone therapy

- Hormone Therapy: FDA-approved for the treatment of menopausal symptoms
  - **Estrogen alone** – unopposed estrogen for women who are s/p hysterectomy; or can be used locally for GSM
  - **Estrogen + Progestogen** – for women with intact uterus to protect endometrial lining
    - Reasons to consider progestogen use in hysterectomized women
      - History of endometriosis with concern for remnant endometrial tissue
      - For significant sleep/nighttime anxiety issues
  - **Bioidentical HT** – chemically identical to those made in the body
    - Unregulated – unapproved and untested from various compounding pharmacies
    - Regulated – FDA approved and tested
- Important counseling points: route/dosing, duration of therapy, side effects, risks/benefits

# Dosage ranges

Have a “go-to” prescription: Transdermal estradiol 0.0375 - 0.05 mg/24h patch 2x/week + 100 mg micronized progesterone nightly

| Estrogen | Route | Typical dose range | Frequency | Equivalent dose |
|---|---|---|---|---|
| 17-β estradiol | Oral | 0.5-2 mg | Daily | 1 mg |
| | Patch | 0.014-0.1 mg | Once or twice weekly | 0.05 mg |
| | Gel pouch | 0.25-1.25 mg | Daily | 1 mg |
| | Gel pump | 1-4 pumps (0.52-0.75 mg/pump) | Daily | 1-2 pumps |
| | Spray | 1-3 sprays (1.53 mg /spray) | Daily | 2-3 sprays |
| Conjugated equine estrogen | Oral | 0.3-1.25 mg | Daily | 0.625 |
| Conjugated estrogen | Oral | 0.3-1.25 mg | Daily | 0.625 mg |
| Ethinyl estradiol | Oral | 0.01-0.03 mg | Daily | 0.01-0.015 mg |
| Esterified estrogen | Oral | 0.3-2.5 mg | Daily | 0.625 mg |
| Estradiol acetate | Vaginal ring | 0.05 mg; 0.10 mg | 90 days | 0.05 mg |



Table adapted from: Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

| Progestogen | Route | Dose range | Frequency | Side effects |
|---|---|---|---|---|
| Micronized progesterone | Oral | 100-300 mg; 200-300 mg (300 mg rarely needed) | Daily; cycled | Somnolence, fatigue, bloating, abdominal pain, nausea, dizziness |
| Levonorgestrel | IUD | 52 mg*† | 5 years (approved in EU, off-label in US) | Pain with placement, pelvic pain, breast pain, irregular bleeding and spotting, acne, abdominal pain, nausea, dizziness, headache, fatigue |
| Drospirenone | Oral | 4 mg*† | Daily | Acne, weight gain, nausea, headache, breast tenderness, low libido, hyperkalemia |
| Medroxyprogesterone acetate | Oral (depo unstudied) | 2.5-5 mg; 5-10 mg | Daily; cycled | Bloating, weight gain, abdominal pain, dizziness, fatigue |
| Norethindrone‡ | Oral | 0.35-0.7 mg*†; 0.7 mg | Daily; cycled | Nausea, headache, breast tenderness |
| Norethindrone acetate | Oral | 2.5 mg*† (lowest dose needed is 0.5 mg, but 2.5 mg is smallest dose available) | Daily; cycled | Edema, nausea, breast tenderness |
| Megestrol acetate | Oral | 20-40 mg | Daily | Hypertension, rash, hot sweats, weight gain, diarrhea, nausea, insomnia, mood swings |
| Micronized progesterone | Capsule inserted vaginally†§ | 100-300 mg; 200-300 mg | Daily; cycled | As above for oral consumption, to a lesser degree |
| Progesterone | Vaginal gel†§ | 4-8% (45-90 mg); 8% | Daily; cycled | Same as oral micronized progesterone, to a lesser degree |



Table adapted from: Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

| Combined estrogen-progestogen | Route | Dose range | Frequency |
|---|---|---|---|
| 17-β estradiol + norethindrone acetate | Patch | 0.05 mg+0.14 mg; 0.05 mg+0.25 mg | Twice weekly |
| | Oral | 0.5 mg+0.1 mg; 1.0 mg+0.5 mg | Daily |
| 17-β estradiol + levonorgestrel | Patch | 0.045 mg+0.015 mg | Weekly |
| Conjugated equine estrogen + medroxyprogesterone acetate | Oral | 0.625 mg+5 mg | CEE daily; CEE+MPA on days 15-28 |
| | | 0.3 mg+1.5 mg; 0.45 mg+1.5 mg; 0.625 mg+2.5 mg; 0.625 mg+5 mg | Daily |
| 17-β estradiol + norgestimate | Oral | 1 mg+0.09 mg | Cyclic |
| 17-β estradiol + micronized progesterone | Oral | 0.5 mg+100 mg; 1 mg+100 mg | Daily |
| 17-β estradiol + drospirenone | Oral | 0.5 mg+0.25 mg; 1mg+0.5 mg; 1 mg+1 mg | Daily |
| Conjugated estrogens + bazedoxifene | Oral | 20 mg+0.45 mg; 20 mg+0.625 mg | Daily |
| Ethinyl estradiol+NETA | Oral | 2.5 µg+0.5 mg; 5 µg+1 mg | Daily |



Table adapted from: Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

# CASE #1 continued…

You recommend menopausal hormone therapy for this patient.

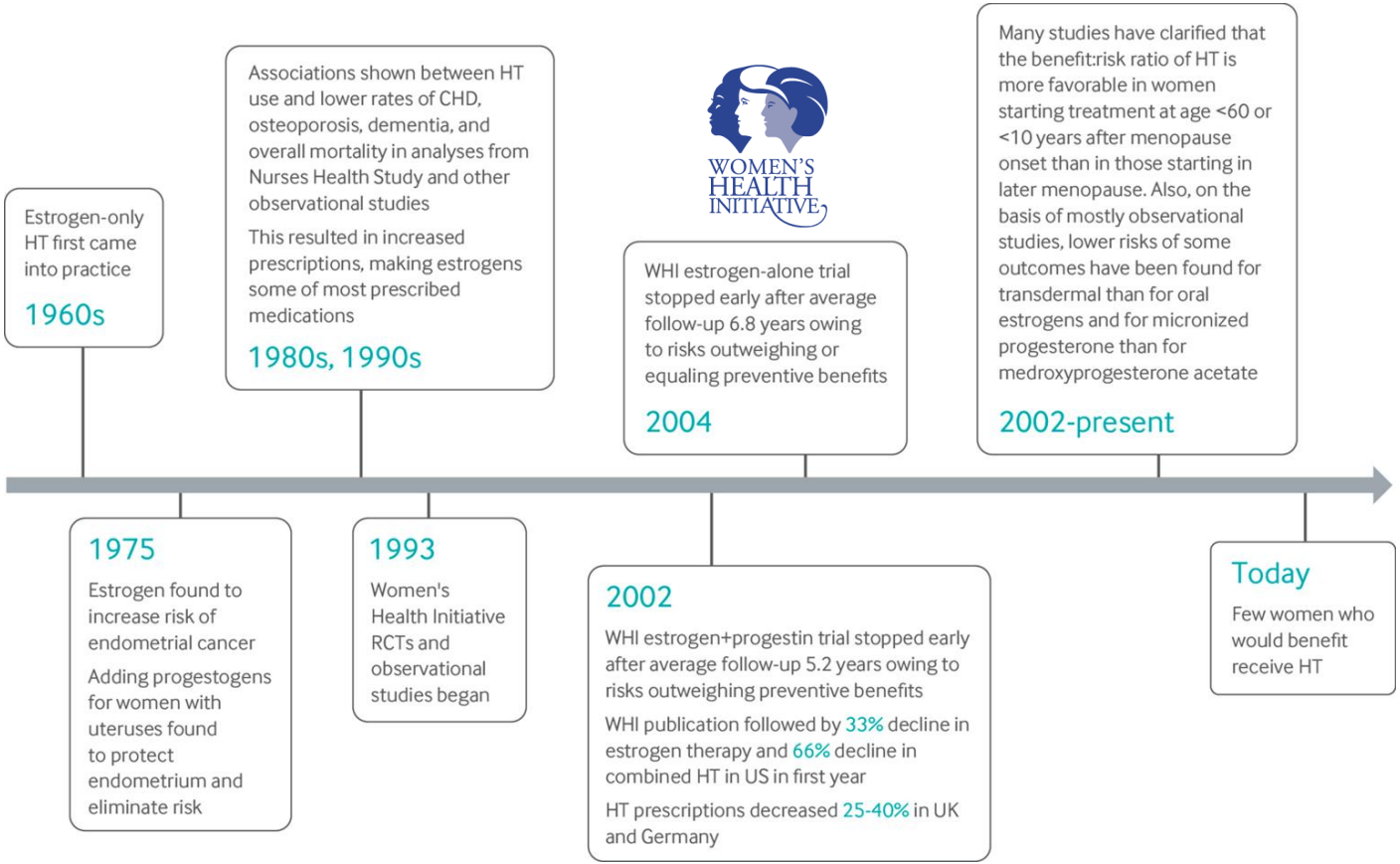
She is weary of taking hormones, reporting she has heard they can cause breast cancer and other health problems. She is also worried about side effects.

*How would you counsel this patient?*



Image from: https://www.health.harvard.edu/blog/menopause-related-hot-flashes-night-sweats-can-last-years-201502237745

# Controversy over hormone therapy explained: a timeline






Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

# The Timing Hypothesis

When initiated under the age of 60 years old or within 10 years from menopause in otherwise healthy women, hormone therapy demonstrates greater benefits than risks, especially with respect to cardiovascular disease outcomes.

| Long term benefits of MHT | Absolute risks of MHT |
|---|---|
| Reduction in all-cause mortality (including cancer and stroke mortality) | Absolute risks for HT use in healthy women after 50-59 are rare but can include VTE, stroke, breast cancer |
| Reduction in CVD incidence and mortality | |
| Reduction in risk of osteoporosis and osteoporotic fractures at the hip and the spine | |
| Reduction in incidence of colon cancer | |

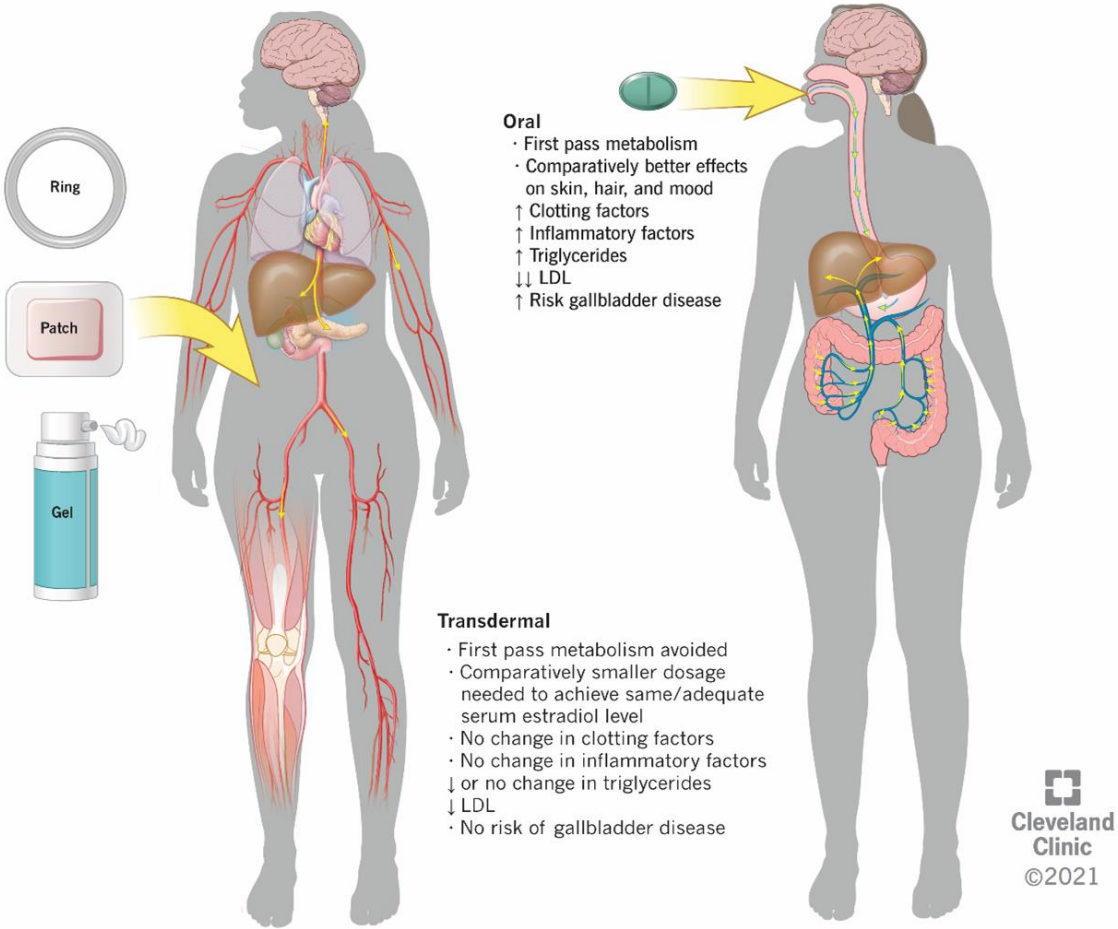
# What do we know today? Breast cancer data

- Evidence from the WHI:
  - The risk of breast cancer (BC) related to HT use is rare (less than one additional case per 1,000 women per year of HT use or three additional cases per 1,000 women when used for 5 years with CEE+MPA)
  - No increased risk of breast cancer mortality
  - CEE-only users experienced a reduction in breast cancer incidence and mortality compared to controls
- 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 (i.e. alcohol consumption, obesity, smoking, etc.)

Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-94.

# VTE/Stroke risk: TD vs oral MHT

- Large two nested case control study 2019: Transdermal HT was NOT associated with any increased risk of VTE and consistent among various regimens
- Transdermal HT has not been associated with VTE/stroke risk in multiple observational studies; though limited observational data and a systematic review suggest less risk(as opposed to no risk) with transdermal HT than oral





Iyer TK, Thacker HL. “Menopause” In: Falcone T, Hurd WW. Editors. Clinical Reproductive Medicine and Surgery: A Practical Guide, 4th Edition Springer Nature; 2022.

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. bmj. 2019 Jan 9;364.

# Menopausal hormone therapy, mood, and sleep

- Depression
  - Some evidence that ET has similar efficacy to antidepressants in depressed perimenopausal women with or without VMS and enhances mood and well-being in non-depressed perimenopausal women
  - HT may prevent onset of depressive symptoms in euthymic perimenopausal women and may positively augment clinical response to antidepressants in perimenopausal and postmenopausal women
- Sleep disturbances
  - Sleep disturbances → negative impact of sleep disruption on QOL, mood, memory, metabolic syndrome, obesity, and CV risk
  - Some evidence that TD ET may benefit sleep of perimenopausal women independent of VMS

Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-94.
Image from: https://www.everydayhealth.com/menopause/women-have-a-harder-time-sleeping-after-menopause/

# Menopausal hormone therapy, cognition, and dementia

- 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
- HRT may have cognitive benefits when initiated immediately after TAH/BSO in surgical menopause patients
- HT in the early natural postmenopausal period has likely neutral or positive effects on cognitive function, but may have detrimental effects when initiated after age 65
    - Data is mixed, though most observational data points to a reduced risk of AD when HT is initiated in early menopause
    - Risk of dementia was increased in women who started hormone therapy at age 65 or later in the WHI trials, however, hormone therapy use was not associated with increased mortality from Alzheimer's disease or dementia at 18 year follow-up

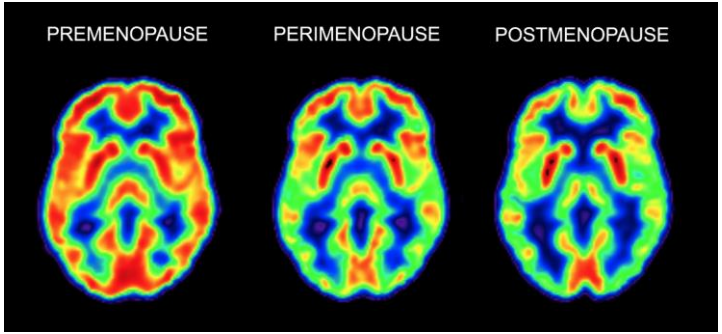



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Image from: https://www.wsj.com/articles/the-link-between-menopause-and-alzheimers-11550509201.

# MHT and the Musculoskeletal Syndrome of Menopause

**~70%**

Prevalence of midlife women will experience the musculoskeletal syndrome of menopause

**Table 1.** Musculoskeletal syndrome of menopause: processes and signs.

| *Process* | *Signs* |
|---|---|
| Inflammation | Arthralgia, joint pain, joint discomfort, frozen shoulder |
| Sarcopenia | Poor balance, falls, decreased muscle mass, loss of stamina, walking slowly |
| Decreased satellite cell proliferation | Decreased muscle mass, inability to gain muscle |
| Osteoporosis | Loss of height, back pain, stooped posture, low-impact fracture |
| Arthritis | Arthralgia, joint pain, joint stiffness |

- Two RCTs (WHI, 2008 Australian RCT) demonstrated modest, but significant, reductions in joint pain and stiffness with HT use compared to controls
- Data is mixed with regard to effects of MHT on osteoarthritis prevalence
- Research is limited and more must be done!



lu cB, liu PF, Zhou YS, et al. Musculoskeletal pain during the meno-pausal transition: a systematic review and meta-analysis. Neural Plast.2020;2020:8842110–8842110. doi: 10.1155/2020/8842110
Wright VJ, Schwartzman JD, Itinoche R, Wittstein J. The musculoskeletal syndrome of menopause. Climacteric. 2024 Oct;27(5):466-472. doi: 10.1080/13697137.2024.2380363. Epub 2024 Jul 30. PMID: 39077777
Magliano M. Menopausal arthralgia: Fact or fiction. Maturitas. 2010 Sep;67(1):29-33. doi: 10.1016/j.maturitas.2010.04.009. PMID: 20537472

# Hormone therapy (HT), weight, and metabolic outcomes

- Women's Health Initiative 3 year trial:
  - HT does not prevent weight gain, but it may minimize lean body mass loss and central adiposity redistribution
- Menopausal Hormone Therapy Is Associated With Reduced Total and Visceral Adiposity: The OsteoLaus Cohort
  - MHT is associated with significantly decreased visceral adipose tissue, BMI, and android fat mass
  - The benefits are not preserved in past users, suggesting caution when MHT is discontinued
- Estrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution
  - Hormone therapy regimens do not cause extra weight gain in addition to that normally gained at menopause

Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, Mechanisms, and Clinical Implications. Endocr Rev. 2017 Jun 1;38(3):173-188. doi: 10.1210/er.2016-1146.
Norman RJ, Flight IH, Rees MC. Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution. Cochrane Database Syst Rev. 2000;(2):CD001018. doi: 10.1002/14651858.CD001018. PMID: 10796730.
Papadakis GE, Hans D, Gonzalez Rodriguez E, Vollenweider P, Waeber G, Marques-Vidal P, Lamy O. Menopausal Hormone Therapy Is Associated With Reduced Total and Visceral Adiposity: The OsteoLaus Cohort. J Clin Endocrinol Metab. 2018 May 1;103(5):1948-1957. doi: 10.1210/jc.2017-02449. PMID: 29596606.

# Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women

- **Objective:** To quantify the effects of HT on the components of metabolic syndrome in postmenopausal women
- **Design:** Comprehensive database review of literature published 1966-2004 of RCTs evaluating effects of HT on metabolic outcomes
- **Results:** 107 trials were reviewed, with pooled results showing:
  - HT reduced abdominal fat [-6.8% (CI,-11.8 to -1.9%)]
  - HT reduced insulin resistance (calculated by homeostasis model assessment or HOMA-IR) [-12.9% (CI, -17.1 to -8.6%)] and new-onset diabetes [relative risk 0.7 (CI, 0.6–0.9)] in women without diabetes
  - In women with diabetes, HT reduced fasting glucose [-11.5% (CI, -18.0 to -5.1%)] and HOMA-IR [-35.8% (CI, -51.7 to -19.8%)]
  - HT reduced low-density lipoprotein/high-density lipoprotein cholesterol ratio [-15.7%(CI, -18.0 to -13.5%)], lipoprotein(a) [Lp(a)] [-25.0% [CI,-32.9 to -17.1%)]
  - HT reduced mean blood pressure [-1.7% (CI, -2.9 to -0.5%)]
- **Conclusions:** **HT reduces abdominal obesity, insulin resistance, new-onset diabetes, lipids, blood pressure, adhesion molecules and procoagulant factors in women without diabetes and reduced insulin resistance and fasting glucose in women with diabetes.**



Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab. 2006 Sep;8(5):538-54. doi: 10.1111/j.1463-1326.2005.00545.x. PMID: 16918589.

# Relative contraindications to HT: Menopause Society 2022 Hormone Therapy Position Statement

| |
|---|
| Severe active liver disease |
| **History of estrogen-sensitive malignancy** |
| Porphyria Cutanea Tarda |
| History of deep vein thrombosis |
| History of pulmonary embolism |
| History of stroke |
| Coronary Heart Disease |
| Unexplained vaginal bleeding that has not been evaluated |

Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-94.

# Counseling on side effects

- Abnormal uterine bleeding can be common in the first 3-6 months and can even occur up to 1 year
  - Can be due to an estrogen-progestogen imbalance
  - If despite making medication changes bleeding persists, must evaluate the endometrium (transvaginal US +/- endometrial biopsy)

**Table 15.** Potential Adverse Events of Estrogen Therapy or Estrogen-Progestogen Therapy

- Uterine bleeding (starting or returning)
- Breast tenderness (sometimes enlargement)
- Nausea
- Abdominal bloating
- Fluid retention in extremities
- Changes in the shape of the cornea (sometimes leading to contact lens intolerance)
- Headache (sometimes migraine)
- Dizziness
- Mood changes with EPT, particularly with progestin
- Angioedema
- Gallstones, pancreatitis

Abbreviations: EPT, estrogen-progestogen therapy; ET, estrogen therapy



Table from: The North American Menopause Society. Menopause Practice: A Clinician's Guide, 6th ed. 2019.

# Duration of use for systemic hormone therapy

- Hormone replacement therapy is gold standard of care in patients < 45 years old to mitigate deleterious effects of early estrogen loss and should be continued at least until the average age of menopause (~52 years old)
- Per Menopause Society Guidelines, hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years
- Longer durations or extended use beyond age 65 years should be considered with periodic reevaluation (at minimum annually) considering severity of symptoms, comorbid conditions, periodic trials of lowering or discontinuing hormone therapy, effectiveness of alternative nonhormone interventions, patient preferences and response to hormone therapy, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer
- As women age, it is recommended to consider risk mitigation using lowest effective dose, nonoral therapy

Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-94.

# CASE #2

48 yo postmenopausal woman with a history of ER+/PR+/HER2- breast cancer currently being treated with tamoxifen with presenting with hot flashes, night sweats, increasing anxiety, weight gain, depressive symptoms, fatigue, and diffuse arthralgias.

She reports she went through menopause at age 47, and only had mild symptoms, but now after starting tamoxifen it feels like her previous symptoms have “returned, but in full force.”

**What therapies may be options for her?**



Image from: https://www.morelandobgyn.com/blog/perimenopause-symptoms-relief-how-to-find-a-perimenopause-doctor

# NK3R and NK1/3R antagonists

- The thermoregulatory center in the hypothalamus is stimulated by neurokinin 3 receptor (NK3R) activation and inhibited by estrogen-negative feedback
  - This balance is disrupted in menopause, producing vasomotor symptoms
- Fezolinetant: VEOZAH approved by FDA 5/2023
  - SKYLIGHT → Fezolinetant 45 mg was efficacious for the treatment of moderate-to-severe VMS associated with menopause
  - Caution with certain medications (CYP1A2 inhibitors, including caffeine)
  - Check liver function tests at baseline, 1, 2, 3, 6, and 9 months
  - Most common side effect: headache, GI disturbances
- Elinzanetant: may become available 2025
  - OASIS 1,2 → Elizanetant is a dual NK1/NK3 receptor antagonist is effective in the treatment of vasomotor symptoms
    - Most common side effects: headache, fatigue
    - OASIS 2 did not demonstrate concern for hepatotoxicity

Lederman, Samuel MD; Shapiro CM, Marla MD; Stute, Petra MD; Lee, Misun PhD; Wang, Xuegong PhD; Neal-Perry, Genevieve PhD. Phase 3 Study of Fezolinetant for Treatment of Moderate-to-Severe Vasomotor Symptoms Associated With Menopause [A132]. Obstetrics & Gynecology: May 2022 - Volume 139 - Issue - p 39S doi: 10.1097/01.AOG.0000825808.38519.3b
Pinkerton JV, Simon JA, Joffe H, Maki PM, Nappi RE, Panay N, Soares CN, Thurston RC, Caetano C, Haberland C, Haseli Mashhadi N, Krahn U, Mellinger U, Parke S, Seitz C, Zuurman L. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22;332(16):1343–54. doi: 10.1001/jama.2024.14618. Epub ahead of print. PMID: 39172446; PMCID: PMC11342219.

# Nonhormone Medications for VMS: How To Choose?

| Class | Medication | Dosing for VMS[a] | Clinical pearls |
|---|---|---|---|
| **SSRIs** | Paroxetine salt[10,11,23,24] | 7.5 mg daily at bedtime | Potent cytochrome P450 CYP2D6 enzyme inhibitors; do not use with tamoxifen as SSRIs reduce tamoxifen bioavailability and efficacy |
| | Paroxetine[10,11,23,24] | 10–25 mg daily | |
| | Fluoxetine[11,23,24,26] | 10–30 mg daily | Paroxetine mesylate 7.5 mg was the first and only US Food and Drug Administration–approved nonhormone medication for moderate to severe menopausal VMS until the development of neurokinin-receptor antagonists |
| | Sertraline[11,23,24,27] | 25–100 mg daily | |
| | Citalopram[10,11,23,24] | 10–20 mg daily | Fluoxetine and sertraline are not recommended for VMS reduction owing to inconsistent data regarding efficacy in hot flash frequency and severity reduction |
| | Escitalopram[10,11,23–25] | 10–20 mg daily | |
| | | | Sertraline has a moderate effect on the CYP2D6 enzyme |
| | | | Citalopram and escitalopram may cause QT prolongation |
| **SNRIs** | Desvenlafaxine[10,11,23,24] | 100–150 mg daily | SNRIs may increase blood pressure, use with caution in patients with hypertension |
| | Venlafaxine[10,11,23,24] | 37.5–75 mg daily | Venlafaxine is the most well studied SNRI in combination with tamoxifen |
| | Duloxetine[11,23,25] | 30–60 mg daily | |
| | | | Duloxetine has a moderate effect on the CYP2D6 enzyme |
| **Gabapentinoid** | Gabapentin[10,11,28–31] | 300–2,400 mg daily (divided doses) | Consider for patients with a history of neuropathic pain or sleep concerns |
| | | | Consider nightly dosing (starting dose of 100–300 mg at bedtime) to minimize any adverse effects of daytime fatigue |
| **Antimuscarinic** | Oxybutynin[11,24,31,32] | 2.5–5 mg twice a day (immediate release), up to 15 mg/day (extended release) | Consider for patients with concurrent overactive bladder or hyperhidrosis |
| | | | Use caution in older adults (≥ 65 years); avoid altogether in patients ≥ 65 years taking concomitant anticholinergic medications |
| **Alpha-2 adrenergic agonist** | Clonidine[11,32,33] | 0.05–0.1 mg once or twice a day | Consider for patients with hypertension, especially if improved blood pressure control is desired |
| | | | Avoid in older adult patients (≥ 65 years) |
| | | | Less often used and no longer recommended by the Menopause Society owing to modest efficacy vs placebo and side-effect profile |



Iyer TK, Fiffick AN, Batur P. Nonhormone therapies for vasomotor symptom management. Cleve Clin J Med. 2024 Apr 1;91(4):237-244. doi: 10.3949/ccjm.91a.23067. PMID: 38561208.

# Evidence-based non-pharmacologic interventions

- Weight loss
- Mind-body techniques
  - Cognitive behavioral therapy (CBT) → literature demonstrates slight reduction in VMS symptoms and benefits in mood, QOL, and overall functioning
  - Clinical hypnosis → RCTs demonstrated it to be effective in reducing VMS in survivors of breast cancer and in postmenopausal women
- Inconclusive or lack of robust evidence: yoga, acupuncture, s-equol, paced respiration, OTC/herbal supplements (including black cohosh)



The North American Menopause Society. Menopause Practice: A Clinician's Guide, 6th ed. 2019, p 49-51.

# CASE #3

A 48 year old woman presents for an annual exam.

She reports her periods have become irregular. Her LMP was 15 days ago and her period was very heavy lasting 9 days. Prior to this month she had not had a period in 2 months. She also endorses intermittent hot flashes/night sweats, sleep changes, and recent weight gain despite no changes to her diet or exercise regimen.

PMHx: Brief hx of tobacco use as a teenager, but has not smoked since she was 19

PSHx: none

Contraception: Husband with vasectomy

**What treatment options should you discuss with her?**



Image from: https://atriumhealth.org/dailydose/2020/03/09/every-woman-goes-through-menopause-at-some-point-know-how-to-manage

# Perimenopause hormone treatment options

- Combined hormonal contraception
  - Consider PMHx, safety, symptoms
  - Do they need contraception? Do they have heavy bleeding?
  - Do they have PMDD or menstrual migraines (with or without aura)?
  - Do they have ovulatory or hyperestrogenic symptoms?

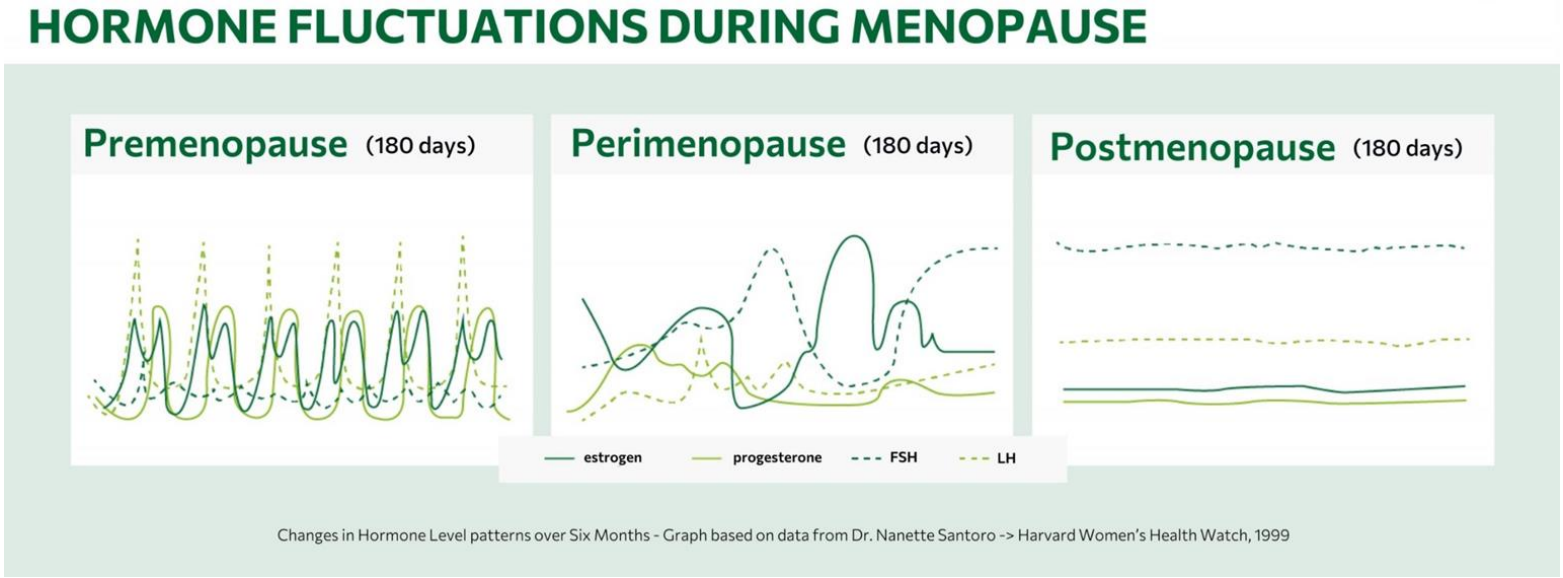





Image obtained from: https://alkmene.de/en/ratgeber/menopausal-skin-problems/

# Perimenopause hormone treatment options (continued)

- Micronized progesterone with or without transdermal ET
  - Prometrium 200 mg days 1-12 of each calendar month or 100-200 mg daily
    - Take at night, it is relaxing and can help sleep
    - Still need to consider contraception
    - Micronized in peanut oil so cannot be allergic to peanuts
    - Micronized progesterone, especially the higher doses, can also reduce hot flashes
- Mirena IUD with or without transdermal ET
  - Great option for endometrial protection, HMB, and contraception
- Symptom-specific nonhormone medications (ex. SSRIs/SNRIs for mood symptoms, anti-obesity medications for weight disorders)

# CASE #4

A 72 year old woman presents to for an annual exam.

LMP: age 50, no further episodes of bleeding, but having persistent vaginal dryness and discomfort, dyspareunia, and some urinary leakage issues

Genitourinary exam demonstrates frank vulvovaginal atrophy

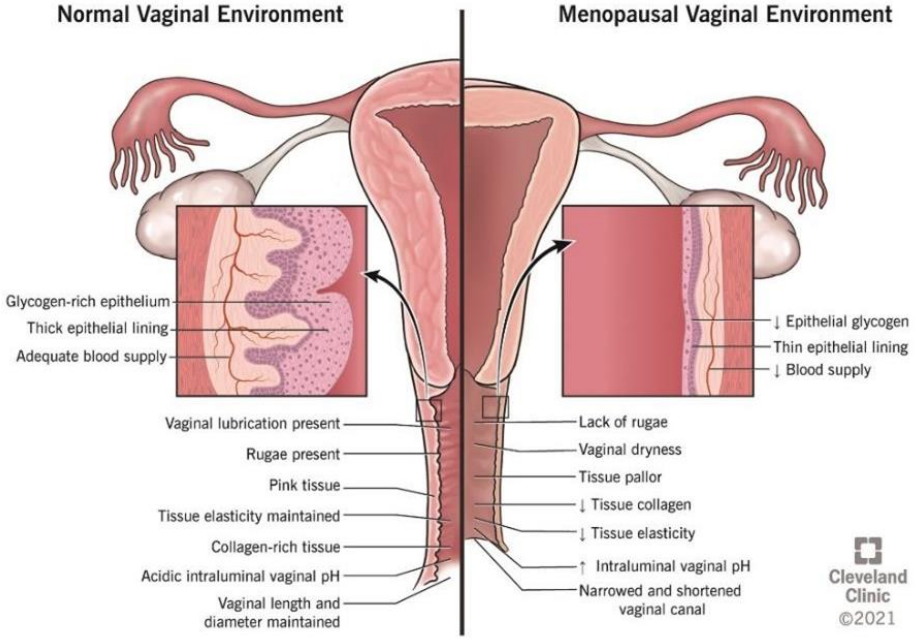


Image from: https://www.forbes.com/sites/debgordon/2021/07/13/73-of-women-dont-treat-their-menopause-symptoms-new-survey-shows/?sh=42774104454f

# GSM: practical considerations for prescribers

- Estradiol Vaginal Ring
  - Vaginal ring (Insert just like nuvaring)
  - One ring q every 3 months
  - Great for patients with incontinence as gives some bladder lift and patients with arthritis/obesity/chronic back pain – where frequent application may be difficult
- Conjugated Estrogen Vaginal Cream
  - Insert via applicator (fill applicator tube with cream then insert) or can use finger to apply to lower 1/2 of vagina
  - Likely only get 1 applicator so need to wash after every use with unscented soap and water
  - Use nightly x 2 weeks then 2-3x/week for maintenance
- Estradiol Vaginal Cream
  - Insertion similar to PVC
  - Use nightly 1-2 g/d x 2 weeks then 1g 2-3x/week
- Estradiol Vaginal Pearls
  - Suppository of estradiol and coconut oil that looks like elongated pearl
  - Less messy than creams because oil is a good bioadhesive
  - Insert into vagina up to knuckles length
  - Nightly x 2-3 weeks then 2x/week for maintenance
- Estradiol Vaginal Suppositories
  - Estradiol inserts placed with an applicator -> insert to knuckle length
  - Nightly x 2 weeks then 2x/week for maintenance
- Vaginal DHEA
  - Precursor hormone to both estrogens and androgens -> may lead to improved sexual and urinary outcomes
  - Stored at room temp or refrigerated
  - Brand name: Intrarosa 6.5 mg vaginal inserts nightly
- Ospemifene
  - FDA-approved for moderate to severe dyspareunia secondary to VVA
  - Oral tablet 60 mg take daily with food
  - SERM with estrogenic effects on vaginal mucosa and bone, no endometrial effects
- Fractional CO2 Vaginal Laser Therapy
  - Requires multiple sessions
  - Typically not covered by insurance
  - Recent double-blind, randomized, sham-controlled trial by Fiona et al. 2021 did not show significant improvement with fractional carbon dioxide laser vs sham treatment after 12 months
- Non-prescription therapy: regular sexual activity, lubricants, moisturizers

# Genitourinary Syndrome of Menopause




| |
|---|
| Labial atrophy |
| Vaginal dryness |
| Introital stenosis |
| Clitoral atrophy |
| Phimosis of the prepuce |
| Reduces mons pubis and labia majora bulk |
| Reduced labia minora tissue and pigmentation |
| Prominence and erythema of the urethral meatus |
| Urethral caruncle |
| Vaginal pallor |
| Lack of vaginal rugae |

- "Go-to" prescription: Vaginal estradiol cream → First 2 wks: Draw up 1 gram with applicator OR create a fingertip to middle knuckle length ribbon of cream. Insert into the vagina, spreading cream around inside and opening of vagina NIGHTLY. After 2 wks: same instructions 2-3 nights a week.
  - Target lower ½ of vaginal canal **and introitus**, also apply peri-urethrally if hx of recurrent UTIs
- No strict contraindications for vaginal estrogen except for possibly for history of uterine sarcomas and ensure appropriate counseling and transparency for breast cancer patients on aromatase



Iyer TK, Thacker HL: "Menopause" In: Falcone T, Hurd WW, Editors. Clinical Reproductive Medicine and Surgery: A Practical Guide, 4th Edition Springer Nature; 2022.

# Key Take Home Points

- Age at menopause is a significant health indicator and an independent risk factor for cardiovascular disease
- HT is the gold standard of treatment for menopausal symptoms in healthy women aged younger than 60 years or within 10 years of menopause onset with no contraindications
    - Absolute risks for HT use in healthy women after 50-59 are rare but can include VTE, stroke, breast cancer
    - Evidence demonstrates improved bone health, cognition, GSM, QOL, CVD risk, all-cause mortality
    - 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 → consider each patient's own risks prior to starting HT
- There are effective non-hormonal options for the treatment of vasomotor symptoms for patients with contraindications or who cannot tolerate or do not want HT
- GSM should be assessed in all postmenopausal women and treated accordingly with one of several effective, safe therapeutic options
- Treatment of menopausal symptoms should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation

*Questions?*

Mass General Brigham