Hot flashes (HF): most common symptom for which women with menopause seek treatment; HF brain-related phenomena, so centrally acting treatment required; most women experience HF; symptoms most pronounced during late perimenopausal transition; young menopausal women experience worst HF, but symptoms improve over time; median duration of bothersome symptoms >10 yr; increased prevalence of bothersome symptoms associated with high body mass index (BMI), induced menopause (due to surgery, chemotherapy, or radiation therapy), black race, smoking, and mood disorders; in contrast, decreased prevalence of bothersome symptoms reported in women who exercise and women of Japanese and Chinese ethnicity.

Treatment: appropriate if symptoms disrupt activities or sleep (many women do not need treatment); efficacy of transdermal therapy similar to that of oral therapy for preventing HF and osteoporosis; progestin therapy nearly as effective as estrogen for treating HF; hormone therapy (HT) most effective treatment for menopausal symptoms.

Women’s Health Initiative (WHI): most patients presenting for treatment older perimenopausal women or young menopausal women (in late 40s or early 50s); mean age of women in WHI ≈63 yr; many patients enrolled in WHI 60 to 69 yr of age, and study included women up to 79 yr of age; ≈17,000 women with intact uterus randomized to conjugated estrogen (CEE) plus medroxyprogesterone (Provera) vs placebo; ≈11,000 hysterectomized women randomized to estrogen therapy (ET) alone vs placebo.

2002 findings for combination estrogen and progestin therapy (EPT): WHI reported 26% increase in breast cancer in treated women, but Kaplan-Meier curves between EPT and placebo did not diverge until ≈3 yr after therapy started; increases in deep venous thrombosis (DVT) and pulmonary embolism (PE) observed as soon as EPT initiated (increase in venous thromboembolism [VTE] considered most important risk demonstrated by WHI); small increased risk for myocardial infarction observed, but this risk differed between younger and older menopausal women; findings published in 2002 did not stratify patients by age, but included entire population of women 50 to 79 yr of age; benefits of HT included reduced risk for colorectal cancer and fracture.

Termination of trials: EPT trial discontinued at ≈5 yr; when ET trial completed, women had been on therapy for mean of 7 yr; ET associated with reduced risk for hip fracture but had no effect on rates of breast cancer.

Effect of trials: in 13 yr since publication of WHI, use of HT has decreased markedly worldwide, and prevalence of use has remained low; WHI has resulted in millions of women receiving no treatment and consequently experiencing reduced quality of life.

Long-term follow-up: for EPT and ET, no effect on mortality observed at 13 yr; risk for invasive breast cancer increased in patients who received EPT (hazard ratio ≈1.3), whereas patients who received ET demonstrated significant decrease (>20%) in risk for breast cancer (hazard ratio 0.79).

Data supporting timing hypothesis: in both trials, HT associated with reduced risk for overall mortality in youngest women, no effect on rates of mortality in women starting treatment at 60 to 69 yr of age, and slight increase in risk for mortality in women starting treatment at ≥70 yr of age; physiologic explanation — HT may increase risk for coronary artery disease (CAD) when initiated late in life, after plaque already present in coronary arteries; however, if therapy started at younger age, increased risk for CAD not observed, and data strongly suggest cardioprotection; other observational studies and randomized trials in primates (including humans) support timing hypothesis.

Breast cancer: HT does not pose greatest risk, but of most concern among patients; in patients treated with EPT in WHI, risk for breast cancer elevated in 2002; elevated risk still present at 13 yr; among participants in EPT trial diagnosed with breast cancer, axillary nodes more likely to be positive for tumor in EPT arm than in placebo arm; EPT may promote preexisting cancers too small to be diagnosed by imaging or clinical assessment; without stimulation by EPT, such cancers may not have progressed during lifetime; elevated risk for breast cancer returned to baseline after therapy discontinued; hazard ratio of 1.28 corresponds to <1 additional case of breast cancer annually per 1000 women on EPT; however, patients understand absolute risk better than relative risk; hazard ratio for EPT slightly higher than that associated daily consumption of 1 glass of wine and slightly lower than that associated with consumption of 2 glasses.

Summary: risk-benefit ratio favorable for initiating systemic HT to relieve symptoms in older perimenopausal women and younger postmenopausal women; risk-benefit ratio for ET
more favorable than that for EPT, primarily because risk for invasive breast cancer higher with EPT than with ET; WHI reveals effect of 5 to 7 yr of EPT or ET but sheds no light on safety of longer term use

Nonprescription treatment: over-the-counter supplements include isoflavones, red clover, soy, black cohosh, and Chinese herbs; high-quality data show these treatments not better than placebo and less effective than conventional HT; in women who benefit from placebo effect, nonharmful treatments need not be discouraged; however, over-the-counter remedies should not be prescribed if patient requires definitive treatment

Nonhormone prescription treatment: several medications that act on brain less effective than HT but more effective than placebo; gabapentin — side effects include fatigue; requires dose escalation; pregabalin may also be used; selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) — well studied and more effective than placebo; may increase risk for sexual and gastrointestinal side effects; may cause dizziness and nausea; low doses may be effective for treating HF; paroxetine best studied SSRI; 7.5-mg formulation of paroxetine lower than dose used to treat mood disorders; gynecologist should convey to patient that drug not used in women on tamoxifen; SSRIs reduce efficacy of tamoxifen for prevention of recurrent breast cancer; SNRIs such as venlafaxine may be used in women on tamoxifen; low-dose paroxetine — dose escalation not required; need not be tapered when patient ready to discontinue use; has no known sexual side effects

Compounded bioidentical hormone therapy: used by 2.5 million women; many women unaware that such formulations not approved by Food and Drug Administration; many practitioners who sell such products also sell salivary hormone testing; serum hormone testing — has only limited role in management of menopausal symptoms; furthermore, salivary testing cannot be used to assess serum hormone levels

Selective estrogen receptor modulator (SERM) plus CEE: may be appropriate in symptomatic women with intact uterus and heightened concern about breast cancer, as conventional EPT increases mammographic density of breasts (which correlates with increased risk for invasive breast cancer); SERM plus CEE does not increase mammographic density of breasts, but whether risk for breast cancer lower compared with EPT unknown

Progestin-releasing intrauterine device: alternative for women with intact uterus who want to avoid systemic progestin (can be expensive)

Transdermal estrogen: based on WHI, VTE (including DVT and PE) greatest risk associated with HT (risk for VTE doubled); no randomized trial has compared transdermal estrogen and oral estrogen; however, 5 large observational studies demonstrated that transdermal estradiol (E2) did not increase risk for thrombosis; American College of Obstetricians and Gynecologists (ACOG) supports use of transdermal preparations, especially in high-risk groups including obese women and older women

Oral estrogen: few comparative data available; CEE (Premarin) most widely used oral estrogen in United States; observational study showed that risk for cardiovascular events lower with oral E2 than with CEE; E2 also less expensive; patients may be started on E2 1 mg; younger patients or those with symptoms at lower doses may take 2 mg; older or long-term users may take 0.5 mg; E2 1 mg equivalent to CEE 0.625 mg or transdermal E2 0.05 mg

Early menopause: WHI did not enroll patients <50 yr of age; younger menopausal women should be provided with HT (if not contraindicated) due to increased risk for CAD, cardiovascular event, neurodegenerative disorder, and all-cause mortality; incidental oophorectomy should be avoided in patient undergoing hysterectomy for benign disease unless risk for ovarian cancer elevated; importance of taking estrogen should be discussed with patient before surgery; dosing — in patients with surgically induced menopause or young menopausal patients, gynecologist should not hesitate to increase dose of estrogen to as high as 2 mg for oral E2, 1.25 mg for CEE, and 0.1 mg for transdermal E2 (occasionally, patients require >1 patch)

Genitourinary syndrome of menopause (GSM): implications — untreated GSM worsens over time and leads to sexual dysfunction, pain, and recurrent urinary tract infection; treatment — includes vaginal estrogen (cream, tablet, or ring); important behavioral interventions include regular sexual activity, use of lubricants with sexual activity, and moisturizers; treatment of GSM has minimal systemic effects; patients with intact uterus do not require concomitant progestin therapy; vaginal ultrasonography may be used to confirm thickness of endometrium; ospemifene — SERM for systemic treatment of GSM; unknown whether risk for VTE lower compared with raloxifene and tamoxifen (raloxifene and tamoxifen associated with increased production of coagulation factors by liver)

Case example: 62-yr-old woman presented for well woman examination; history included hysterectomy for fibroids without oophorectomy 20 yr ago; patient developed HF in early 50s and did well on oral estrogen; patient slender, and family history positive for hip fracture; recently, patient did not take ET during long vacation and experienced no HF; she asked whether she should continue with ET

Osteoporosis: in women with no symptoms of menopause, main indication for systemic HT prevention of osteoporosis and fractures; most standard-dose therapies approved for treatment of osteoporosis as well as HF; lowest-dose conventional patch delivers 0.025 mg of E2, and ultra-low-dose patch (Menostar) delivers 0.014 mg of E2; ultra-low-dose patch associated with serum E2 levels in menopausal range; although ultra-low-dose patch may be prescribed with or without progestin, 3- and 5-yr data not yet available, so gynecologist should consider endometrial monitoring if patch used long term without progestin in women with intact uterus; women with BMI of 30 to 35 not at high risk for osteoporosis in absence of other risk factors such as use of corticosteroids; woman in case study had low BMI and positive family history; when systemic therapy used only to protect bone health, decreased dose should be used; HT and denosumab (Prolia) do not protect bone after medication discontinued (unlike bisphosphonates); prolonged ET — reasonable in patients without uterus; in patients with uterus, long-cycle progestin (given every 1-3 mo for 10 days) should be considered; as in any menopausal woman, evaluation of endometrium indicated if spotting or bleeding occurs; risk of venous and arterial vascular events lower with transdermal estrogen than with oral estrogen

Management: starting therapy — in 52-yr-old woman with typical symptoms, standard dose may be initiated; patch preferred if patient obese or has other CV risk factors; continuing therapy — if patient does well on starting dose for several years, reduction of dose should be discussed; original dose may be reinstated if HF resume or patient reports loss of sense of well-being; in patient doing well for years on ultralow-dose formulation and not at high risk for osteoporosis, systemic therapy may be stopped; treatment may be restarted if symptoms occur; however, GSM commonly begins when systemic therapy stopped, so vaginal ET may be needed; in patient at elevated risk for osteoporosis, indefinite use of low-dose or ultra-low-dose therapy should be offered; when little or no progestin used, endometrium should be monitored

Case follow-up: patient chose to continue estrogen for bone health but switched from oral therapy to low-dose patch; few years later, dual-energy x-ray absorptiometry showed normal bone density; patient continued patch into her 70s and
planned to use it indefinitely; however, insurer denied coverage for systemic hormonal therapy

**Summary:** ACOG and North American Menopause Society (NAMS) support HT in women >65 yr of age; extended use of HT controversial because no data from clinical trials available; therapy of extended duration should be individualized and decision making should be shared with patient; NAMS offers decision support application and sponsors certification for practitioners

**Suggested Reading**


**Acknowledgments**

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MENOPAUSE

To test online, go to www.audiodigest.org and sign in to online services.
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1. The median duration of bothersome menopausal symptoms is:
   (A) 3 yr  (B) 5 yr  (C) 7 yr  (D) >10 yr

2. The increased prevalence of bothersome menopausal symptoms is associated with:
   1. White race
   2. Smoking
   3. Mood disorders
   4. Japanese ethnicity
   (A) 1,2  (B) 2,3  (C) 1,2,3  (D) 2,3,4

3. The increase in which of the following was considered the most important risk associated with estrogen plus progestin therapy in the Women’s Health Initiative?
   (A) Colorectal cancer  (B) Venous thromboembolism  (C) Myocardial infarction  (D) Breast cancer

4. All the following statements about the Women’s Health Initiative are true, EXCEPT:
   (A) No data from clinical trials are available to support extended HT
   (B) The American College of Obstetricians and Gynecologists does not support extended HT
   (C) Extended HT is inferior to the use of denosumab and bisphosphonates
   (D) Extended HT is associated with increased risk for breast cancer

5. Which of the following statements about treating a patient with hot flashes (HF) is true?
   (A) Black cohosh and paroxetine are equally effective
   (B) Hormone therapy (HT) and paroxetine are equally effective
   (C) Black cohosh is more effective than venlafaxine
   (D) Gabapentin is more effective than black cohosh

6. All the following can be used in a patient who is taking tamoxifen for breast cancer and requires treatment for HF, EXCEPT:
   (A) Paroxetine  (B) Venlafaxine  (C) Gabapentin  (D) Oral estrogen

7. Which of the following treatment modalities for menopausal symptoms increases the mammographic density of breasts?
   (A) Oral estradiol  (B) Transdermal estradiol  (C) Selective estrogen receptor modulator plus conjugated equine estrogen  (D) Estrogen plus progestin

8. Several large observational studies have demonstrated that transdermal estrogen does not increase risk for thrombosis.
   (A) True  (B) False

9. Which of the following is the most appropriate starting dose of oral estradiol in a 60-yr-old perimenopausal patient initiating treatment for HF?
   (A) 0.5 mg  (B) 0.625 mg  (C) 1 mg  (D) 2 mg

10. The main indication for systemic HT in women with no symptoms of menopause if for the prevention of:
    (A) Depression  (B) Kidney disease  (C) Osteoporosis  (D) Essential tremor

Answers to Audio Digest Obstetrics/Gynecology Volume 62, Issue 18: 1-D, 2-C, 3-D, 4-B, 5-A, 6-B, 7-A, 8-B, 9-D, 10-D