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Menopause

This 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.

Diagnosis

Treatment

Practice Improvement

CME/MOC activity available at Annals.org.

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Management of symptoms and conditions associated with menopause is challenging. The variety of symptoms and their fluctuating nature, menopause's effect on other conditions, and uncertainty about the safety and effectiveness of available treatments contribute to the confusion. The demand for nonhormonal treatments as well as for alternative formulations and routes of delivery of hormonal medications has increased since the publication of the Women's Health Initiative (WHI) findings (1, 2). The importance of considering patient preferences and values in addition to their symptoms and health risks further complicates care of menopausal women.

Diagnosis

What is menopause?

Menopause is the cessation of the menstrual cycle and the end of a woman's reproductive years. It is a clinical diagnosis that is defined retrospectively, 12 months after the final menstrual period. Progressive oocyte depletion, through either atresia or ovulation, leads to the normal process of menopause. Irregular menses mark the menopausal transition, which typically begins 4 years before the final menstrual period (3). The final menstrual period occurs at a median age of 51.4 years (4). Various genetic and environmental factors, such as maternal age at menopause onset, current smoking, parity, and use of oral contraceptives, have been associated with onset of menopause (4). Surgery, chemotherapy, or radiation can induce premature menopause (onset before age 40 years) or early menopause (onset before age 45 years).

What symptoms characterize menopause?

The timing, prevalence, severity, range, and duration of symptoms vary markedly across individuals and cultures (5, 6).

Menstrual cycle changes are common and varied. In the late reproductive years, hormone changes are characterized by a decrease in serum inhibin B and antimüllerian hormone levels and a slight increase in serum follicle-stimulating hormone (FSH) level. Estradiol levels remain unchanged, but luteal phase progesterone levels decrease along with fertility potential. Though cycles initially remain ovulatory, the follicular phase begins to shorten. Thus, the first change seen in menstrual cycles is a decrease in the interval between them. This is followed by a lengthening in the interval between cycles, which may increase to 40 to 50 days. During this time, FSH levels are high but variable and may be normal one month and abnormal the next. Because of this variability during the menopausal transition, FSH measurements are not routinely recommended for diagnosis (7). Women subsequently develop anovulatory cycles interspersed with ovulatory cycles. Anovulatory cycles are characterized by intermittent and irregular bleeding that can be heavy at times because of prolonged unopposed estrogen.

Vasomotor symptoms (for example, hot flashes) are the most common symptoms during menopause, reported by 80% of menopausal women. A hot flash or flush is a sudden sensation of intense warmth that usually begins in the face or chest and spreads throughout the body, often with coincident sweating and palpitations. Hot flashes can last for 2 to 30 minutes. Night sweats are hot flashes that occur at night and can interrupt sleep. Vasomotor symptoms typically

1. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-33. [PMID: 12117397]
2. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004;291:47-53. [PMID: 14709575]
3. McKinlay SM. The normal menopause transition: an overview. Maturitas. 1996;23:137-45. [PMID: 8735352]
4. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2001;153:865-74. [PMID: 11323317]
5. Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. Soc Sci Med. 2001;52:345-56. [PMID: 11330770]
6. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. Am J Epidemiol. 2000;152:463-73. [PMID: 10981461]
7. Freeman EW, Sammel MD, Gracia CR, et al. Follicular phase hormone levels and menstrual bleeding status in the approach to menopause. Fertil Steril. 2005;83:383-92. [PMID: 15705379]
8. Avis NE, Crawford SL, Greendale G, et al; Study of Women's Health Across the Nation. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015;175:531-9. [PMID: 25686030]
9. Crandall CJ, Aragaki A, Cauley JA, et al. Associations of menopausal vasomotor symptoms with fracture incidence. J Clin Endocrinol Metab. 2015;100:524-34. [PMID: 25522264]
10. Zhu D, Chung HF, Dobson AJ, et al. Vasomotor menopausal symptoms and risk of cardiovascular disease: a pooled analysis of six prospective studies. Am J Obstet Gynecol. 2020;223:898.e1-898.e16. [PMID: 32585222]

Table 1. **Stages of Menopause**

Characteristic	*Menopausal Transition*		*Postmenopause*	
	Early Perimenopause	*Late Perimenopause*	*Early Postmenopause*	*Late Postmenopause*
Menstrual cycle	Variable length (>7 d different from normal)	≥2 skipped cycles and an interval of amenorrhea ≥60 d	None	None
Median age at onset	47.5 *y*	–	51.3 *y*	56.3 *y*
FSH level	Elevated	Elevated	Very elevated	Very elevated
Prevalence of vasomotor symptoms	15%–20%	20%–30%	35%–55%	30% initially, gradually decreasing
	50% overall		80% overall	
Prevalence of vaginal dryness/dyspareunia	–	–	10%–30%	35%–47%

FSH = follicle-stimulating hormone.

peak around the final menstrual period and then decrease in prevalence and severity. Although they usually resolve without treatment, they persist for a median of 7.4 years, and approximately 10% of women have persistent bothersome vasomotor symptoms 7 to 10 years after the final menstrual period (8). Vasomotor symptoms have been linked to increased cardiovascular risk and bone loss (9, 10).

Genitourinary syndrome of menopause (GSM) results in vaginal atrophy and dryness and can lead to discomfort, itching, and painful intercourse (dyspareunia). Studies suggest that vaginal dryness affects from one third to nearly one half of menopausal women, with symptoms increasing during late postmenopause (11).

Sleep disturbances are common during the menopausal transition (12) and may be related to night sweats and severity of vasomotor symptoms (13). Other symptoms reported include mood disorders (depressive symptoms, anxiety, irritability), cognitive disturbances (forgetfulness, difficulty thinking), somatic symptoms (back pain, stiff or painful joints, tiredness, myalgia), urinary incontinence, vertigo, headache, palpitations, and sexual dysfunction that is not related to dyspareunia (11) (see the **Box:** Common Symptoms in Women During the Menopausal Transition). However, these symptoms are considered atypical because they have not been conclusively linked to menopausal hormonal changes.

What are the stages of the menopausal transition?

The menopausal transition manifests as a series of symptom complexes that follow a somewhat predictable pattern over a highly variable time course. The Stages of Reproductive Aging Workshop describes menopause as a series of distinct stages (**Table 1**) (14). Early postmenopause is the interval within 4 years of the final menstrual period, and late postmenopause is 5 or more years after the final menstrual period. Early perimenopause results from anovulatory menstrual cycles and is characterized by irregularity in cycle length and duration. Late perimenopause is marked by progressive menstrual irregularity and onset of vasomotor symptoms and ends 1 year after the final menstrual period. Though bleeding patterns may change during perimenopause, women remain at risk for pregnancy.

Predicting the final menstrual period is challenging. Investigators from SWAN (Study of Women's Health Across the Nation)—a

11. Nelson HD, Haney E, Humphrey L, et al. Management of menopause-related symptoms. Evidence Report/Technology Assessment no. 120. AHRQ Publication no. 05-E016-2. Agency for Healthcare Research and Quality; 2005.
12. Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. Am J Med. 2005;118 Suppl 12B:14-24. [PMID: 16414323]
13. Oldenhave A, Jaszmann LJ, Haspels AA, et al. Impact of climacteric on well-being. A survey based on 5213 women 39 to 60 years old. Am J Obstet Gynecol. 1993;168:772-80. [PMID: 8456878]
14. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Climacteric. 2001;4:267-72. [PMID: 11770182]
15. Santoro N, Brockwell S, Johnston J, et al. Helping midlife women predict the onset of the final menses: SWAN, the Study of Women's Health Across the Nation. Menopause. 2007;14:415-24. [PMID: 17303963]
16. Taffe JR, Cain KC, Mitchell ES, et al. "Persistence" improves the 60-day amenorrhea marker of entry to late-stage menopausal transition for women aged 40 to 44 years. Menopause. 2010;17:191-3. [PMID: 19713872]

17. Wilkin JK. Flushing reactions: consequences and mechanisms. Ann Intern Med. 1981;95:468-76. [PMID: 6169300]
18. Sowers M, Luborsky J, Perdue C, et al; SWAN. Thyroid stimulating hormone (TSH) concentrations and menopausal status in women at the mid-life: SWAN. Clin Endocrinol (Oxf). 2003;58:340-7. [PMID: 12608940]
19. ACOG committee opinion no. 773 summary: the use of antimüllerian hormone in women not seeking fertility care. Obstet Gynecol. 2019;133:840-1. [PMID: 30913192]
20. Gold EB, Block G, Crawford S, et al. Lifestyle and demographic factors in relation to vasomotor symptoms: baseline results from the Study of Women's Health Across the Nation. Am J Epidemiol. 2004;159:1189-99. [PMID: 15191936]
21. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. Am J Public Health. 2006;96:1226-35. [PMID: 16735636]
22. Thurston RC, Sowers MR, Chang Y, et al. Adiposity and reporting of vasomotor symptoms among midlife women: the Study of Women's Health Across the Nation. Am J Epidemiol. 2008;167:78-85. [PMID: 17881385]
23. Thurston RC, Sowers MR, Sutton-Tyrrell K, et al. Abdominal adiposity and hot flashes among midlife women. Menopause. 2008;15:429-34. [PMID: 18204407]
24. Schwingl PJ, Hulka BS, Harlow SD. Risk factors for menopausal hot flashes. Obstet Gynecol. 1994;84:29-34. [PMID: 8008318]
25. Avis NE, Stellato R, Crawford S, et al. Is there an association between menopause status and sexual functioning. Menopause. 2000;7:297-309. [PMID: 10993029]
26. Huang AJ, Subak LL, Wing R, et al; Program to Reduce Incontinence by Diet and Exercise Investigators. An intensive behavioral weight loss intervention and hot flushes in women. Arch Intern Med. 2010;170:1161-7. [PMID: 20625026]

Common Symptoms in Women During the Menopausal Transition

Symptoms definitely associated with menopausal hormonal changes:
- Hot flashes
- Night sweats
- Vaginal dryness

Symptoms not definitively related to hormonal changes:
- Depression, anxiety, and irritability
- Cognitive disturbances
- Back pain, stiff or painful joints, myalgia
- Fatigue
- Urinary incontinence
- Vertigo
- Headache
- Palpitations
- Sexual dysfunction

multisite, longitudinal, epidemiologic study designed to examine the health and life experience of a multiethnic cohort of midlife U.S. women—have developed an algorithm utilizing 1 current and 1 previous serum level of estradiol and FSH to estimate whether a woman is within 1 to 2 years of her final menstrual period (15). Data suggest that women who have had at least 2 months of amenorrhea can expect their final menstrual period within the next 5 years (16).

What other conditions should clinicians consider in patients with vasomotor symptoms, menstrual irregularity, or abnormal vaginal bleeding?

Although vasomotor symptoms are highly suggestive, they are not specific to menopause. Hot flashes and night sweats can also occur with emotional stress, panic attacks, alcohol, certain drugs (such as tamoxifen; raloxifene; danazol; the gonadotrophin-releasing hormone agonists leuprolide, nafarelin, and goserelin; and aromatase inhibitors), thyroid disease, infections, carcinoid syndrome, pheochromocytoma, systemic mastocytosis, leukemia, and other malignant conditions (17). However, vasomotor symptoms without other worrisome symptoms in a healthy woman of menopausal age in the context of progressive menstrual irregularity or amenorrhea do not typically require further evaluation.

Other conditions that can cause menstrual irregularity or vaginal bleeding include thyroid disease; pregnancy; vaginal, cervical, or endometrial pathology; hormonal contraceptive use; hyperprolactinemia; virilizing tumors; and elevated serum androgen levels. Abnormal thyroid-stimulating hormone levels have high prevalence among middle-aged women (9.6% in 1 study [18]) and are associated with menstrual irregularity. However, thyroid-stimulating hormone measurements are not indicated in women with typical menopause symptoms and no evidence of thyroid disease.

GSM is diagnosed clinically with a pelvic examination using a well-lubricated speculum. Concordant findings include loss of vaginal rugae with thin, shiny, or friable vaginal tissue.

When should clinicians consider laboratory studies to confirm menopause?

Menopause is a clinical diagnosis that is usually made by obtaining a history of menstrual changes and typical symptoms. Laboratory studies are rarely necessary given their variability (7). However, in women with underlying menstrual disorders (such as polycystic ovary syndrome), hysterectomy, or

Table 2. **Laboratory Tests to Aid in the Differentiation of Menopause From Other Conditions**

Test	*Notes*
Pregnancy test (BhCG)	Although unlikely in this age group, pregnancy can occur
FSH	Elevated FSH level (>30 mIU/mL) is consistent with diagnosis In women aged <40 y, 2 to 3 levels (best checked on day 3 of cycle) may be needed for diagnosis
Thyroid-stimulating hormone	To detect hypothyroidism or hyperthyroidism
Prolactin	To diagnose hyperprolactinemia
Estradiol	May be useful in women using hormonal contraception Checked 7 d after discontinuation of oral contraceptives Result <20 pg/mL is consistent with menopause
Endometrial biopsy	Consider in women aged >45 y or those aged <45 y with additional risk factors for unopposed estrogen (obesity, chronic ovulatory dysfunction) to rule out endometrial hyperplasia or cancer as cause of abnormal uterine bleeding

BhCG = human chorionic gonadotrophin; FSH = follicle-stimulating hormone.

history of endometrial ablation, measurement of FSH levels can help confirm menopause and differentiate it from other conditions (14). An elevated FSH level (>30 mIU/mL) is objective evidence of menopause. Levels of FSH gradually increase throughout the menopausal transition but can vary greatly during perimenopause. In women prescribed exogenous hormones (for example, hormonal contraceptives), FSH levels are unreliable and should be measured 2 to 4 weeks after oral contraceptives are discontinued (and replaced with an alternate form of contraception). Although levels of antimüllerian hormone decrease across the reproductive lifespan, insufficient data exist to support its use (19). Clinicians may wish to perform additional laboratory tests to exclude non–menopause-related causes of menstrual dysfunction in patients lacking typical symptoms (**Table 2**).

Diagnosis... Menopause is a clinical diagnosis that is defined retrospectively, 12 months after the final menstrual period. The menopausal transition manifests as a series of symptom complexes that follow a somewhat predictable pattern over a variable time course. Hot flashes, night sweats, and vaginal dryness are consistently associated with menopausal hormonal changes. Laboratory studies are rarely necessary for diagnosis, but measurement of FSH levels (sustained levels >30 mIU/mL) can confirm menopause and help differentiate it from other conditions. An elevated FSH level is objective evidence of menopause.

CLINICAL BOTTOM LINE

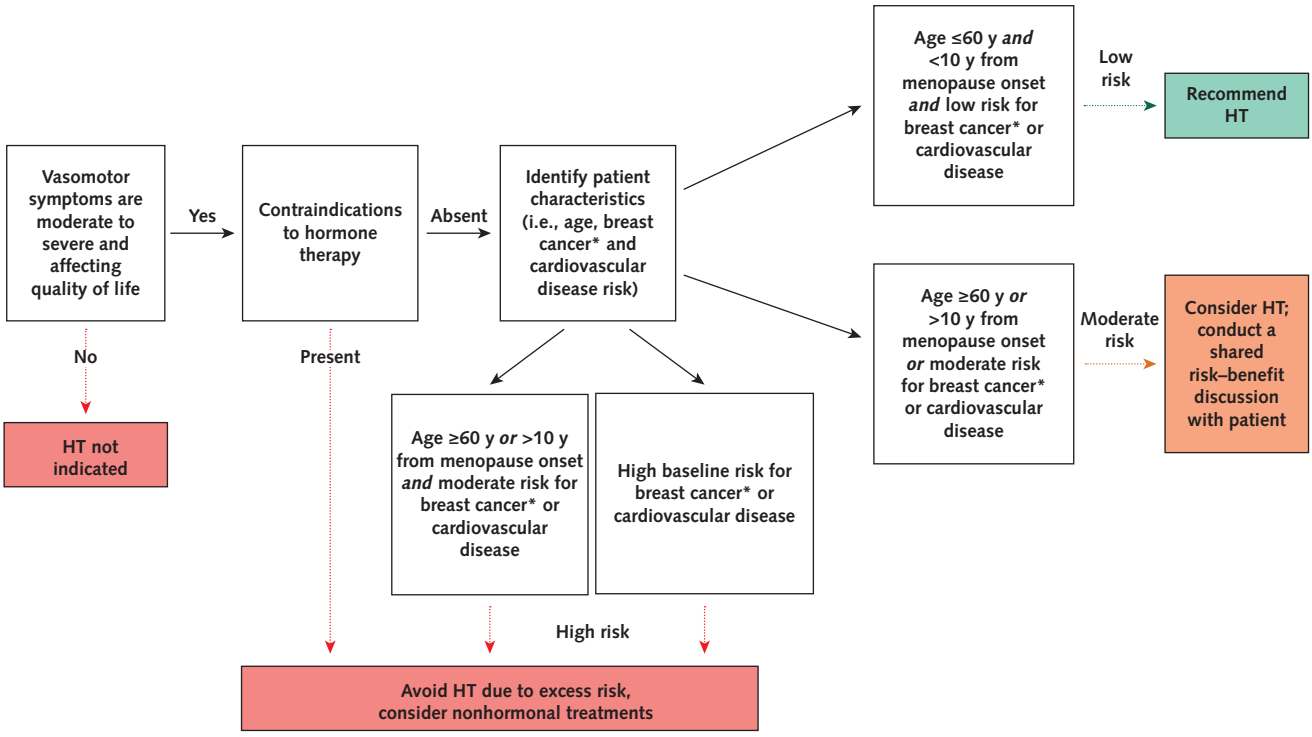
Treatment

What is the initial approach to treatment?

The initial treatment approach for a woman with menopause symptoms is to determine whether she has vasomotor symptoms, vaginal symptoms, or both. Hormone therapy (HT) is the most effective treatment for moderate to severe vasomotor symptoms and should be considered as first-line treatment in early menopause, assuming there are no contraindications. We recommend an algorithmic approach (**Figure**) to determining whether a patient with vasomotor

27. Thurston RC, Ewing LJ, Low CA, et al. Behavioral weight loss for the management of menopausal hot flashes: a pilot study. Menopause. 2015;22:59-65. [PMID: 24977456]
28. Col NF, Guthrie JR, Politi M, et al. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. Menopause. 2009;16:453-7. [PMID: 19188852]
29. Daley A, Stokes-Lampard H, Thomas A, et al. Exercise for vasomotor menopausal symptoms. Cochrane Database Syst Rev. 2014:CD006108. [PMID: 25431132]
30. Anderson DJ, Chung HF, Seib CA, et al. Obesity, smoking, and risk of vasomotor menopausal symptoms: a pooled analysis of eight cohort studies. Am J Obstet Gynecol. 2020;222:478.e1-478.e17. [PMID: 31705884]
31. Maclennan AH, Broadbent JL, Lester S, et al. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev. 2004:CD002978. [PMID: 15495039]
32. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. JAMA. 2004;291:1610-20. [PMID: 15069049]
33. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465-77. [PMID: 17405972]

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.

34. Manson JE, Kaunitz AM. Menopause management –getting clinical care back on track. N Engl J Med. 2016;374:803-6. [PMID: 26962899]
35. Manson JE, Aragaki AK, Rossouw JE, et al; WHI Investigators. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. JAMA. 2017;318:927-38. [PMID: 28898378]
36. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. JAMA. 2020;324:369-80. [PMID: 32721007]
37. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev. 2015:CD002229. [PMID: 25754617]

symptoms is a candidate for HT. If a woman is not interested or is not a candidate, various non-HT treatments can be considered. For women with GSM alone, non-HT treatments (lubricants and moisturizers) are considered first-line treatment; vaginal estrogens should be reserved for patients who do not respond to non-HT treatments.

What lifestyle modifications should clinicians recommend for women with vasomotor symptoms?

Lifestyle modifications can be an appropriate first step to consider before initiation of or in conjunction with pharmacologic therapies for mild vasomotor symptoms. Clinicians should counsel women that hot flashes are part of the normal process of estrogen withdrawal. Smoking is consistently associated with worsening of vasomotor symptoms (20, 21), and women can decrease the number and severity of symptoms by quitting or decreasing smoking. Although alcohol is not consistently associated with vasomotor symptoms, limiting consumption is prudent because it is a vasodilator. Some studies have shown an association between obesity and vasomotor symptoms (6, 21–23), but others have not (24, 25). Although some data suggest that weight loss in overweight or obese women may improve vasomotor symptoms, available evidence has not shown a consistent reduction in vasomotor symptoms with exercise (26, 27). Nevertheless, exercise favorably affects mood, perceived stress, body image (28), and body weight. If symptoms do not remit with lifestyle changes, clinicians

should consider pharmacologic therapy.

A 2014 systematic review of randomized controlled trials (RCTs) compared exercise interventions versus other treatments or no treatment in the management of menopausal vasomotor symptoms (29). *Only 1 small trial that compared exercise with HT suggested a trend favoring exercise. In 3 trials that compared exercise with no active treatment, all studies favored exercise, but effect estimates were nonsignificant. The authors concluded that the overall evidence was insufficient to suggest that exercise was effective in reducing vasomotor symptoms.*

A pooled analysis of 8 cohort studies prospectively followed 11 986 women to investigate associations between body mass index (BMI) and smoking on risk for vasomotor symptoms (30). *Higher BMI and heavier smoking were associated with more frequent and severe vasomotor symptoms, with a dose-dependent interaction between smoking and obesity (that is, the adverse effect of obesity was worse with more pack-years of smoking). Risk for vasomotor symptoms in those who quit smoking before age 40 years was similar to that of never-smokers. Although higher BMI was associated with increased risk for vasomotor symptoms in premenopausal and perimenopausal women, it was associated with reduced symptoms after menopause. The authors concluded that maintaining normal body weight before the menopausal transition and quitting smoking before age 40 years might mitigate excess risk for vasomotor symptoms later in midlife.*

When should clinicians consider HT to treat menopause symptoms?

Because the greatest benefit of HT is for vasomotor symptoms, the treatment decision rests primarily on the severity of hot flashes and night sweats and personal preference. Approximately 15% to 20% of women have moderate to severe vasomotor symptoms warranting pharmacologic therapy. Estrogen reduces the severity and frequency of vasomotor symptoms by more than 70%, usually within 1 month (11). When making treatment decisions, women must balance benefits against risks. **Table 3** summarizes some longer-term risks of HT. Degree of risk depends on dose, duration, route of administration, timing of initiation, and whether a progestogen is needed. When

Table 3. **Absolute Risk Differences of Conjugated Equine Estrogen Plus Progestin and Conjugated Equine Estrogen Alone Versus Placebo in Women Aged 50 to 59 Years***

End Point	*Intergroup Difference in Number of Events per 1000 Women Over 5 Years*	
	E + P vs. Placebo	*CEE Alone vs. Placebo*
Coronary heart disease	2.5	−5.5
Stroke	2.5	−0.5
Deep venous thrombosis	5.0	2.5
Breast cancer	3.0	−2.5
Colorectal cancer	−0.5	−1.5
All cancers	−0.5	−4.0
All fractures	−12.0	−8.0
Death (any cause)	−5.0	−5.5

CEE = conjugated equine estrogen; E + P = conjugated equine estrogen plus progestin.
** Adapted from reference 34.*

38. 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;364:k4810. [PMID: 30626577]
39. Collaborative Group on Hormonal Factors in Breast Cancer.. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019;394:1159-68. [PMID: 31474332]
40. Georgakis MK, Kalogirou EI, Diamantaras AA, et al. Age at menopause and duration of reproductive period in association with dementia and cognitive function: a systematic review and meta-analysis. Psychoneuroendocrinology. 2016;73:224-43. [PMID: 27543884]
41. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA. 2001;285:2891-7. [PMID: 11401611]
42. Cauley JA, Robbins J, Chen Z, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290:1729-38. [PMID: 14519707]
43. Kiel DP, Felson DT, Anderson JJ, et al. Hip fracture and the use of estrogens in postmenopausal women. The Framingham Study. N Engl J Med. 1987;317:1169-74. [PMID: 3657888]
44. Cauley JA, Seeley DG, Ensrud K, et al. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med. 1995;122:9-16. [PMID: 7985914]
45. Wren BG, Champion SM, Willetts K, et al. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. Menopause. 2003;10:13-8. [PMID: 12544672]

46. Mattson RH, Cramer JA, Darney PD, et al. Use of oral contraceptives by women with epilepsy. JAMA. 1986;256:238-40. [PMID: 3723710]
47. Taylor HS, Tal A, Pal L, et al. Effects of oral vs transdermal estrogen therapy on sexual function in early postmenopause: ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). JAMA Intern Med. 2017;177:1471-9. [PMID: 28846767]
48. Utian WH, Shoupe D, Bachmann G, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril. 2001;75:1065-79. [PMID: 11384629]
49. Pinkerton JV, Faubion SS, Kaunitz AM, et al. The National Academies of Science, Engineering, and Medicine (NASEM) report on compounded bioidentical hormone therapy [Editorial]. Menopause. 2020;27:1199-201. [PMID: 33110032]
50. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel.. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24:728-53. [PMID: 28650869]
51. Grossman DC, Curry SJ, Owens DK, et al; US Preventive Services Task Force. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. JAMA. 2017;318:2224-33. [PMID: 29234814]
52. Rada G, Capurro D, Pantoja T, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev. 2010: CD004923. [PMID: 20824841]
53. Shams T, Firwana B, Habib F, et al. SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. J Gen Intern Med. 2014;29:204-13. [PMID: 23888328]
54. Loprinzi CL, Sloan J, Stearns V, et al. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol. 2009;27:2831-7. [PMID: 19332723]

counseling about HT, clinicians should present absolute risks, making the distinction between combination HT and estrogen alone.

What are the short-term adverse effects of HT?

The most commonly reported acute adverse effects associated with estrogen therapy are breast tenderness and uterine bleeding (31). Other adverse effects include atypical bleeding and endometrial hypertrophy (but not with adequate progestogen use), nausea and vomiting, headache, weight change, dizziness, venous thromboembolism (VTE) and cardiovascular events, rash and pruritus, cholecystitis, and liver effects (32).

What are the long-term risks and benefits of HT?

In addition to short-term considerations, longer-term risks (**Table 3**) and benefits influence decisions about treatment with HT.

To determine the balance of risks and benefits of postmenopausal HT in healthy women, the WHI randomly assigned 16 608 postmenopausal women aged 50 to 79 years with an intact uterus at baseline to either conjugated equine estrogens (CEEs), 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 oral tablet or placebo. The trial was terminated early, after a mean of 5.2 years of follow-up, because interim results indicated that the risks of HT exceeded its benefits. Absolute excess risks per 10 000 person-years attributable to estrogen plus progestin were 6 more coronary heart disease (CHD) events, 9 more strokes, 9 more pulmonary embolisms, and 9 more cases of invasive breast cancer; absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancer cases and 6 fewer hip fractures (1, 33). The WHI also randomly assigned 10 739 women without an intact uterus to estrogen alone (n = 5310) or placebo (n = 5429). Absolute excess risks per 10 000 person-years attributable to estrogen therapy alone were 11 more strokes and 4 more pulmonary embolisms, with no increase in CHD events or breast cancer. Subsequent reanalyses of these data have supported the "timing hypothesis" (that is, HT is safer and the benefit–risk ratio is more favorable in younger vs. older menopausal women) (34).

Mortality

Long-term data from the WHI do not support any difference in all-cause, breast cancer, or CHD mortality between HT users and nonusers.

Two recent analyses of 18 and 20 years of follow-up data from the WHI, respectively (35, 36), found no differences in all-cause mortality for either estrogen plus progestin therapy versus placebo or estrogen therapy alone versus placebo, providing reassurance that short-term use of either HT regimen does not increase overall mortality risk later in life.

Cardiovascular risk

The effect of HT on CHD varies depending on when HT is initiated relative to age or years since menopause onset. Meta-analysis data suggest reduced CHD risk in women who initiate HT within 10 years of menopause onset (33, 35). However, there is no recommendation for HT for primary or secondary prevention of CHD due to other risks. Women who initiate HT more than 10 years from menopause onset have potential increased risk for CHD but not mortality (37).

A 2017 analysis of 18 years of follow-up data from the WHI assessed mortality outcomes in 27 347 women (35) and found no difference in cardiovascular disease (CVD) mortality due to HT, with CVD death rates in the

pooled cohort of 8.9% in the HT group versus 9.0% in the placebo group (hazard ratio, 1.00 [95% CI, 0.92 to 1.08]).

Stroke and VTE risk

Data from the WHI show increased risk for stroke and VTE in women treated with both systemic estrogen-only HT and combined HT. The highest absolute risk was in women more than 10 years from menopause onset. There is no evidence of increased risk for these conditions with low-dose vaginal estrogen therapy. Observational studies have found that transdermal formulations of estrogen carry lower risk for stroke and VTE than do oral formulations (38), but large-scale randomized trials of transdermal HT in relation to clinical CVD events are not available.

Breast cancer risk

Breast cancer risk assessment should be included as part of routine menopause counseling. The strongest predictors of breast cancer are older age, family history of breast cancer, younger age at menarche, older age at menopause, and having had a breast biopsy. It is important to note that women without a uterus receiving estrogen alone do not carry a clinically significant increased risk for breast cancer. However, use of combination HT does increase risk for invasive breast cancer diagnosed at a more advanced stage.

A 2020 analysis of 20 years of follow-up data from the WHI (36) found that women randomly assigned to combination HT had a statistically significantly higher incidence of breast cancer than those randomly assigned to placebo; there were 584 cases among 8506 women in the combination HT group (annualized rate, 0.45%) versus 447 cases in 8102 placebo users (annualized rate, 0.36%) (hazard ratio, 1.28 [CI, 1.13 to 1.45]). However, there was no significant increase in breast cancer deaths. Compared with women randomly assigned to placebo, those randomly assigned to estrogen alone had a statistically significantly lower breast cancer incidence, with 238 cases among 5310 women (annualized rate, 0.30%) compared with 396 cases among 5429 placebo users (annualized rate, 0.37%) (hazard ratio, 0.78 [CI, 0.65 to 0.93]).

A recent meta-analysis also showed that risk for breast cancer depends on the type and duration of HT (39). Increased risk was significant in women with a uterus receiving combined HT (estrogen plus progestogen) (risk ratio, 1.60 [CI, 1.52 to 1.69]). Risk increased with duration of use and was greater for estrogen receptor–positive tumors. Five years of HT started at age 50 years would increase absolute risk for breast cancer by 1 in 50 for estrogen combined with daily progestogen, 1 in 70 for estrogen combined with cyclic progestogen, and 1 in 200 for estrogen alone.

Cognition

Although women often report difficulty concentrating or forgetfulness during menopause, data on the effect of HT on cognition are mixed (40). In the WHI, HT was associated with increased risk for dementia in women randomly assigned at age 65 years or older. However, early initiation of HT in young postmenopausal women with normal baseline cognitive function did not seem to affect cognition (40).

Bone density and osteoporosis

HT prevents bone loss and reduces osteoporotic fracture in postmenopausal women (41–44). In the WHI, both combined and CEE-alone HT were associated with reduced hip fracture risk. However, the protective effect

55. Shan D, Zou L, Liu X, et al. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020;222:564-579.e12. [PMID: 31870736]
56. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause. 2015;22:1155-72. [PMID: 26382310]
57. Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012:CD007244. [PMID: 22972105]
58. Society of Obstetricians and Gynaecologists of Canada.. SOGC clinical practice guidelines. The detection and management of vaginal atrophy. Number 145, May 2004. Int J Gynaecol Obstet. 2005;88:222-8. [PMID: 15779109]
59. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. Menopause. 2008;15:661-6. [PMID: 18698279]
60. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020;27:976-92. [PMID: 32852449]
61. Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. JAMA Intern Med. 2018;178:681-90. [PMID: 29554173]
62. Dennerstein L, Alexander JL, Kotz K. The menopause and sexual functioning: a review of the population-based studies. Annu Rev Sex Res. 2003;14:64-82. [PMID: 15287158]
63. Dennerstein L, Lehert P, Burger H, et al. Sexuality. Am J Med. 2005;118 Suppl 12B:59-63. [PMID: 16414328]

was short-lived after treatment discontinuation.

What are the contraindications to use of HT?

Absolute contraindications to HT include pregnancy, unexplained vaginal bleeding, active liver disease, acute CVD or immobilization, history of breast or endometrial cancer, history of CVD, history of VTE related to HT, recent vascular thrombosis, and hypertriglyceridemia (see the Box: Contraindications to Hormone Therapy). Relative contraindications include increased risk for breast cancer or CVD, active gallbladder disease, and migraine with aura.

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

Which systemic HT options are appropriate for treatment of vasomotor symptoms?

Once the decision has been made to initiate HT, clinicians must first determine whether combination HT (estrogen combined with a progestin) or unopposed estrogen therapy (estrogen without a progestin) is warranted. Women with an intact uterus should use combination HT to avoid the increased risk for endometrial cancer associated with unopposed estrogen. Women without a uterus may be safely prescribed estrogen alone (11, 45). Combination HT and unopposed estrogens are equally effective in reducing hot flashes.

Various menopausal HT products are available (**Table 4**). Most studies establishing the efficacy and safety of HT used estradiol or CEEs. HT products are available for different routes of administration (oral, transdermal, vaginal). Transdermal estrogen is preferred for some women because it is as effective as oral estrogen in treating menopause symptoms and preserving bone density and is associated with lower risk for VTE and stroke than oral estrogen (38). However, the choice should depend on the patient's symptoms, risk–benefit profile, and personal preferences. Because oral estrogen increases thyroid-binding globulin, women treated with levothyroxine may require increased dosing. Similarly, some anticonvulsants, such as carbamazepine and phenytoin, may increase hepatic clearance of estrogen, and women treated with these agents may require a higher estrogen dosage to control symptoms (46). Women with low libido who are being treated with HT may want to choose transdermal over oral preparations because of less effect on increasing sex hormone–binding globulin and decreasing free testosterone levels (47).

Women with a uterus require a progestogen component. Progestogens may be dosed in a cyclic regimen (for example, 5 to 10 mg of medroxyprogesterone acetate daily or 200 mg of

64. Avis NE, Zhao X, Johannes CB, et al. Correlates of sexual function among multi-ethnic middle-aged women: results from the Study of Women's Health Across the Nation (SWAN). Menopause. 2005;12:385-98. [PMID: 16037753]
65. Santen RJ, Stuenkel CA, Davis SR, et al. Managing menopausal symptoms and associated clinical issues in breast cancer survivors. J Clin Endocrinol Metab. 2017;102:3647-61. [PMID: 28934376]
66. Rowland N, Bower P, Mellor C, et al. Effectiveness and cost effectiveness of counselling in primary care. Cochrane Database Syst Rev. 2001:CD001025. [PMID: 11686973]
67. Shifren JL, Crandall CJ, Manson JE. Menopausal hormone therapy. JAMA. 2019;321:2458-9. [PMID: 31145419]
68. ACOG practice bulletin no. 141: management of menopausal symptoms. Obstet Gynecol. 2014;123:202-16. [PMID: 24463691]
69. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100:3975-4011. [PMID: 26444994]

Table 4. **Selected Hormonal Preparations for Treatment of Vasomotor Symptoms**

Preparation	*Generic Name*	*Daily Dosage*
Combination hormone therapy (for women with a uterus)		
Oral continuous	CEs and MPA	0.625 mg CE plus 2.5 or 5.0 mg MPA; 0.45 mg CE plus 2.5 mg MPA; or 0.3 or 0.45 mg CE plus 1.5 mg MPA
Oral continuous	Estradiol and norgestimate	1 mg estradiol (days 1–3) 1 mg estradiol and 0.09 mg norgestimate (days 4–6)
Oral sequential	CEs and MPA	0.625 mg CE plus 5.0 mg MPA
Transdermal continuous	17β-estradiol–norethindrone acetate	1.0 mg estradiol plus 0.5 mg norethindrone 0.05 mg estradiol plus 0.14 or 0.25 mg norethindrone (patch applied twice weekly)
Transdermal continuous	17β-estradiol–levonorgestrel	0.045 mg estradiol plus 0.015 mg levonorgestrel (patch applied weekly)
Unopposed estrogens (for women without a uterus)		
Oral	CEs	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg
Oral	17β-estradiol	0.5 mg, 1.0 mg, 2.0 mg
Transdermal	17β-estradiol	0.025 mg, 0.05 mg, 0.075 mg, 0.1 mg (patch applied twice weekly)
Transdermal	Estradiol patch	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg (patch applied weekly)

CE = conjugated estrogen; MPA = medroxyprogesterone.

micronized progesterone 12 days per month), which is associated with periodic withdrawal bleeding, or a continuous regimen (for example, 2.5 mg of medroxyprogesterone acetate or 100 to 200 mg of micronized progesterone daily), which will eventually result in amenorrhea. If a woman early in postmenopause has bothersome irregular bleeding on a continuous regimen, a cyclic regimen should be considered. Levonorgestrel intrauterine devices have also been used off label for endometrial protection. Long-cycle therapy with use of a progestin for 14 days every 3 months has not been well tested for endometrial protection but has been proposed to reduce breast exposure to progestins.

Data are limited on safety and efficacy of lower-dose HT regimens, but early evidence suggests they are less effective in reducing hot flashes (48). However, the differences in efficacy are small. Standard-dose HT (oral CEE at 0.625 mg/d) reduces the frequency of hot flashes (48) by approximately 94% (vs. 44% with placebo), whereas lower doses (0.45 or 0.30 mg/d) reduce symptoms by 78% (44). Data on differences in safety between lower-dose HT and more traditional dosing are limited. Low-dose combination oral contraceptives are an option for healthy perimenopausal women with hot flashes who need contraception and do not smoke. To avoid hot flashes during the placebo interval, low-dose supplemental estrogen can be added or the placebo interval can be eliminated.

Custom-compounded, bioidentical hormones are no more effective than commercially available preparations approved by the U.S. Food and Drug Administration (FDA) and have not been rigorously tested in RCTs. Concerns about product impurities, inconsistencies in doses, and lack of rigorous quality control have been raised. Moreover, FDA-approved bioidentical formulations of estradiol and progesterone are available in a wide range of doses (49).

How long should patients use HT?

In general, HT should be prescribed for the shortest time needed to achieve treatment goals and at the lowest effective dose. For women treated with combined HT, the dose-dependent increased risk for breast cancer becomes clinically significant after around 5 years of use in an average-risk woman (39). As such, it is reasonable to try a nonhormonal treatment (see section on nonhormonal drug therapies) or engage in shared decision making about risks and benefits of continuing treatment after 5 years of combined HT use (50). In women prescribed estrogen-only systemic HT, the risk for breast cancer is lower and it may be reasonable to continue HT for longer. It is advisable to engage in shared decision making about risks and benefits of HT after 10 years of use or at age 60 years

given the increased risk for VTE (with oral estrogen) and stroke. Long-term use of HT for disease prevention is not recommended (50, 51).

No consensus exists about stopping HT abruptly versus gradually tapering it with regard to symptom management and successful discontinuation. If the decision is made to taper, the dosage can be reduced every 2 to 4 weeks until the lowest dosage is attained. Hormone treatments can be replaced with nonhormonal methods if vasomotor symptoms persist.

What is appropriate follow-up for postmenopausal women treated with HT?

For women prescribed HT, the first monitoring point should occur within 4 to 6 weeks of treatment initiation to assess for effectiveness and adverse effects. If symptoms are not reduced satisfactorily, the dosage should be adjusted. HT should be discontinued in patients who do not respond to the full dose.

Patients should have regular follow-up to reassess menopause symptoms and should be asked about unexpected vaginal bleeding and adverse effects. Women with heavy or extended duration of vaginal bleeding or a change in bleeding pattern—including persistent light bleeding or spotting for more than 12 months—should be evaluated with a pelvic examination and screened for endometrial cancer with either transvaginal ultrasonography or endometrial biopsy.

Clinicians should assess risk factors for CVD, osteoporosis, and breast cancer and promote age-appropriate cancer screening. Lipid profiles should be monitored after initiation of HT because oral estrogens may reduce low-density lipoprotein cholesterol levels but increase high-density lipoprotein cholesterol and triglyceride levels.

Which non–HT drug therapies are effective in treating vasomotor symptoms?

Non-HT pharmacologic treatments are appropriate for women who have contraindications to or decline HT. Prescription drugs, including clonidine and some antidepressants and anticonvulsants (for example, gabapentin), can improve vasomotor symptoms for menopausal women who have no specific contraindications (**Table 5**).

SSRIs and SNRIs

High-quality data support use of selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) to treat vasomotor symptoms in perimenopause and in breast cancer survivors (52–54). Among the non-HT treatment options, SSRIs and SNRIs are considered first-line treatments and can reduce symptom burden by 25% to 69% (53). No head-to-head trials have directly compared efficacy of individual SSRIs and SNRIs. Paroxetine, escitalopram, citalopram, venlafaxine, and desvenlafaxine have been studied in large, randomized, double-blind, placebo-controlled trials; efficacy data are less consistent for sertraline and fluoxetine (53).

Gabapentinoids

A 2019 meta-analysis of 7 RCTs comparing gabapentin with placebo for vasomotor symptoms showed a reduction in frequency, duration, and severity of hot flashes. Lower doses (900 to 2400 mg) were associated with fewer adverse effects (50). Clinicians may preferentially recommend gabapentin in women with severe nocturnal vasomotor symptoms given that drowsiness is a side effect of this medication.

A 2020 systematic review and meta-analysis explored efficacy and safety of gabapentin in patients with vasomotor symptoms and found significant reductions in hot flash frequency (mean differences, −1.62 [CI, −1.98 to −1.26] at 4 weeks and −2.77 [CI, −4.29 to −1.24] at 12 weeks) and severity (55). Only 2 included trials assessed pregabalin's effectiveness, and both reported improved symptom burden.

Clonidine

Although this α_2-adrenergic agonist has been shown to be more effective than placebo in treating hot flashes, its efficacy is lower than that of previously discussed non-HT pharmacologic treatments. This, along with its adverse effect profile, limits its utility.

For all non-HT medications, treatment should begin with a low dose and be titrated upward as tolerated, balancing management of symptoms and adverse effects. To avoid withdrawal, treatment should be tapered over a span of weeks. **Table 5** provides additional prescribing considerations.

What is known about the effectiveness of CAM treatments for vasomotor symptoms?

Although many women turn to complementary–alternative medicine (CAM) for menopause symptoms, evidence for its effectiveness is limited (56). Studies tend to be small, of short duration, and conducted in selected samples. Lack of product standardization, questions about safety, and interactions with other medications indicate that CAM should be used with caution. Of nonbotanical CAM treatments, cognitive behavioral therapy and clinical hypnosis are supported by level I evidence as effective and carry little risk (56); in contrast, evidence is lacking for over-the-counter supplements; cooling

Table 5. **Selected Nonhormonal Treatments for Vasomotor Symptoms**

Treatment	*Daily Dosage*	*Contraindications*	*Adverse Effect Profile*
SNRIs/SSRIs			
SNRIs	Venlafaxine, 37.5–75 mg Desvenlafaxine, 100–150 mg	Prior serotonin or neuroleptic syndrome, use of MAO inhibitors, seizure disorder Caution in uncontrolled hypertension	Dry mouth, decreased appetite, nausea, constipation
SSRIs	Paroxetine, 7.5–25 mg Escitalopram, 10–20 mg Citalopram, 10–20 mg	Prior serotonin or neuroleptic syndrome, use of MAO inhibitors, uncontrolled hyponatremia Caution with SSRIs (especially paroxetine and fluoxetine) in women prescribed tamoxifen	Headache, dizziness, nausea, diarrhea, insomnia, drowsiness
Gabapentinoids			
Gabapentin	900–2400 mg in divided doses (titrate up from 100–300 mg every night at bedtime)	Caution in renal impairment	Dizziness, drowsiness, unsteadiness May be useful for nocturnal hot flashes that disrupt sleep
Pregabalin	150–300 mg	Less well studied	–
Antihypertensives			
Clonidine	0.1-mg transdermal patch or 0.1-mg oral tablet	–	Insomnia, dry mouth, headache, hypotension

MAO = monoamine oxidase; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

techniques; exercise; calibration of neural oscillations; acupuncture; chiropractic interventions; or mind–body techniques, such as paced respiration, yoga, and mindfulness-based stress reduction. Although some women may find CAM beneficial for menopause symptoms, delay in conventional pharmacologic treatment for women with high symptom burden is not recommended.

A 2012 Cochrane review (57) examined 16 RCTs of more than 2000 perimenopausal or postmenopausal women treated with black cohosh (median daily dose, 40 mg; mean duration, 23 weeks) and found no significant effect on hot flash frequency.

The North American Menopause Society 2015 position statement on nonhormonal management of menopause-associated vasomotor symptoms (56) cites level II or lower evidence that many over-the-counter therapies are likely to be beneficial (including crinum, Dioscorea, dong quai, evening primrose, flaxseed, ginseng hops, omega-3s, pine bark, pollen extract, puerperia, vitamin supplementation, and maca), with overall guidance of "do not recommend." Soy isoflavones and extracts receive guidance of "recommend with caution" based on level II evidence.

What nondrug treatments should clinicians recommend for women with urogenital symptoms?

GSM occurs in approximately half of postmenopausal women and is associated with vaginal dryness, itching, and irritation; painful urination; and dyspareunia (58, 59). Guidelines recommend non-HT treatments as first-line treatment, to be used before local or systemic HT (60). Vaginal moisturizers used 2 to 3 times per week are as effective as vaginal estrogen in studies with short-term follow-up (61). For women who report pain during sexual activity, vaginal lubricants applied just before may be helpful. Regular sexual activity also may improve symptoms, presumably because of increases in vaginal blood flow (58). Nonetheless, research has documented a marked decline in several measures of sexual functioning after menopause (62, 63), although sexual function in women is complex and varies with factors that include the nature of the relationship and the culture and values of the woman (64).

Which HT options are appropriate for treatment of GSM?

Vaginal estrogens should be reserved for patients who do not respond to first-line non-HT treatments. Low-dose vaginal estrogens may be prescribed as a cream, tablet, or ring (**Appendix Table**, available at Annals.org). As opposed to vaginal tablets and rings, estrogen creams may have some degree of systemic absorption because the application

amount is variable. Low-dose vaginal estrogen preparations do not increase risk for breast or endometrial cancer if dosed as prescribed. However, safety data for low-dose vaginal estrogen in breast cancer survivors are not robust; as such, it should be prescribed in consultation with the patient's treating oncologist and avoided in patients using aromatase inhibitors (65). Patients should be counseled that these products may take several weeks to a month to reach their full effect. A newer option for GSM is vaginal dehydroepiandrosterone (DHEA, or prasterone).

Ospemifene is an oral selective estrogen receptor modulator that is FDA-approved for treatment of moderate to severe vaginal atrophy and dyspareunia in postmenopausal women. It is recommended for symptomatic vulvovaginal atrophy that is not relieved with vaginal moisturizers and lubricants and in women who prefer not to use a vaginal product. Patients should be counseled that this treatment requires daily dosing and carries risk for adverse effects, such as hot flashes and thromboembolism.

What nondrug treatment should clinicians recommend for women with menopause–related psychological distress?

Although psychological distress, including depression, anxiety, and irritability, is relatively common among women of menopausal age, it does not seem to be directly related to menopause (11). Counseling and psychotherapy are appropriate nondrug approaches, with many RCTs documenting their effectiveness (66).

Other nondrug therapies aimed at improving psychological symptoms include exercise, progressive muscle relaxation, paced respiration and relaxation techniques, stress reduction education, and education on menopausal changes. With the exception of exercise, these have not been consistently effective in clinical trials. Similarly, evidence is limited on the effectiveness of herbal therapies, acupuncture, and other alternative therapies on treating psychological distress in menopausal women.

Treatment... HT is the gold standard for treatment of vasomotor symptoms and has a complex risk–benefit profile that is most favorable for younger women initiating treatment early in menopause. In general, HT should be prescribed for the shortest time needed to achieve treatment goals and at the lowest effective dose. For women who are not candidates for or decline HT, nonhormonal treatments (such as antidepressants and gabapentin) are moderately effective in treating vasomotor symptoms. An algorithmic approach is recommended to determine a woman's candidacy for HT. Nondrug interventions (such as vaginal moisturizers and lubricants) are appropriate before initiation of low-dose vaginal estrogen therapy for genitourinary symptoms of menopause.

CLINICAL BOTTOM LINE

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.

In the Clinic
Tool Kit

Menopause

Patient Information

https://medlineplus.gov/menopause.html
https://medlineplus.gov/languages/menopause.html
Information and handouts in English and other languages from the National Institutes of Health's MedlinePlus.

www.nia.nih.gov/health/topics/menopause
Information from the National Institute on Aging.

www.womenshealth.gov/menopause
Information and handouts from the Office on Women's Health in the Office of the Assistant Secretary for Health at the U.S. Department of Health and Human Services.

www.menopause.org/for-women
Information from the North American Menopause Society.

Information for Health Professionals

https://uspreventiveservicestaskforce.org/uspstf/recommendation/menopausal-hormone-therapy-preventive-medication
2017 recommendation statement from the U.S. Preventive Services Task Force on hormone therapy for primary prevention of chronic conditions in postmenopausal women.

https://academic.oup.com/jcem/article/100/11/3975/2836060
2015 clinical practice guideline from the Endocrine Society on treatment of menopause symptoms.

www.menopause.org/docs/default-source/professional/2015-nonhormonal-therapy-position-statement.pdf
2015 position statement from the North American Menopause Society on nonhormonal management of menopause-associated vasomotor symptoms.

www.menopause.org/docs/default-source/default-document-library/2020-gsm-ps.pdf
2020 position statement from the North American Menopause Society on genitourinary syndrome of menopause.

WHAT YOU SHOULD KNOW ABOUT MENOPAUSE

What Is Menopause?

Menopause is when a woman's menstrual periods stop, meaning that her reproductive years have come to an end. The natural process leading up to the final period, called perimenopause, happens over several years. It typically begins when a woman reaches her mid-40s to early 50s but may happen earlier. Smoking, oral birth control, surgery, chemotherapy, and radiation may cause menopause to occur earlier.

What Are Common Symptoms?

Symptoms are caused by changing hormone levels and can vary from woman to woman. The most common symptoms leading up to menopause include:

- Irregular periods
- Hot flashes
- Night sweats
- Vaginal dryness

How Is It Diagnosed?

- Your doctor will consider your age and ask about your symptoms and menstrual changes.
- Menopause is diagnosed after you have gone 12 months without a menstrual period.
- Blood tests are usually not needed to diagnose menopause. However, if you have a history of other menstrual conditions, your doctor may run blood tests to look at your hormone levels. This can help your doctor rule out other conditions and confirm menopause.

How Is It Treated?

- Lifestyle changes like quitting smoking, limiting alcohol use, exercising, and maintaining a healthy weight may make symptoms less severe.
- Hormone therapy is the first treatment for women with moderate to severe hot flashes and night sweats. It is also an effective treatment for vaginal dryness.
- The most common side effects of hormone therapy are breast soreness and vaginal bleeding. Hormone therapy may increase the risk for serious health problems like blood clots, heart attacks, strokes, breast cancer, and gallbladder disease. Risk level depends on age, length of treatment, and other factors. Talk to your doctor about your personal risk, benefits, and preferences before starting hormone therapy.
- You should be monitored for 4 to 6 weeks after starting treatment to make sure it is working for your symptoms and to assess side effects.
- If you are not interested in hormone therapy or there is a medical reason why you should not take it (for example, a history of breast or endometrial cancer, heart disease or stroke, or recent blood clots), nonhormonal prescription drugs have been shown to improve hot flashes and night sweats.
- For isolated symptoms of vaginal dryness or itching, painful urination, or pain during sex, nonhormonal treatments are usually recommended first. These include vaginal moisturizers and lubricants. If these are not effective, low-dose vaginal estrogen is likely to relieve these symptoms with little risk.

Questions for My Doctor

- Should I take hormone therapy?
- What are the benefits and risks?
- What nonhormonal treatments can help ease my symptoms?
- Will lifestyle changes help my symptoms?
- How often should I be seen for follow-up?

For More Information

MedlinePlus
https://medlineplus.gov/menopause.html

National Institute on Aging
www.nia.nih.gov/health/what-menopause

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Patient Information

Appendix Table. **Selected Treatments for Vaginal Dryness**

Treatment	*Dosage*
Nonhormonal over-the-counter treatments	
Vaginal moisturizer	Apply 2–3 times per week
Water-based vaginal lubricant	Apply as needed before intercourse
Hormonal prescription drugs (local vaginal estrogens)	
Estradiol vaginal ring	0.05 and 0.1 mg/d, 1 ring every 3 mo 2 mg per ring (0.0075 mg/d), 1 ring every 3 mo
Conjugated estrogen vaginal cream	0.625 mg estrogen per gram of cream, 1 g (one half of applicator) once or twice weekly
Estradiol vaginal cream	0.1 mg estradiol per gram of cream
Estradiol vaginal tablet	10-mcg tablet placed in vagina twice weekly
Selective estrogen receptor modulator	
Ospemifene oral tablet	60 mg daily
Other	
Vaginal dehydroepiandrosterone	6.5 mg cream placed in vagina once daily