

Menopausal Hormone Therapy

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Hormone therapy is the most effective treatment for managing menopausal vasomotor symptoms. Hot flashes and night sweats affect approximately 70% of midlife women and may persist for a



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decade or longer.¹ Bothersome vasomotor symptoms have a significant adverse effect on sleep, daily functioning, and quality of life. Cognitive and mood symptoms often accompany disruptive hot flashes. Although lifestyle changes and nonhormonal options are available, women with frequent, severe vasomotor symptoms may greatly benefit from hormone therapy.²

Menopausal hormone therapy also has beneficial effects on bone mineral density and the urogenital tract, reducing fracture risk and managing atrophic changes and associated symptoms known as the genitourinary syndrome of menopause. In the absence of vasomotor symptoms, alternatives to systemic hormone therapy are recommended for managing fracture risk and genitourinary symptoms. Very low doses of estrogen placed directly in the vagina effectively manage the sexual and quality of life symptoms associated with the genitourinary syndrome of menopause with minimal systemic absorption and risk.³

Many options are available for providing systemic menopausal hormone therapy for the management of vasomotor symptoms ([Supplement](#)). Women without a uterus should receive estrogen alone. Women with a uterus require progestogen in addition to estrogen to prevent endometrial hyperplasia. Menopausal hormone therapy typically raises the very low estrogen levels of women during menopause to physiologic levels seen during the reproductive years. Menopausal hormone therapy has a high degree of safety compared with contraceptive doses of hormones, which are supraphysiologic to suppress ovulation. A wide range of doses and formulations are available, and the lowest dose that can manage a woman's symptoms should be used. Maximum hot flash reduction is not seen until approximately 3 months of use, so women should be informed not to expect immediate symptom relief.

The most commonly used formulations are the oral pill and transdermal patch, but other options (eg, transdermal gels, vaginal ring) also are available ([Supplement](#)). For women with a uterus, many formulations of estrogen-progestogen therapy combine both hormones for greater convenience and cost savings. Estrogen is provided daily, while the progestogen is provided daily (continuous combined) or cyclically for 12 to 14 days a month. Continuous combined regimens typically result in amenorrhea and are preferred by most women. "Breakthrough bleeding" may be a disruptive adverse effect of continuous combined regimens, especially for women early in the menopause transition. Cyclic regimens result in regular, predictable withdrawal bleeding.

Transdermal estrogen therapy has many advantages compared with oral therapy, especially for women with obesity or cardiovascular disease risk factors. All estrogen patches contain estradiol (the natural hormone made by the ovaries during the reproductive years), are changed only once or twice weekly, and result in very stable blood

levels. Multiple doses are available, which can simplify identifying the lowest effective dose and weaning over time. Most importantly, by avoiding the hepatic first pass effect, transdermal estradiol does not increase levels of coagulation factors or hepatic-binding globulins. No increase in venous thromboembolism risk is seen with transdermal estradiol in observational studies, even in women with obesity or an underlying thrombophilia. Patches that contain both estradiol and a progestogen are available. If higher or lower estradiol doses or natural progesterone are preferred, combining an estradiol patch with oral progesterone is a popular option. Progesterone often causes drowsiness, which can be a benefit when taken at bedtime.

Many women request bioidentical or natural hormones because of a perception of increased safety. Women should be informed that "bioidentical" is a marketing term rather than a medical term, but a preference for natural hormones may be met by providing the same hormones made by the ovaries during the reproductive years, estradiol and progesterone, using products approved by the US Food and Drug Administration. Estradiol is available as a pill, transdermal patch, or topical gel and progesterone is available as a pill ([Supplement](#)). Compounded hormone therapy should not be prescribed because there is limited quality control regarding purity, dose, bioavailability, and batch-to-batch consistency and because no clinical trial data support its safety or efficacy.

Vasomotor symptoms are most prevalent during the year of the final menstrual period, but often begin in menopause transition. Oral contraceptives containing estrogen are an ideal way to manage hot flashes prior to menopause. In addition to managing vasomotor symptoms, they control the irregular and/or heavy bleeding that is common during perimenopause. Healthy women in their late 40s and early 50s are generally good candidates for this option. Older women who smoke or have other cardiovascular disease risk factors may still be candidates for menopausal hormone therapy that results in blood levels within the physiologic range, but should not use oral contraceptives. If a woman elects to use a progestin-releasing intrauterine system for perimenopausal contraception and/or bleeding, physiologically dosed estrogen therapy may be initiated for hot flash management because endometrial protection is provided by the intrauterine system.

The decision to initiate or continue hormone therapy involves a careful assessment of the potential benefits and risks ([Figure](#)).⁴ The majority of symptomatic women will experience a significant quality of life benefit from hormone use during the menopause transition. For healthy women with bothersome hot flashes younger than 60 years or within 10 years of the onset of menopause, the benefits of hormone therapy typically outweigh the risks. Absolute contraindications include breast cancer, endometrial cancer, cardiovascular disease, active liver disease, and undiagnosed vaginal bleeding. Clinical decision support tools can assist with identifying appropriate candidates for hormone therapy and facilitate shared decision making.⁵

The Women's Health Initiative clinical trials identified no significant increased risk of heart disease in women randomized to receive estrogen or estrogen-progestogen therapy who were younger than 60 years or within 10 years of menopause onset.⁶ Although the

Figure. Approach to Initiating Menopausal Hormone Therapy

① Vasomotor symptom assessment Confirm that hot flashes and/or night sweats are adversely affecting sleep, daytime functioning, or quality of life.		
② Risk factor assessment Confirm that there are no absolute contraindications to menopausal hormone therapy: <ul style="list-style-type: none"> • Breast or endometrial cancer • Cardiovascular disease (heart disease, stroke, transient ischemic attack) • Active liver disease • Undiagnosed vaginal bleeding 		
③ Menopausal hormone therapy initiation		
Recommend	Consider with caution	Avoid
Age <60 years and Menopause onset within 10 years and Low risk of breast cancer and cardiovascular disease	Age ≥60 years or Menopause onset >10 years prior or Moderate risk of breast cancer or cardiovascular disease	High risk of breast cancer or cardiovascular disease or Age ≥60 years or menopause onset >10 years prior and Moderate risk of breast cancer or cardiovascular disease

Modified from Manson et al and Kaunitz et al.^{4,5}

relative risk of stroke increased with hormone therapy use, it is a rare event in this age group, with an absolute attributable risk of less than 0.5 additional cases per 1000 women per year. Venous thrombotic events increase with oral estrogen use, but large observational studies do not identify an increased risk with transdermal estradiol use.⁷ Breast cancer risk increases slightly with estrogen-progestogen therapy, but not until 4 to 5 years of use. The attributable risk of breast cancer with estrogen-progestogen therapy in the Women's Health Initiative was low (<1 additional case per 1000 women per year). There was no increased risk of breast cancer with short-term estrogen-progestogen therapy or in women using estrogen alone. Gallbladder disease increases with oral estrogen use, an outcome not seen with transdermal estradiol in observational studies. Over 18 years of cumulative follow-up in the Women's Health Initiative, the use of estrogen-progestogen therapy for a median of 5.6 years

or estrogen therapy for a median of 7.2 years was not associated with increased risk of all-cause, cardiovascular, or cancer mortality.⁸

In the Women's Health Initiative, initiating hormone therapy in women older than 60 years or more than 10 years beyond the onset of menopause was associated with greater risk, and initiating hormones in women older than 70 years was associated with the highest risk. It is not known whether women who initiate hormone therapy at the time of menopause and continue use at older ages will incur the same risks as women initiating hormones later in life. Despite increasing risks with advancing age and duration of use, benefits may still outweigh risks for healthy older women electing long-term hormone therapy use for persistent, bothersome vasomotor symptoms. In addition, the Women's Health Initiative studied only 1 formulation of oral hormones (conjugated estrogens with or without medroxyprogesterone acetate). Observational data suggest lower cardiovascular disease risk with other hormone formulations, including transdermal estradiol, lower-dose estrogens, and different progestogens.

There are few studies to guide the optimal way for women to stop hormone therapy. For women with a uterus using estrogen-progestogen therapy, slowly decreasing the dose with the goal of stopping after 4 to 5 years of use when breast cancer risk slightly increases is a reasonable approach. For women without a uterus using estrogen alone, breast cancer risk did not increase after 7 years, so a longer duration of use may be acceptable.

Women experiencing early surgical or natural menopause (before 45 years) should be encouraged to use hormone therapy until the typical age of natural menopause, approximately 51 years, unless contraindicated. In addition to increased fracture risk from early and prolonged estrogen deficiency, observational studies identify an increased risk of cardiovascular disease and dementia in women experiencing early menopause who do not take hormones through 45 years.⁹

The optimal duration of hormone therapy to manage vasomotor symptoms and related adverse effects on quality of life varies across women. In the absence of contraindications, a woman should determine her preferred hormone therapy dose, formulation, and duration of use, with ongoing reassessment of risks and benefits, through shared decision making with her clinician.

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