Menopause

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**KEYWORDS**
- Menopause
- Hot flashes
- Vulvovaginal atrophy
- Vasomotor symptoms
- Hormone therapy
- Estrogen

**KEY POINTS**
- Hot flashes and menstrual irregularity are hallmarks of the menopausal transition.
- Genitourinary symptoms predominate in the postmenopause phase.
- Although various treatment options are available, systemic estrogen is the most effective treatment of vasomotor symptoms, and vaginal estrogen is the most effective treatment of vulvovaginal atrophy.
- Estrogen therapy is safe for most women; it should be prescribed at the lowest effective dose and for the shortest period of time necessary to control symptoms.

**DEFINITION OF MENOPAUSE**

Menopause is defined retrospectively as the cessation of spontaneous menses for 12 months. Worldwide, most women enter menopause between the ages of 49 and 52 years.\textsuperscript{1} In the United States, the average age of menopause is 51 years. An estimated 6000 US women reach menopause each day, and with increasing life expectancy, will spend approximately 40\% of their lives in the postmenopause phase. Factors associated with earlier menopause include smoking, lower body mass index, nulliparity, and lower educational attainment\textsuperscript{2,3}

Although menopause is often seen as a single point in time, correlating with the cessation of ovarian production of oocytes, the menopausal transition actually occurs over several years and is a dynamic period when women experience...
predictable changes to their menstrual cycle. The Stages of Reproductive Aging Workshop staging system (STRAW+10) is considered the gold standard for characterizing the changes associated with reproductive aging. This staging system consists of three phases (reproductive, menopausal transition, and postmenopause), and includes seven stages within the phases. It describes the typical duration, menstrual cycle characteristics, hormone levels, antral follicle count, and symptoms for each stage.4

PHYSIOLOGY OF MENOPAUSE

Women are born with their full complement of oocytes and during their reproductive years, these oocytes are gradually depleted through ovulation and atresia. The decreased numbers of oocytes secrete less inhibin B, decreasing the ovarian negative feedback on follicle-stimulating hormone (FSH). The resultant increase in FSH level leads to more follicular recruitment and an accelerated follicular loss, with preservation of estradiol levels in early menopausal transition. Eventually, the depletion of follicles results in variability in the ovarian response to FSH, widely fluctuating estrogen levels, and loss of the normal reproductive cycle. When all the ovarian follicles are depleted, the ovary is unable to respond to even high levels of FSH and estrogen levels decline. The postmenopausal period is characterized hormonally by an elevated FSH (>30 mIU/mL) and low estradiol levels (Box 1).5

VASOMOTOR SYMPTOMS

Hot flashes and night sweats are common, affecting 65% of women.6 Women experience hot flashes as spontaneous sensations of warmth, usually felt on the chest, neck, and face, often associated with perspiration and then a chill, and sometimes with palpitations and anxiety. They usually last less than 5 minutes but sometimes last up to 30 minutes. They are sometimes triggered by warm environments, stress, or hot food and beverages.6 Night sweats are hot flashes that occur at night and often interfere with sleep. The precise cause of vasomotor symptoms is not known but is thought to be related to low estrogen levels (and possibly changes in FSH and inhibin B), which affect endorphin concentrations in the hypothalamus.

| Box 1 |
| Signs and symptoms of menopause |
| Menopausal Transition |
| • Menstrual irregularity |
| • Hot flashes |
| • Night sweats |
| • Sleep disruption |
| Postmenopause |
| • Vaginal dryness |
| • Vulvovaginal atrophy |
| • Lower urinary tract symptoms |
| • Dyspareunia |
The normal thermoregulatory zone (the core temperature range within which a person can maintain their temperature without resorting to symptomatic vasodilation or sweating) in the hypothalamus seems to be narrowed in menopause, so that vasodilation and sweating are triggered at a lower temperature. Vasomotor symptoms typically persist for 4 years, but this is variable. In fact, 29% of 60-year-old women have persistent hot flashes. A meta-analysis of two longitudinal and several cross-sectional studies concluded that vasomotor symptoms generally begin 2 years before menopause, peak 1 year after menopause, and then diminish over the next 10 years.

**EVALUATION OF VASOMOTOR SYMPTOMS**

Vasomotor symptoms in a woman in her late 40s to mid-50s do not require laboratory tests for confirmation unless there is reason to suspect another cause. Careful history taking can generally rule out other causes (Box 2).

Panic attacks and high stress can cause symptoms similar to hot flashes. Interestingly, in a large longitudinal study, anxiety symptoms at baseline were strongly associated with later vasomotor symptoms.

Measuring an FSH level is generally not helpful to confirm the diagnosis of perimenopausal vasomotor symptoms. Although levels rise and fall predictably with the menstrual cycle in premenopausal women, they fluctuate greatly during the perimenopause. FSH is persistently elevated (>30 mIU/mL) after menopause, but by then menstruation has stopped and the diagnosis is obvious. FSH levels can be helpful when evaluating premature menopause (amenorrhea before age 40), or occasionally to look for evidence of menopause in women who are amenorrheic for other reasons (eg, hysterectomy without oophorectomy, or levonorgestrel intrauterine device use).

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**Box 2**

**Other causes of hot flashes**

- Alcohol consumption
- Carcinoid syndrome
- Dumping syndrome
- Hyperthyroidism
- Narcotic withdrawal
- Pheochromocytoma
- Panic attacks/high stress
- Medications, including
  - Tamoxifen
  - Raloxifene
  - Danazol
  - Leuprolide
  - Goserelin

TREATMENT OF VASOMOTOR SYMPTOMS

Studies have consistently shown a very strong placebo effect, so placebo-controlled randomized trials are required to assess efficacy of any treatment.

Lifestyle Modifications

Lowering the room temperature, dressing in layers, keeping a fan nearby, and avoiding hot drinks, caffeine, and hot or spicy foods can be helpful to manage hot flash symptoms. Smoking is associated with frequency of vasomotor symptoms, providing another reason to encourage smoking cessation in perimenopausal women.

Hormonal Treatment

Estrogen therapy (ET) is the most effective intervention for menopausal hot flashes and also improves vaginal and urogenital atrophic symptoms. Oral estrogen decreases hot flash frequency by 75% relative to placebo.

Estrogen for vasomotor symptoms can be prescribed orally, transdermally, or in a vaginal ring (Table 1). A progestin must be added to prevent endometrial hyperplasia and cancer unless the patient has had a hysterectomy. The progesterone is given separately in a tablet, via a levonorgestrel-releasing intrauterine device, or combined with the estrogen in a tablet or patch. It can be given either continuously (daily, as in the conjugated equine estrogen [CEE] + medroxyprogesterone acetate [MPE] tablet or the estradiol + norethindrone patch) or sequentially (as in the CEE + MPE dose pack, where the progesterone is included in the tablets for days 14–28). Low-dose oral contraceptive pills containing only 20 μg ethinyl estradiol plus a progestrone are not only effective for hot flashes, but also provide contraception and cycle control for perimenopausal women. Because 5 μg of ethinyl estradiol is equivalent to CEE 0.625 mg, they are four times stronger than standard hormone-replacement therapy (HRT) and should be avoided in women who smoke, are obese, have migraines, or have hypertension. Other than oral contraceptive pills, the only treatment listed in Table 1 that is effective for contraception is the levonorgestrel intrauterine system.

Oral HRT undergoes first pass hepatic metabolism, which promotes prothrombotic hemostatic changes. In case control studies, transdermal estrogen is associated with a significantly lower risk of deep venous thrombosis compared with the equivalent dose of oral estrogen.

Ultra-low-dose estrogen formulations are also available and are effective for treating hot flashes in some women. They are available as transdermal gels, emulsions, patch, or spray.

Duration of Therapy, Perioperative Management, and Side Effects

Short-term HRT (up to 5 years) is reasonable for most patients with disabling hot flashes. Vasomotor symptoms decrease after menopause for many women, so it is reasonable to try discontinuing hormone therapy every 6 to 12 months and restarting if necessary. Tapering versus abruptly stopping does not prevent hot flash recurrence. However, some women may prefer tapering.

Whether HRT should be held before surgery to avoid perioperative venous thromboembolism (VTE) is controversial because of lack of compelling evidence that HRT increases the risk of VTE greater than that associated with surgery. One expert recommends holding HRT only in patients with other strong risk factors, such as prior VTE or anticipated prolonged immobility, and others recommend stopping HRT for 4 to 6 weeks before surgery for women undergoing procedures associated with moderate or high risk for VTE.
Side effects of ET include breast tenderness, vaginal bleeding, and nausea and some women experience mood symptoms and bloating with progestin therapy. Contraindications are listed in Box 3.

**Interpreting the Risks Identified by the Women's Health Initiative**

Estrogen was used for many years for treatment of vasomotor symptoms, and also taken by millions of women in hopes of preventing chronic illness, including osteoporosis and cardiovascular disease. In 2002 the initial results from the Women’s Health Initiative (WHI) suggested overall harms exceeded benefits of estrogen for prevention of disease. Both ET and estrogen and progesterone therapy (EPT) decreased the risk of osteoporosis, but were associated with an increased risk of stroke, venous
thrombosis, gallbladder disease, and incontinence. EPT was also associated with an increase in invasive breast cancer and coronary artery disease. After the release of these data, most women stopped HRT for disease prevention, and were wary of taking it even for severe vasomotor symptoms.

When considering HRT for perimenopausal women, who are almost always in their late 40s to early 50s, it is important to remember that their personal risk of complications is much lower than the absolute risks documented in the WHI. The WHI enrolled primarily older women (mean age, 63). According to the Endocrine Society, for 1000 women ages 50 to 59 taking ET for 5 years, two to three cases of stroke and/or VTE would be expected, and about 14 cases of gallbladder disease. Adding progesterone also increases the risk of breast cancer, but this risk may be much smaller than a woman may anticipate (about 7 cases per 1000)\textsuperscript{17}. Using HRT for only a year or two may have lower risks. Providing these data is important so patients can make informed choices about their options. Because most would experience an improvement in their vasomotor symptoms, the quality of life benefits may outweigh the risks for many women.\textsuperscript{18} Further analysis of WHI data also revealed an important age effect: women starting HRT within 10 years of the onset of menopause had a reduced risk of coronary artery disease, compared with those who started later.\textsuperscript{6,18} The US Preventive Services Task Force and other organizations recommend against the use of HRT for the prevention of chronic conditions in average-risk postmenopausal women (Grade D recommendation).\textsuperscript{19}

**Nonhormonal Prescription Treatment of Hot Flashes**

Although less effective than estrogen, the selective serotonin reuptake inhibitors paroxetine (10–20 mg per day) and fluoxetine (20 mg per day) and the serotonin-norepinephrine reuptake inhibitor venlafaxine (75 or 150 mg per day) have been shown to decrease hot flash frequency. Potential side effects are dry mouth and nausea. Paroxetine decreases the most effective metabolite of tamoxifen and should not be

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**Box 3  Contraindications to hormonal therapy**

- History of breast or endometrial cancer
- Atypical ductal hyperplasia of the breast
- History of venous thromboembolic disease
- History of coronary artery disease or stroke
- Unexplained vaginal bleeding
- Uncontrolled hypertension
- Migraine headaches (may increase risk of stroke)
- Active liver disease (decreases estrogen metabolism)
- Immobilization
- Active gallbladder disease
- Porphyria (may be exacerbated)
- Hypertriglyceridemia (may increase venous thromboembolic disease)

prescribed to women taking it for breast cancer treatment.\textsuperscript{11} Gabapentin, 900 mg per day, also decreases hot flash frequency and severity\textsuperscript{6} and its tendency to sedate may make it useful at bedtime. Clonidine has some efficacy but has difficult-to-tolerate side effects (dry mouth, insomnia, drowsiness).\textsuperscript{20} Fig. 1 summarizes the effectiveness of estrogen, nonestrogen prescription medications, and two herbal supplements for hot flash treatment.\textsuperscript{5}

\textbf{Nonprescription Treatments}

Alternative therapies are tried by 50\% to 75\% of postmenopausal women. They are not regulated by the Food and Drug Administration and are not well studied. Most evidence suggests that alternative therapies, such as soy, black cohosh, and acupuncture, are no more effective than placebo for hot flashes.\textsuperscript{21,22} Phytoestrogens (eg, isoflavones in red clover and soy) are plant-derived nonsteroidal compounds that bind to estrogen receptors. Randomized trials do not demonstrate the efficacy of red clover isoflavone extracts and reveal mixed results for soy isoflavone extracts.\textsuperscript{19} Women with a personal or strong family history of hormone-dependent cancers (breast, uterine, or ovarian), thromboembolic events, or cardiovascular events should not use soy-based therapies.\textsuperscript{23}

\textbf{GENITOURINARY SYNDROME OF MENOPAUSE}

Genitourinary syndrome of menopause encompasses vulvovaginal atrophy (VVA) and lower urinary tract symptoms associated with menopause and aging.\textsuperscript{24}

\textbf{Vulvovaginal Atrophy}

In premenopausal women, the lining of the vagina is thickened, rugated, well-vascularized, and lubricated. After menopause, when estrogen levels decline, the vaginal lining thins and becomes dry and pale. The vagina becomes less elastic and

\begin{tabular}{|c|c|c|}
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& Number of & Number of hot flashes per day & Number of hot flashes per day \\
& trials & (mean difference 95\% CI) & (mean difference 95\% CI) \\
\hline
Oestrogen & & & \\
Transdermal oestradiol & 6 & $-3.2 (-5.1$ to $-1.3)$ & \\
Oral oestradiol & 9 & $-2.6 (-3.3$ to $-1.9)$ & \\
Oestradiol + progesterone & 3 & $-2.8 (-3.8$ to $-1.8)$ & \\
Oestradiol alone & 6 & $-2.1 (-2.9$ to $-1.2)$ & \\
Gabapentin & 2 & $-2.05 (-2.80$ to $-1.30)$ & \\
SSRI/SNRI antidepressants & 3 & $-1.13 (-1.70$ to $-0.57)$ & \\
Paroxetine & 2 & $-1.66 (-2.43$ to $-0.89)$ & \\
Fluoxetine & 2 & $-1.37 (-3.03$ to $0.29)$ & \\
Venlafaxine & 2 & $-0.49 (-2.40$ to $1.41)$ & \\
Citalopram & 1 & $-0.20 (-1.45$ to $1.05)$ & \\
Clonidine & 4 & $-0.95 (-1.44$ to $-0.47)$ & \\
Soy extract isoflavones & 5 & $-1.15 (-2.33$ to $0.03)$ & \\
Red-clover isoflavones & 6 & $-0.44 (-1.47$ to $0.58)$ & \\
\hline
\end{tabular}

\textbf{Fig. 1.} Nonhormonal treatments for hot flashes. CI, confidence interval; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor. (\textit{From} Nelson HD. Menopause. Lancet 2008;371(9614):764.)
can narrow and shorten. Atrophic vaginitis, or inflammation of the vagina, can occur, resulting in brownish or yellow discharge. A shift in the vaginal bacteria to less acid-producing bacilli results in a higher pH, typically greater than 5.0. On wet mount microscopy, white blood cells outnumber epithelial cells, parabasal cells (immature epithelial cells with large nuclei) are present, and there are few or no lactobacilli. These changes to the vagina and vulva can result in a variety of symptoms that can negatively impact a woman’s quality of life and sexual function (Box 4).

An estimated 45% of postmenopausal women experience symptoms of VVA. Vaginal dryness is the most commonly reported symptom, followed by dyspareunia and irritation. Despite the high prevalence of symptoms related to VVA in postmenopausal women, 44% of women do not seek care for their symptoms and few health care providers initiate discussion of vaginal symptoms. When evaluating post-menopausal women who report symptoms of vaginal or vulvar itching, irritation, and vaginal discharge, clinicians should consider other conditions that can cause those symptoms, in addition to VVA (Box 5).

### Treatment of Vulvovaginal Atrophy

**Nonprescription therapies**

Lubricants are used primarily before intercourse to reduce friction and irritation, whereas moisturizers can be used more regularly for vaginal dryness. Several formulations exist that are water-based, silicone-based, or oil-based (Box 6). Because oil-based lubricants can degrade condoms, women should be counseled about the reduced protection of condoms against sexually transmitted infections and pregnancy.

**Prescription therapies**

**Vaginal estrogen** Local application of estrogen in the vagina is more effective than systemic hormones (oral or transdermal) in alleviating VVA symptoms; up to 80% of women experience an improvement in symptoms, which typically occurs within 1 to 3 months of starting therapy. Various effective preparations are available in the United States (Table 2).

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**Box 4**

<table>
<thead>
<tr>
<th>Genitourinary symptoms</th>
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<tr>
<td><strong>Vaginal Symptoms</strong></td>
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<tr>
<td>• Dryness</td>
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<tr>
<td>• Itching</td>
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<tr>
<td>• Irritation</td>
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<tr>
<td>• Discharge</td>
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<tr>
<td>• Dyspareunia</td>
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<tr>
<td><strong>Lower Urinary Tract Symptoms</strong></td>
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<tr>
<td>• Frequency</td>
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<tr>
<td>• Burning</td>
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<tr>
<td>• Dysuria</td>
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<tr>
<td>• Recurrent urinary tract infections</td>
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<tr>
<td>• Nocturia</td>
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Clinicians should prescribe the lowest dose of vaginal estrogen that alleviates symptoms. Low-dose vaginal estrogen (≤50 μg of estradiol or ≤0.3 mg of conjugated estrogens) has minimal systemic absorption and women using it for less than a year generally do not need endometrial surveillance or progesterone. Monitoring for endometrial hyperplasia or use of progesterone for endometrial protection may be appropriate for women at increased risk of endometrial cancer, or when using vaginal estrogen higher than recommended dosing. Any vaginal bleeding requires evaluation for endometrial hyperplasia or cancer.

Potential side effects of topical estrogen include breast pain, vaginal bleeding, and perineal pain, which seem to be dose related. Low-dose vaginal estrogen has not been associated with deep venous thrombosis. Because there is some systemic absorption of vaginal estrogen, women with a history of breast cancer should discuss its use with their oncologist. Women with undiagnosed vaginal bleeding or with endometrial cancer should not use vaginal ET.

Ospemifene (Osphena) Ospemifene is a selective estrogen receptor modulator that was approved by the Food and Drug Administration in 2013 for treatment of moderate to severe dyspareunia from VVA. It acts as an estrogen agonist on the vaginal epithelium but has little or no estrogen effect on breast tissue and endometrium. Ospemifene, 60 mg daily, significantly reduced dyspareunia and vaginal dryness in women with VVA. Hot flushes occurred in 7.2% of those taking ospemifene compared with 2% of those in the placebo group. There was no increase in risk of VTE, although the studies may not have been powered to detect this.

Urinary Symptoms

Postmenopausal women can develop lower urinary tract symptoms of urgency, frequency, dysuria, nocturia, and urinary incontinence. It is unclear whether these lower urinary tract symptoms are caused by aging or by low estrogen.

Up to 10% of postmenopausal women report having a urinary tract infection within the past 12 months. It has been hypothesized that low estrogen alters the vaginal flora and pH, allowing enteric coliforms to colonize more easily and increasing...
susceptibility to urinary tract infections. Although systemic estrogen has not been shown to reduce the incidence of recurrent urinary tract infections, several studies have shown a reduction with vaginal estrogen.\textsuperscript{37}

**OTHER COMMON CONDITIONS DURING MENOPAUSE**

**Depression**

Longitudinal studies have found that women are two to four times more likely to experience depressive symptoms during the menopausal transition compared with premenopause. Depressive symptoms have been associated with hormonal fluctuations,

<table>
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<tr>
<th>Box 6</th>
<th>Examples of nonhormonal therapeutic options for dyspareunia secondary to VVA</th>
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<tbody>
<tr>
<td><strong>Lubricants</strong></td>
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<tr>
<td><strong>Water-based</strong></td>
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<td>Astroglide liquid</td>
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<td>Astroglide gel liquid</td>
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<td>Astroglide</td>
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<td>Just Like Me</td>
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<td>K-Y Jelly</td>
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<td>Slippery Stuff</td>
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<td>Liquid Silk</td>
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<td><strong>Silicone-based</strong></td>
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<td>Astroglide X</td>
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<td>ID Millennium</td>
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<td>K-Y Intrigue</td>
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<td>Pink</td>
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<td>Pjur Eros</td>
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<td><strong>Oil-based</strong></td>
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<td>Elégance Women’s Lubricants</td>
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<td>Olive oil</td>
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<td><strong>Moisturizers</strong></td>
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<td>Replens</td>
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<tr>
<td>Me Again</td>
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<td>Vagisil</td>
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<td>Feminease</td>
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<td>K-Y SILK-E</td>
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<td>Luvena</td>
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<td>Silken Secret</td>
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*Courtesy of The North American Menopause Society, Mayfield Heights, OH; with permission.*
and with the presence of vasomotor symptoms.\textsuperscript{38,39} It remains unclear whether ET should be recommended to alleviate depressive symptoms. Small randomized controlled trials have found transdermal estrogen to be more effective than placebo in improving symptoms of depression during the menopausal transition.\textsuperscript{40,41}

**Cognitive Function**

Although up to 40\% of women report episodes of forgetfulness during the perimenopausal period, any cognitive decline noted in observational studies has been subtle and transient.\textsuperscript{42,43} Similarly, it has been difficult to establish whether older women later in menopause have higher rates of dementia compared with men because of differences in survival.\textsuperscript{44} The effect of hormone therapy on cognitive function may be variable, depending on when it is initiated during menopause. Analyses of pooled data from the ET and the EPT arms of the WHI show that hormone therapy initiated in women 65 years and older increased the risk of developing probable dementia, and resulted in more cognitive decline and greater brain atrophy. The decrease in cognitive function was small and of unclear clinical significance.\textsuperscript{45–51} In contrast, the WHI Memory Study of Younger Women evaluated the effect of hormone therapy on cognitive function in women aged 50 to 55 years and did not find a sustained benefit or decline.\textsuperscript{52}

**Cardiovascular Disease, Osteoporosis, and Malignancy**

These are important issues and more prevalent among postmenopausal women. These issues are addressed elsewhere in this issue.

**SUMMARY**

Hot flashes and menstrual irregularity are hallmarks of the menopausal transition, although vasomotor symptoms can persist for years in some women. Genitourinary symptoms predominate in the postmenopause phase and can impact sexual function and quality of life. Although various treatment options are available, systemic estrogen is the most effective treatment of vasomotor symptoms, and vaginal estrogen is the most effective treatment of VVA, using the lowest dose of estrogen to alleviate symptoms. Other common conditions in menopause include cardiovascular disease, depression, and cognitive dysfunction. The understanding of the relationship between menopause, HRT, and these conditions continues to evolve.
REFERENCES


