Vasomotor Symptoms: An Evidence-Based Approach to Medical Management

Case Study and Commentary, Jeffrey Campbell Andrews, MD, FRCSC

Abstract

- **Objective:** To present an evidence-based approach to medical management of vasomotor symptoms.
- **Methods:** Literature review.
- **Results:** Vasomotor symptoms are the most common problem occurring during the menopause transition. The degree of severity of vasomotor symptoms varies from mild to severe. Treatment may be indicated if menopausal symptoms interfere with a woman’s daily functioning and quality of life. The prevailing symptoms should be clarified, and the different options should be explained. Some women simply wait for the menopause to pass. Many women choose self-care and lifestyle changes. Many women are interested in herbal options or other complementary or alternative remedies. There is a range of hormone treatments, and there are nonhormonal prescription medications as well.
- **Conclusion:** The most effective intervention for relief of vasomotor symptoms is estrogen. Tibolone may have similar effectiveness. Phytoestrogens may provide a modest benefit.

**CASE STUDY**

**Initial Presentation**

Identical twin sisters, AS and BT, age 52 years old, present with the complaint of a 9-month history of moderately severe hot flashes and night sweats that are interfering with their quality of life and sleep. Although they had initially decided to have natural menopause, they are unhappy with their symptoms and are now seeking advice regarding therapy.

- What is the nature and prevalence of menopausal symptoms?

Menopause is defined as the permanent cessation of menses resulting from reduced ovarian hormone secretion. Menopause can occur as a natural physiologic event or be induced by surgery, chemotherapy, or radiation. A dogmatic diagnostic criterion for natural menopause is 12 months of amenorrhea that is not associated with a pathologic cause. From the woman’s perspective, menopause is a transition that begins before the last menstrual period and continues over a period of approximately 4 to 6 years, beginning on average at age 47.5 years, with the final menstrual period on average at 50 years of age, and menopause (defined as 12 months of amenorrhea) at 51 years of age [1–4].

Vasomotor symptoms are the most common problem occurring during the menopause transition [5–8]. Commonly known as “hot flashes” or “hot flushes,” the symptoms can be described as spontaneous “recurrent, transient periods of flushing, sweating, and a sensation of heat, often accompanied by palpitations, feelings of anxiety, and sometimes followed by chills.” These sudden sensations of heat, sweating, and flushing most often occur in the face, head, neck, and chest. They generally last 1 to 5 minutes, and only 6% of women experience hot flashes that last longer than 6 minutes. Night sweats are hot flashes or flushes occurring at night, often while sleeping.

The degree of severity of vasomotor symptoms varies from mild to severe. Women who experience the sensation of heat without sweating are classified as having mild symptoms. Women who experience the sensation of heat with sweating, causing cessation of activity, or report that their daily activities, work, or sleep are seriously disturbed, are classified as having severe symptoms. The moderate category describes women who experience the sensation of heat with sweating who are able to continue their activities. The severity of vasomotor symptoms varies between women and can vary in the same woman throughout the day and over a period of time. Women who experience mild symptoms do not usually seek medical attention.

Clinical studies of interventions for vasomotor symptoms usually include women with moderate to severe symptoms. FDA study inclusion criteria are as follows: at least 7 severe or moderate hot flush attacks per day or 50 to 60 moderate...
to severe hot flashes per week at baseline [9]. Measures of vasomotor symptoms typically consider frequency, severity, presence versus absence, or a combination measure of frequency and severity. Hot flushes and night sweats often result in disturbed sleep, fatigue, and irritability. For this reason, consideration of interventions for relief of vasomotor symptoms will often include secondary effects on sleep and psychological well being and quality of life.

**Prevalence**

In the United States, approximately 4000 women enter menopause daily. Between one-half to two-thirds of women will have hot flashes and sweats during the menopause [1,5–8]. A survey focusing on menopausal symptoms was completed by a nationally representative sample of 4402 U.S. women aged 40 to 65 years [10]. The prevalence of vasomotor symptoms was 79% in perimenopausal women and 65% in postmenopausal women. Women with daily vasomotor symptoms had an average of 2.5 very mild/mild, 2.6 moderate, 2.5 severe, and 1.4 very severe daytime hot flushes in a typical day. Women with night sweats every night had an average of 2.4 moderate, 3.2 severe, and 2.7 very severe night sweats in a typical night. Overall, 9% of perimenopausal and 7% of postmenopausal women reported at least 7 moderate to very severe vasomotor symptoms in a typical day [10,11]. There appear to be cultural differences in the reporting or experiencing of hot flashes. For example, only 10% to 25% of Indonesian and Chinese women report experiencing them. Hot flashes peak at around age 53 and usually end before age 65.

**Case Continued: History**

Both AS and BT estimate that they have 6 to 13 hot flashes per day and 1 to 4 night sweats. They have identical chief complaints and history of present illness and past medical history is very similar except for 1 important difference: AS is G2P2, both by cesarean section, and had a bilateral tubal ligation with the second cesarean. BT is G2P2, both by cesarean, but at the time of her second cesarean had placenta percreta with hemorrhage and had a cesarean hysterectomy, with preservation of both ovaries. Both patients are married. They have no heart disease and no coronary risk factors. They have no cancer history. Their maternal aunt died of breast cancer at age 67. Their last 3 annual Pap tests have been normal. They just had negative mammograms. They take no medications or supplements. They have no heart disease and no coronary risk factors. They have no cancer history. Their maternal aunt died of breast cancer at age 67. Their last 3 annual Pap tests have been normal. They just had negative mammograms. They take no medications or supplements. They both had a recent bone mineral density test. Hip T-score for AS was –0.9, which is considered normal. For BT, it was –1.1, interpreted as osteopenia. Spine T-scores were both –0.9. They have concerns about hormone replacement therapy (HRT) and are interested in learning about alternatives to HRT for vasomotor symptoms as well as open to learning about risks and benefits of HRT.

**Physical and Laboratory Examination**

Pelvic examination of AS was normal, with intact pelvic anatomy. Pelvic examination of BT was normal, with surgical absence of the uterus and cervix. Vaginal mucosa was slightly pale in both women, and they both found insertion of the speculum to be uncomfortable, consistent with early vaginal atrophy. The remainder of the physical exam was unremarkable.

- What are key features of clinical assessment?

**Past and Current Medical Health**

In addition to asking about the vasomotor symptoms, assessment includes a complete medical history. Of particular interest is whether or not the patient has a uterus, existing breast cancer, mammographic screening results, bone mineral density assessment, BMI, concurrent diseases, and current medications. Also of interest are current over-the-counter product use and use of complementary and alternative therapies. Exploration of mental health concerns is important, with particular emphasis on depression and anxiety disorders. Additionally, the patient’s knowledge, values, and preferences with regard to menopause and vasomotor symptoms should be sought.

**Risk Factor Assessment**

As part of the history of past and current medical health, each individual woman should have a risk factor assessment to guide future recommendations (Table 1).

**Physical Examination and Laboratory Testing**

There are no tests that are reliable in making the diagnosis of impending menopause. Serum follicle-stimulating hormone (FSH) and estrogen levels are not reliable because of wide variability from day to day during the menopausal transition. After several months of amenorrhea, the FSH level may be definitive. For women without a uterus, FSH may be helpful for supporting the diagnosis of menopause in cases where the diagnosis is not clear. High FSH levels indicate that menopausal changes are occurring in the ovary. As the ovary becomes less responsive to stimulation by FSH from the pituitary gland (and produces less estrogen), the pituitary gland increases production of FSH to try to stimulate the ovary to produce more estrogen. Other tests include the maturation index; an evaluation of the vaginal epithelium using the Papanicolaou technique and assessing the percent-ages of parabasal, intermediate, and superficial cells.
• How is the diagnosis of vasomotor symptoms made?

Frequently, the diagnosis of vasomotor symptoms is made through a conversation between the woman and her provider. Within clinical studies, there are common validated instruments which are used to assess vasomotor symptoms and categorize patient experiences as mild, moderate, or severe (Table 2).

• What are the goals of therapy for patients with vasomotor symptoms?

The goals of therapy for vasomotor symptoms are multifold. On the surface, interventions are targeted to reduce the frequency and intensity of hot flashes and night sweats. Many women are seeking elimination of all hot flashes and night sweats and a return to “normal.” Others may be satisfied with a reduction in the number and frequency of hot flashes. There is not an established standard for a clinically significant reduction; for instance, we do not know how many women would consider a reduction by 1 hot flash per day to be effective. There may be a mismatch between research reports of statistically significant reductions in hot flash scores and a woman’s report of whether the intervention was of value, in consideration of effectiveness balanced against side effects, cost, and inconvenience. Since the hot flashes and night sweats interfere with normal living activities, enjoyment, and sleep, other goals of therapy include improved relationship quality, work performance, sleep, sexual function, global measure of wellness, and quality of life. Table 3 summarizes the benefits and harms of selected therapeutic interventions.

• What are the 5 main management options?

There are basically 5 options for women who are experiencing vasomotor symptoms: wait and allow the menopause to pass; self-care and lifestyle changes; herbal options or other complementary or alternative remedies; hormone treatments; or nonhormonal prescription medications.

Published randomized controlled trials of interventions for managing vasomotor symptoms have included studies of estrogens, progestogens, androgens (testosterone and DHEA [dehydroepiandrosterone]), tibolone, antidepressants (selective serotonin reuptake inhibitors, moclobemide, veralipride), and other drugs (clonidine, methyldopa, gabapentin, Bellerigal), phytoestrogens (dietary and extract forms of soy isoflavones, other forms of phytoestrogen, combinations), and other interventions (acupuncture, Chinese herbs, red clover, black cohosh, combinations, other types of supplements, manual therapies, energy therapies), and behavioral interventions (exercise and other types of interventions). Placebo effects in trials are large: 37% of placebo patients had at least a 50% reduction in hot flash scores [12]. Estrogen, with or without progesterone, is the most common therapy for vasomotor symptoms.

Women find their own way through the menopause. There is no one right way to manage menopause [2,13,14]. Some women pay little attention to vasomotor symptoms. Others see it as an important phase in their life, with a generally positive perspective.

Treatment of vasomotor symptoms is elective. The patient should have the opportunity to make choices about therapeutic interventions [14–18]. The role of the clinician is to provide information and respond to questions and provide decision-support. The algorithm provided in
Figure can be useful for collaborative decision-making. Key input from the clinician is the risk factor assessment and the detailing of benefits and risks.

**Option 1: EXPERIENCE NATURAL MENOPAUSE WITHOUT SEEKING THERAPEUTIC INTERVENTIONS**

A valid option for women is to simply wait until the menopausal symptoms pass. There are support groups for women who choose this option.

**Option 2: SELF-CARE/LIFESTYLE OPTIONS**

Women may be encouraged to lose weight (where appropriate) and to increase exercise [19]. Other self-care measures include avoidance of spicy foods, alcohol, and caffeine, but there is no evidence that measures confer benefit. Other self-care measures include avoidance of warm environments and stress, and advice to wear layered clothing and to use cooling methods such as handheld fans, drinking cold water, and mist bottles [20]. Other lifestyle interventions include paced abdominal breathing, relaxation techniques, meditation, yoga, and tai chi. However, there is no good research evidence for efficacy of any of these approaches [8,21].

There is some evidence that women who are more active and exercise regularly tend to suffer less from the symptoms of the menopause [8]. Not all types of activity lead to an improvement in symptoms. High-impact infrequent exercise can sometimes make symptoms worse; the best activity is likely to be aerobic, sustained, regular exercise such as swimming or running [8,22–24].

Relaxation training has been shown to moderately decrease hot flashes. Paced respiration, a technique using slow, controlled, diaphragmatic breathing, may decrease the frequency of hot flashes by about 50% [25].

**Option 3: OVER-THE-COUNTER PRODUCTS**

Over-the-counter or nonprescription interventions may also be considered alternative therapies.

Alternative therapies for the menopause are very popular [26,27]. The majority of women rate them as helpful, because their symptoms reduced while they were using the product [26,27]. From a scientific point of view, that is not proof that they “work.” Menopausal symptoms would have improved for many women even without any treatment at all. Although a review of randomized controlled trials found that most herbal therapies did not show consistent benefit, their use continues to rise because women feel that these “natural” remedies may be safer [28,29].

**Phytoestrogens**

Populations who consume a diet naturally high in isoflavones, such as the Japanese, appear to have lower rates of menopausal vasomotor symptoms, cardiovascular disease, osteoporosis, and breast, colon, endometrial and ovarian cancers [30]. However, the evidence from randomized placebo-controlled trials in North American and European populations is conflicting for both soy and phytoestrogen derivatives [31,32].

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**Table 2. Common Scoring Systems for Postmenopausal Vasomotor Symptoms**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Calculation</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flash Score</td>
<td>Severity score = [([#mild flashes/day]+(2x #mod flashes/day)+(3x #severe flashes/day)] / total # flashes/day</td>
<td>Higher scores indicate worse symptoms</td>
</tr>
<tr>
<td>Greene Climacteric Score</td>
<td>Scoring on different scales for subcomponents: psychological (possible score 0–33), somatic (0–21), vasomotor symptoms (0–6), and sexual (0–3)</td>
<td>Higher scores indicate worse symptoms. Total score can range from 0–63. For the vasomotor subscore, 0–2 indicates no or mild hot flashes and 3–6 indicates moderate-to-severe hot flashes</td>
</tr>
<tr>
<td>Modified Kupperman Index</td>
<td>Assessment of 11 components: hot flashes, sweating, insomnia, nervousness, depression, vertigo, tiredness, joint ache, headache, palpitations, and vaginal dryness. All are scored from 0–3 based on symptoms: 0 = none, 1 = weak, 2 = moderate, 3 = strong. Hot flash score is multiplied by 4; sweating, insomnia, and nervousness scores are multiplied by 2; then all subcomponents are added together for the total score.</td>
<td>Higher scores indicate worse symptoms. Total score can range from 0–51.</td>
</tr>
</tbody>
</table>
### Table 3. Efficacy and Harms of Interventions for Relief of Postmenopausal Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>Effect (Benefit for Vasomotor Symptoms)</th>
<th>Strength of Evidence for Effect*</th>
<th>Harms</th>
<th>Strength of Evidence for Harms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-care/lifestyle interventions</td>
<td>Menopausal women with symptoms</td>
<td>Uncertain</td>
<td>Poor</td>
<td>Uncertain, probably minimal</td>
<td>Poor</td>
</tr>
<tr>
<td>Phytoestrogens</td>
<td>Menopausal women with symptoms</td>
<td>Reduction of 1 hot flash per day</td>
<td>Moderate</td>
<td>Uncertain</td>
<td>Poor</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Menopausal women with symptoms</td>
<td>Minimal-none</td>
<td>Fair</td>
<td>Important</td>
<td>Fair</td>
</tr>
<tr>
<td>Dong quai</td>
<td>Menopausal women with symptoms</td>
<td>None</td>
<td>Fair</td>
<td>Uncertain</td>
<td>Poor</td>
</tr>
<tr>
<td>Evening primrose oil</td>
<td>Menopausal women with symptoms</td>
<td>None</td>
<td>Fair</td>
<td>Uncertain</td>
<td>Poor</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Menopausal women with symptoms</td>
<td>None</td>
<td>Poor</td>
<td>Important</td>
<td>Good</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Menopausal women with symptoms, without a uterus</td>
<td>Absolute effect, compared with placebo, 40%; NNT = 2.5</td>
<td>Good</td>
<td>Important, some vary by risk factors</td>
<td>Good</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Menopausal women with symptoms, with a uterus</td>
<td>Absolute effect, compared with placebo, 40%; NNT = 2.5</td>
<td>Good</td>
<td>Important, some vary by risk factors + risk of endometrial cancer</td>
<td>Good</td>
</tr>
<tr>
<td>Estrogen + progestogen</td>
<td>Menopausal women with symptoms, with a uterus</td>
<td>Absolute effect, compared with placebo, 40%; NNT = 2.5</td>
<td>Good</td>
<td>Important, some vary by risk factors</td>
<td>Good</td>
</tr>
<tr>
<td>Progestogen</td>
<td>Menopausal women with symptoms</td>
<td>Absolute effect of 50% reduction in hot flashes in 75% of selected patients using higher-dose therapy</td>
<td>Fair</td>
<td>Important, some vary by risk factors</td>
<td>Good</td>
</tr>
<tr>
<td>Androgen</td>
<td>Menopausal women with symptoms</td>
<td>Uncertain</td>
<td>Poor</td>
<td>Important</td>
<td>Good</td>
</tr>
<tr>
<td>Tibolone</td>
<td>Menopausal women with symptoms</td>
<td>Absolute effect, compared with placebo, 40%; NNT = 2.5</td>
<td>Moderate</td>
<td>Important, some vary by risk factors</td>
<td>Moderate</td>
</tr>
<tr>
<td>SSRI/SNRI</td>
<td>Menopausal women with symptoms, without use of tamoxifen</td>
<td>Minimal</td>
<td>Fair</td>
<td>Uncertain</td>
<td>Fair</td>
</tr>
<tr>
<td>SSRI/SNRI</td>
<td>Menopausal women with symptoms, with use of tamoxifen and history of breast cancer</td>
<td>Reduction of 1 hot flash per day</td>
<td>Fair</td>
<td>Important increased risk of breast cancer and mortality</td>
<td>Fair</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Menopausal women with symptoms, and history of breast cancer</td>
<td>Reduction of 1 hot flash per day</td>
<td>Fair</td>
<td>Side effects</td>
<td>Good</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Menopausal women with symptoms, and history of breast cancer, and taking tamoxifen</td>
<td>Reduction of 1 hot flash per day</td>
<td>Fair</td>
<td>Side effects</td>
<td>Good</td>
</tr>
</tbody>
</table>

NNT = number needed to treat.

Clinical judgment whether symptoms are menopausal vasomotor symptoms

Yes

Discuss symptoms with patient to categorize as minimal-mild or moderate-severe

Minimal-mild

Recommend lifestyle interventions, self-help, support groups

Second-line: discuss/consider phytoestrogens

With uterus

Evaluate risk factors for E+PRT use and if patient is a candidate, discuss benefits and risks: establish values and preferences

Decision for HRT

Discuss choices of route of administration and drugs, including off-label use of LNG-IUS, including intermittent or non-use of progestogen, (and including tibolone)

Second-line: discuss/consider phytoestrogens (isoflavones) – benefits and risks

Third-line: discuss/consider clonidine and gabapentin; and SSRI/SNRI if not taking tamoxifen

Decision against HRT

Decision against ERT

Decision for ERT

Second-line: discuss/consider phytoestrogens (isoflavones) – benefits and risks

Third-line: discuss/consider clonidine and gabapentin; and SSRI/SNRI if not taking tamoxifen

No

Re-evaluate

Evaluate risk factors for ERT use and if patient is a candidate, discuss benefits and risks: establish values and preferences

Second-line: discuss/consider phytoestrogens

With uterus

Second-line: discuss/consider phytoestrogens (isoflavones) – benefits and risks

Third-line: discuss/consider clonidine and gabapentin; and SSRI/SNRI if not taking tamoxifen

Without uterus

Second-line: discuss/consider phytoestrogens

Third-line: discuss/consider clonidine and gabapentin; and SSRI/SNRI if not taking tamoxifen

Figure. Decision algorithm. E+PRT = estrogen + progestogen replacement therapy; ERT = estrogen replacement therapy; HRT = hormone replacement therapy; LNG-IUS = levonorgestrel-releasing intrauterine system; SSRI/SNRI = selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor.
**VASOMOTOR SYMPTOMS**

**Soy Foods and Soy Extracts**
A meta-analysis of 178 studies published in 2005 found that the effects of soy products on menopausal symptoms were inconsistent across studies [30]. Long-term treatment with soy has raised some concerns from the point of view of a low risk of endometrial hyperplasia [33]. In women with estrogen-dependent tumors, such as breast cancer, use of phytoestrogens must be considered carefully, since these preparations may have an effect on breast tissue. In women with clotting disorders or a previous venous thromboembolism (VTE), no safety data are available for phytoestrogens.

**Soy Isoflavone Preparations**
Results of studies of soy isoflavones are inconclusive [34–46]. The combined weighted mean difference (WMD) in the number of daily hot flashes for soy isoflavones compared with placebo was −1.15 (95% confidence interval [CI], −2.33 to 0.03) after 4- to 6-weeks use in 5 trials, −0.97 (95% CI, −1.82 to −0.12) after 12- to 16-weeks use in 4 trials, and −1.22 (95% CI, −2.02 to −0.42) after 6 months in 2 trials [8,47].

**Red Clover Extracts**
Published trials do not support the efficacy of red clover (Trifolium pratense) isoflavone extracts compared with placebo [48,49]. The largest study showed a lack of benefit [50]. Results of meta-analyses indicated no significant differences in hot flash frequency between treatment and placebo groups (WMD, −0.44 [95% CI, −1.47 to 0.58] and −0.60 [95% CI, −1.71 to 0.51]) [47,51].

**Black Cohosh**
There is a paucity of good quality evidence on the efficacy of black cohosh (Cimicifuga racemosa or Actaea racemosa) for hot flashes [28,48,52,53]. Of the randomised controlled trials using black cohosh, the 5 placebo-controlled trials reported no benefit to very minimal benefit for vasomotor symptoms [54–58]. A systematic review of the safety of black cohosh suggests that there is a slight risk of minor, transient adverse events, such as gastrointestinal upsets, headaches, dizziness, and rashes, if products are taken for a limited length of time at the recommended dose [53,59]. There have been more serious adverse events reported, including hepatotoxicity, one case requiring liver transplantation [53,60]. Black cohosh is contraindicated in women with aspirin sensitivity as it contains salicylates.

**Dong Quai**
Dong quai is a perennial plant native to southwest China, commonly used in traditional Chinese medicine. There is fair evidence that dong quai has no effect on vasomotor symptoms [61]. Interaction with warfarin and photosensitisation has been reported, due to the presence of coumarins.

**Evening Primrose Oil**
Evening primrose oil is rich in gamma-linolenic acid. Even though widely used by women, there is no evidence for efficacy in the menopause. In fact, there is fair evidence that evening primrose oil has no effect on vasomotor symptoms [8,48,62].

**Vitamin E**
There are only 2 published controlled trials of vitamin E for menopause symptoms [63,64]. One trial investigated the effect of vitamin E therapy on hot flushes in women with breast cancer [64]. A statistically significant reduction in hot flush frequency was observed with vitamin E 800 IU/day when compared with placebo; however, the authors noted that this reduction was small and may not be clinically significant. A meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality was published in 2005 and this revealed an increase in all-cause mortality with doses greater than or equal to 400 IU/day [65].

**Other Over-the-Counter Substances**
A variety of other herbal substances have been used to try to relieve the symptoms of the menopause, including ginseng, Chinese herb mixtures, mai quan, melatonin, rhubarb (rheum rhaponticum), monk’s pepper (Vitex agnus castus), flaxseed, topical wild yam extract, and kava (Piper methysticum). There is not adequate evidence that any of these can relieve symptoms like hot flashes [8,48,49,66,67]. Some of these preparations can have adverse effects, or they cause problems if they are taken with other medicines. For example it is possible that taking ginseng at the same time as an anticoagulant drug (like heparin or acetylsalicylic acid), or evening primrose oil, could cause bleeding. Kava can cause allergic reactions and skin problems. Liver damage or an impact on the nervous system might be possible [49]. DHEA is increasingly being used in the US, where it is classed as a food supplement, for its supposed anti-ageing effects. There is no evidence that DHEA has any effect on hot flashes. The short-term effects of taking DHEA are still controversial and possible harmful effects of long-term use are, as yet, unknown.

**Integrative Health Interventions**
There is insufficient evidence about acupuncture and electroacupuncture to make statements about possible efficacy [8,21,48,68]. There is insufficient evidence about magnet therapy, manual therapies, and energy therapies to make
Option 4: HORMONAL THERAPY

Estrogens

Estrogen, either oral or transdermal, and either alone or in combination with progestogens, is the most consistently effective therapy for vasomotor symptoms, reducing vasomotor symptoms by 85% to 90% [8,69–72]. Estrogen can be delivered in the following ways: oral, vaginal, intramuscular, implant, skin patch, topical application. When the results of these reports are looked at together, it shows that out of 10 women with moderate to severe hot flashes who take estrogen-based therapy, after 3 to 6 months about 8 to 9 of the women will no longer have hot flashes (85%–90%), and about 1 or 2 of the women will still have hot flashes (10%–15%). The reports also show that out of 10 women with moderate to severe hot flashes who took placebo or did not take estrogen therapy, after 3 to 6 months about 5 of the women will no longer have hot flashes (50%).

The current recommended approach for estrogen therapy is to take the lowest effective dose of estrogen for the shortest time for relief of vasomotor symptoms [13,14,73–76]. The dose needed for optimal symptom relief varies but should begin with the lowest dose, titrating as needed. Doses as low as 0.5 mg/day of estradiol were as effective as higher doses for hot flash relief when compared with placebo [14]. It may take 2 to 12 weeks to achieve maximal effects. Every 6 months, tapering the dose or frequency may be considered, or stopping the estrogen to see if the woman’s symptoms are subsiding on their own. Women should be counseled to consider stopping hormone therapy after 4 years because of increased long-term risks of breast cancer, cardiovascular disease, and stroke [14,77].

Estrogens for Women Without a Uterus

Women without a uterus can take estrogen alone if they do not have contraindications for systemic estrogen therapy. Women without a uterus who take hormone therapy should not be prescribed a progestogen with the estrogen. A progestogen is not indicated, and progestogen combined with estrogen poses greater risks than estrogen alone [14,78]. Transdermal estrogen may be preferable to oral estrogen in women who are taking other medications, already have borderline triglyceride levels, are at risk for gallstones, or have difficulty adhering to daily pill taking [72,79]. Transdermal estrogen might carry less risk for thromboembolism than oral estrogen because there is no first-pass effect, but this has not been studied in a randomized controlled trial. Long-term complications of transdermal estrogen are probably the same (breast cancer, stroke, thromboembolic, cardiovascular events) as those for oral estrogen, although they were not specifically studied in the Women’s Health Initiative (WHI) [78,80]. A meta-analysis of similarly designed randomized controlled trials of estrogen indicated reductions of approximately 2.5 to 3 hot flashes per day [70].

Estrogen replacement therapy (ERT) is associated with potentially increased risks of stroke and thromboembolic and cardiovascular events [80,81]. Breast tenderness is the most commonly reported adverse outcomes in estrogen trials; others include nausea and vomiting, headache, weight change, dizziness, rash and pruritus, cholecystitis, and liver effects. Therapy with estrogen alone does not reduce the risk of bowel cancer [82–85]. An association between estrogen therapy and ovarian cancer risk has not been established with certainty [86,87].

After 12 months of ERT there are no significant changes in stroke risk, cholecystectomy incidence, or hip fracture. After 4 to 5 years of use, in a population of women with average age at onset of therapy of 67 years, there was increased risk of stroke (8 extra strokes for every 1000 women, or 2 per 1000 women-years), increased risk of cholecystectomy (extra 21 operations for every 1000 women or 4–5 per 1000 women-years), and decreased risk of hip fracture (4–5 fewer hip fractures for every 1000 women or 1 per 1000 women-years) [80].

A further analysis of the WHI data focused on the women who initiated hormone therapy soon after menopause [88]. After up to 4 years from ERT initiation among women with no prior use of ERT, there were no statistically significant increased hazard ratios (HR) for conditions of interest. This could be because there are not increased risks or because the total number of subjects and low event rates did not yield sufficient power to identify a difference in risk. After more than 5 years of use of ERT, the adjusted hazard ratio for stroke was 1.68 (95% CI, 1.06–2.66), or 2 extra strokes per 1000 women-years [88]. The WHI found no increase in breast cancer risk with estrogen alone (without a progestin) among women with hysterectomy over an average of 7 years of randomized treatment. The 11-year follow-up of the enrolled cohort after completion of the randomized WHI found no increase in breast cancer risk with estrogen alone (without a progestin) among women with hysterectomy over an average of 7 years of randomized treatment [89].

Estrogens for Women With a Uterus

The standard recommendation for hormone replacement for women with a uterus has been to include a progestogen with an estrogen (estrogen + progestogen replacement therapy: E+PRT) [90]. The benefit of the progestogen is to reduce the risk of endometrial cancer.
There is good evidence that both the frequency and severity of vasomotor symptoms are reduced by E+PRT. Women on E+PRT experienced about 17 less hot flashes per week when compared with placebo (WMD, –17.5 [95% CI, –24.7 to –10.2]), and the severity of hot flashes was reduced as well (odds ratio, 0.13 [95% CI, 0.08–0.22]) [71,91]. There is good evidence that E+PRT reduces the frequency of night sweats and improves the quality of sleep [71,91–95]. The WHI conducted a subanalysis of 50- to 59-year-old participants and showed a 76.7% reduction in vasomotor symptoms at 12 months in HRT users compared with 51.7% in placebo users [78,94]. In addition to vasomotor symptoms benefits, the WHI study of E+PRT found additional benefits over a 5-year period of therapy: bowel cancer risk reduction from 3/1000 women-years to 2/1000 women-years, and bone fracture risk reduction (hip, vertebrae, wrist) from 1/1000 women-years to 0.67/1000 women-years [78,85]. Women on E+PRT also reported improved sleep [96,97].

E+PRT is associated with potentially increased risks of breast cancer, stroke, and thromboembolic and cardiovascular events [81,98,99]. The WHI study of E+PRT found increased breast cancer risk over a 5-year period of therapy: breast cancer diagnosis increased from 11/1000 women-years to 15/1000 women-years (mean age of enrolled subjects was 67) [78]. Abnormal screening mammogram test results were increased from 84/1000 in controls to 139/1000 in women treated with E+PRT [100]. A prolonged follow-up of women from the WHI study of E+PRT found increased breast cancer risks over a mean intervention time of 5.6 years and followed a mean total of 11 years [89]. E+PRT was associated with more invasive breast cancers compared with placebo (385 cases [0.42% per year] vs 293 cases [0.34% per year]; HR, 1.25 [95% CI, 1.07–1.46]; P = 0.004). Breast cancers in the E+PRT group were similar in histology and grade to breast cancers in the placebo group but were more likely to be node-positive (81 [23.7%] vs 43 [16.2%]), respectively; HR, 1.78 [95% CI, 1.23–2.58]; P = 0.03) [89]. The increased risk was 0.13 extra deaths from breast cancer per 1000 women-years. Specifically, for every 1000 women in the study who were randomized to placebo, there were 0.13 deaths from breast cancer per year; for every 1000 women randomized to combined hormone therapy, there were 0.26 deaths from breast cancer per year [89]. These results apply to combination estrogen plus progestin and not to estrogen alone.

A prolonged follow-up of women from the WHI study of E+PRT found an increased risk of lung cancer [101]. The WHI study of E+PRT found other increased health risks over a 5-year period of therapy: stroke risk increased from 4/1000 women-years to 6/1000 women-years, and serious thromboembolic events increased from 3/1000 women-years to 8/1000 women-years [78]. There appears to be an increased risk of heart attack in the first 12 months of E+PRT therapy (extra 2 heart attacks per 1000 women-years) [85].

A further analysis of the WHI data focused on the women who initiated hormone therapy soon after menopause [88]. After up to 2 years from E+PRT initiation among women with no prior use of E+PRT, there were no statistically significant increased hazard ratios for conditions of interest. This could be because there are not increased risks, or because the total number of subjects and low event rates did not yield sufficient power to identify a difference in risk. After more than 2 years of use of E+PRT, the adjusted hazard ratio for VTE was 2.17 (95% CI, 1.16–4.04), or 2 extra VTE events per 1000-women-years. After more than 2 years of use of E+PRT, the adjusted hazard ratio for invasive breast cancer was 1.99 (95% CI, 1.30–3.04), or 3.5 extra invasive breast cancers per 1000 women-years [88]. After more than 4 years of use of E+PRT, the adjusted hazard ratio for invasive breast cancer was 2.79 (95% CI, 1.82–4.30), or 6.3 extra invasive breast cancers per 1000-women-years [88]. A more recent subanalysis of over 5000 women who were in their early 50s at the time of randomization in the WHI, did not find a statistically significant difference in breast cancer risks after 11 years of follow-up [89].

Symptom reports from women taking E+PRT include breast tenderness [93] and uterine bleeding [102]. There is insufficient evidence of effect of E+PRT on ovarian cancer [87,103], mental health [92], general health [92], weight gain [93,104], satisfaction with sex [92], memory loss and dementia [105,106].

There are different formulations of progestogens. Progestogens can be administered continuously (continuous combined estrogen-progestogen therapy), on a monthly cycle, or on a periodic cycle longer than a month. Many women prefer the simple daily combined regimen, and most users do not have any uterine bleeding. The cyclic regimens are hypothesized to lower the adverse effect on breast cancer risk, but are associated with periodic predictable and unpredictable uterine bleeding.

In consideration of the trade-off of risks and benefits, there is a rational basis for using a periodic cycle longer than 1 month, or even to use estrogen without progestogen and monitor the endometrium for possible hyperplasia or cancer [13,14,107,108]. Micronized progesterone has a lower incidence of breakthrough bleeding and metabolic lipid effects than medroxyprogesterone, and is the preferred progestin. Furthermore, there is a rational basis and empiric evidence to support the use of a levonorgestral-releasing intrauterine system (LNG-IUS) for prevention of endometrial hyperplasia, and avoid the risks of systemic progestogen administration (see Text Box, page 121).

**Progestogens Alone**

In the past, progestogens have been a popular alternative to combined HRT in women with intractable vasomotor
Levonorgestrel-Releasing Intrauterine System: Off-Label Use for Endometrial Protection During Estrogen Replacement Therapy

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an option for endometrial protection from hyperplasia in women who choose to take estrogen replacement therapy for relief of vasomotor symptoms. The LNG-IUS is licensed for this use in the UK but not currently listed with the FDA. This use of LNG-IUS is not contraindicated, and there are no FDA warnings; therefore, the use is evidence-based off-label in the US.

There is good evidence supporting the use of LNG-IUS for endometrial suppression during estrogen replacement therapy [1]. Seven randomized controlled clinical trials have examined the efficacy and acceptability of LNG-IUS as a method of endometrial protection in peri- and postmenopausal women taking estrogen replacement therapy [2–8]. In addition, 4 cohort and 9 prospective observational studies have been published on the subject [9–16]. Long-term studies of 3 and 5 years’ duration have reported no cases of endometrial hyperplasia [11,15,16]. Of note, several studies reported high drop-out rates among the LNG-IUS users. The total number of enrolled subjects is not high, and the event rate is very low; therefore, larger longer-term studies are needed to establish harms evidence and safety. The only LNG-IUS approved for general public use releases 20 μg of levonorgestrel per day directly into the uterine cavity. However, new lower-dose (10 and 14 μg per day) and smaller-sized systems are currently under clinical development and investigation.

References
symptoms who have contraindications to estrogen, such as breast cancer or VTE. New evidence shows that women who cannot take estrogen because of heightened breast cancer risk should also not take progestogens [78,89]. Trials of progestin indicate mixed results for treatment of vasomotor symptoms; placebo-controlled randomized trials have shown a benefit for higher-dose progestogens (40 mg megestrol acetate daily) compared with placebo for the treatment of vasomotor symptoms in women with a history of breast cancer and in men with a history of prostate cancer [109]. Furthermore, doses of progestogens that achieve vasomotor symptom control also increase the risk of VTE.

**Progesterone Transdermal Creams**

There is insufficient evidence to support the use of progesterone creams for relief of vasomotor symptoms [110,111]. Claims have been made that steroids (diosgenin) in yams (Dioscorea villosa) can be converted in the body to progesterone, but this is not biochemically plausible in humans. Manufacturers of wild yam progestogen creams have added a synthetic progestogen to the cream [67].

**Androgens**

There is insufficient evidence regarding potential efficacy for relief of vasomotor symptoms with testosterone therapy [112–114]. For postmenopausal women using testosterone combined with estrogen, acne and hirsutism occur significantly more often than for women using estrogen alone.

**Tibolone**

Tibolone is a synthetic steroid hormone drug that is fairly nonselective in its binding profile, acting as an agonist at all 5 of the type 1 steroid hormone receptors, resulting in effects similar to estrogen and progesterone. Based on a systematic review of 20 randomized controlled trials, 4 fair and 3 good-quality trials reported that tibolone demonstrated benefit for vasomotor symptoms, sleep, and somatic complaints compared with placebo and was similar to estrogen for most symptoms [8,115–118]. Taking tibolone can cause vaginal bleeding or spotting, as well as weight gain and headaches [8]. European drug regulatory agencies have expressed a suspicion that long-term use of tibolone might increase the risk of breast and uterine cancer [119,120].

**Option 5: NONHORMONAL PRESCRIPTION THERAPY**

**Antidepressants**

The evidence for efficacy of antidepressants for relief of vasomotor symptoms is confounded by the inclusion in the studies of many women with a history of breast cancer and current usage of tamoxifen. Antidepressant trials have included the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine [121–123] and the selective serotonin reuptake inhibitors (SSRIs) paroxetine [124,125], fluoxetine [126], citalopram [122,123], and sertraline [69,127–129]. The studies were almost all limited to a short number of weeks’ duration. For women without current tamoxifen use, the preponderance of evidence demonstrates that the medications are not more effective than placebo for relief of vasomotor symptoms; some studies demonstrated a small effect [69,121–123,125–128].

The combined weighted mean difference in the number of daily hot flashes for trials of SSRIs or SNRIs compared with placebo was −1.13 (95% CI, −1.70 to −0.57) [48]. Although this is a statistically significant difference, the reduction by approximately 1 hot flash per day may not have clinical significance to women, who must pay for the medication and tolerate possible side effects. Sensitivity analysis indicated that trials that enrolled women with breast cancer and tamoxifen use reported significantly decreased hot flashes (mean difference, −1.40; 95% CI −1.97 to −0.82), and the trials of women without breast cancer (and no tamoxifen use) did not demonstrate a benefit (−0.17; 95% CI −1.41 to 1.07) [48,121,122,124,126,130–133]. A 9-month placebo-controlled study of citalopram and fluoxetine showed no benefit [123]. More recent studies have shown that both tamoxifen and SSRIs are metabolized by inhibiting bioactivation of tamoxifen by cytochrome P450 2D6 (CYP2D6), and that coadministration of an SSRI with tamoxifen lowers the circulating metabolite of tamoxifen. Thus, SSRIs may be alleviating hot flashes in these women by lowering the drug effect of tamoxifen; however, the indication for tamoxifen is to reduce the risk of recurrent breast cancer and this is likely to be given greater preference weight by almost all patients, compared to relief of hot flashes [8,48,130]. Furthermore, a recent cohort study reported increased risk of breast cancer death in patients on tamoxifen who received SSRIs compared with those who did not. The risk increase was estimated to be 1 additional breast cancer death within 5 years of cessation of tamoxifen for every 19.7 (95% CI, 12.5–46.3) treated patients [134].

Other antidepressant medications have been tried for the treatment of vasomotor symptoms in menopause, including mirtazapine [135] and trazodone [136]. There is insufficient evidence about these medications to make statements about possible efficacy.

**Clonidine**

Clonidine, a centrally active alpha-2 agonist, was a popular alternative preparation for the treatment of vasomotor symptoms in the past. Clonidine was hypothesized to relieve hot flashes by reducing peripheral vascular reactivity. There is fair
Evidence for minimal efficacy. An early double-blind randomized controlled trial using oral clonidine showed no evidence for hot flush reduction [137]. Clonidine was reported to reduce hot flashes by 15% to 20% compared with placebo (number needed to treat = 5 to 7), in women with a history of breast cancer [138–140]. A meta-analysis of 4 clonidine studies found the combined WMD in the number of daily hot flashes for clonidine compared with placebo was −0.95 (95% CI −1.44 to −0.47) after 4 weeks’ use; for the subgroup of 130 women who were not taking tamoxifen, there was no significant effect (WMD, 0.53, 95% CI −2.09 to 1.04). There are significant side effects with clonidine, including dry mouth. Individual patients would need to judge whether the benefit of 1 fewer hot flash per day would outweigh the side effects and the cost.

**Gabapentin**

Trials of the antiepileptic drug gabapentin in women with a history of breast cancer using tamoxifen have shown efficacy for hot flush reduction when compared with placebo [141–144]. The largest trial reported no effect compared with placebo at a dose of 300 mg/day, and a reduction of 2 hot flashes per day at a dose of 900 mg/day [143]. Gabapentin has common side effects such as drowsiness, dizziness, and dry mouth. The mechanism of action of gabapentin is unclear; given the drug-drug interaction problem of SSRIs and tamoxifen, there is reason for caution.

**Bellergal**

Bellergal (a combination of belladonna, ergotamine, and phenobarbital) has been tried for the treatment of vasomotor symptoms in menopause [145,146]. There is insufficient evidence about this medication to make statements about possible efficacy; it is not available for use in the US due to concerns about addiction and adverse effects.

**Case Continued: Treatment**

BT decided to try estrogen therapy in the form of a transdermal gel and was given a prescription and arrangements for follow-up. AS decided to try estrogen therapy in the form of an oral estradiol tablet and oral micronized progesterone for protection against endometrial hyperplasia.

- **What happens when a woman stops taking hormones?**

Estrogen therapy only helps relieve symptoms of the menopause while the hormones are being taken regularly. So an important question for women is what happens if a woman stops taking the hormones, after 6 months or a year for example? Unfortunately, there is no clear answer. There are 2 possibilities. One possibility is that the phase with symptoms is already over, so that stopping causes no problems. The other possibility is that the symptoms will return once the hormones are stopped. The best evidence comes from a trial with about 16,000 women in the US [147]. The women in this study were taking hormones for 6 years on average. After they stopped, the symptoms came back for more than half the women. That raises the possibility that by taking estrogen therapy, some women might have delayed the time when they would need to cope with hot flashes and sweats but did not completely avoid it.

**What are the future research directions for treatment of menopause-related symptoms and conditions?**

In order to fill current evidence gaps, future research is likely to focus on:

- Understanding the precise cause and physiology of vasomotor symptoms
- Understanding the variation in women’s experiences
- Harms research for hormone therapy in women at the onset of menopause (reflecting the typical age-group)
- Better reporting of adverse effects in trials and use of standardized categories of adverse effects so data can be combined across trials
- Enrollment of women with specific characteristics who have not previously been evaluated such as nonwhite women, women with premature ovarian failure, women with surgical-induced menopause, women with very high or low BMI, and those with lifestyle and behavioral factors influencing symptoms
- Determination of optimally effective doses, combination regimens, durations of use, and timing of therapy
- Head-to-head and placebo comparisons of estrogen alone and combined with other types of therapies including non-drug interventions
- Trials demonstrating how to discontinue estrogen when symptoms subside, including the effectiveness of tapering doses and/or replacing with other therapies including non-drug interventions
- More comprehensive trials to determine the role of regular exercise, sleep management, optimal nutrition, healthy relationships, social support, and relaxation
- Trials in the US of the use of estrogen and LNG-IUS in postmenopausal women with vasomotor symptoms

**Summary**

Vasomotor symptoms affect more than 75% of perimenopausal women and about 65% of menopausal women. In
the United States, approximately 4000 women enter menopause daily. Vasomotor symptoms are the most common problem occurring during the menopause transition. The degree of vasomotor symptoms varies between mild and severe. The prevailing symptoms should be clarified, and the different options should be explained. Many women choose natural experience of the change. Women with mild symptoms are advised to consider lifestyle changes, self-help, and support groups. For women with moderate to severe symptoms, estrogen is the mainstay of therapy. The benefits of estrogen therapy must be weighed against the risks. The risks differ between individuals, and therefore an individual risk assessment is necessary. For women with a uterus, there is an additional risk of endometrial hyperplasia and cancer. Historically, this has been mitigated by the use of cyclic or continuous systemic progestogen. The addition of systemic progestogens confers additional risks. Recently, options for managing this balance of risks and benefits include not using a progestogen and periodically sampling the endometrium as a screening test, giving the progestogen sporadically such as every 3 months for 10 to 14 days [13,14,107,108] or using intrauterine delivery of levonorgestrel. Other interventions that may have a small effect on vasomotor symptoms include phytoestrogens, SSRI/SNRI, gabapentin, and clonidine. Many other prescription medications have been utilized but scientific evidence is either poor or demonstrates lack of effectiveness. There are any over-the-counter products that women may use; most of them have insufficient evidence or are ineffective and some may be harmful. For many women, menopausal vasomotor symptoms last a few years; for an unfortunate subset of women, the symptoms persist for many years.

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