

Treatment Strategies for Reducing the Burden of Menopause-Associated Vasomotor Symptoms

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ABSTRACT

BACKGROUND: Vasomotor symptoms (VMS), such as hot flashes and night sweats, are the most bothersome symptoms of menopause and affect an estimated 75% of women aged over 50 years.

OBJECTIVE: To discuss the burden, pathophysiology, and management of menopause-associated VMS and to evaluate pharmacologic options available for the treatment of VMS, including herbal remedies, hormone replacement therapy (HRT), and nonhormonal therapies.

SUMMARY: Lifestyle changes, including regulation of core body temperature, relaxation techniques, regular physical activity, weight loss, and smoking cessation may help reduce the risk of VMS and should be implemented by all women with menopause-associated VMS. The role of herbal remedies in the treatment of VMS remains unclear, as clinical trial efficacy data are inconsistent and inconclusive. Nevertheless, soy isoflavones, red clover isoflavones, black cohosh, and vitamin E are commonly used to treat VMS and may be considered in women with mild symptoms that are not controlled by lifestyle changes alone. These herbal remedies appear to be safe when used for short durations (≤ 6 months). HRT, consisting of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus) is the most widely studied and most effective treatment option for relief of menopause-associated VMS and is considered the standard of care for women with moderate-to-severe VMS. HRT should be used at the lowest effective dose and for the shortest duration possible (preferably ≤ 5 years) in women in whom the potential benefits outweigh the potential risks. Nonhormonal therapies, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin, and clonidine, may be appropriate alternatives in women who cannot or will not use HRT for VMS relief, such as those with a history of or at risk for breast cancer.

CONCLUSION: The physical and financial burden imposed by menopause-associated VMS is immense. Optimum management of VMS includes lifestyle changes in all women and HRT in women with moderate-to-severe symptoms. Less effective herbal remedies or nonhormonal therapies may be appropriate in certain women, such as those with mild symptoms or those who cannot or will not take HRT.

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Introduction

Menopause, the cessation of menses that results from loss of ovarian hormone secretion, affects all women.¹ Menopause can occur naturally or be induced through surgery, chemotherapy, or pelvic radiation. When menopause occurs naturally, it generally affects women aged 40 to 58 years (median onset of menopausal transition: 47.5 years), although premature menopause (i.e., menopause that occurs in women aged <40 years) may occur. Menopause is a term that is often used to describe perimenopause or the menopausal transition when in fact it refers to a specific point in time. Menopause does not technically occur until 12 months after the last menstrual period. The time frame leading up to the last menstrual period, during which menstrual and hormonal changes occur, is termed perimenopause or the menopausal transition, and typically lasts for several years (average: 4 years) before the final menstrual period (Figure). Postmenopause is the term used to define the time period after the occurrence of the final menstrual period; it begins with the final menstrual period and ends with death. Symptoms of perimenopause include irregular menstrual periods, vasomotor symptoms (VMS) (i.e., hot flashes [rapid onset of intense heat sensation, sweating, and flushing lasting approximately 5-10 minutes], night sweats), sleep disturbances, vulvovaginal atrophy (e.g., dryness, itching, burning), sexual dysfunction, and mood disturbances.²⁻⁴ Of these, VMS are the most bothersome and are the main focus of menopausal treatment guidelines. The purpose of this review is to discuss the burden, pathophysiology, and management of menopause-associated VMS and to evaluate pharmacologic options available for the treatment of VMS.

Vasomotor Symptoms

Physical and Financial Burden

Although all women will eventually go through the menopausal transition, not all women will experience symptoms other than cessation of menstruation. As previously stated, VMS are the most bothersome symptoms of the menopausal transition. In fact, VMS are the leading reason why women seek medical attention for menopause. The top 4 reasons for seeking medical attention identified in a 2002 Gallup poll of menopausal women were hot flashes (70%), night sweats (68%), mood disturbances (50%), and sleep disturbances (49%).⁵ These data are supported by results of a more recent poll, which showed that 60% of peri- and postmenopausal women sought care for their menopausal symptoms.⁶

It is estimated that 75% of women aged over 50 years experience hot flashes;⁵ however, the prevalence of VMS varies considerably with menopausal status and ethnicity. In fact, VMS is estimated to affect 14% to 51% of premenopausal women, 35% to 50% of perimenopausal women, and 30% to 80% of postmenopausal women.⁴ In a community-based survey of 16,065 women aged

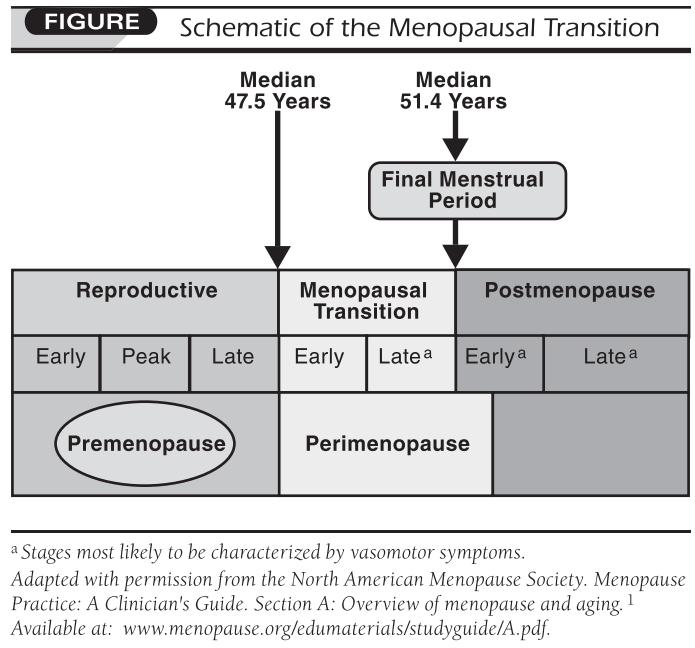
40 to 55 years conducted between 1995 and 1997, the prevalence of VMS, defined as hot flashes and/or night sweats, was found to be highest among African-American women (45.6%), followed by Hispanic-Americans (35.4%), Caucasians (31.2%), Chinese-Americans (20.5%), and Japanese-Americans (17.6%).⁷ These rates were mirrored by a more recent longitudinal study of 3,198 women followed from 1996 to 2002, in which the risk of VMS was highest among African-Americans (odds ratio [OR], 1.63; 95% confidence interval [CI], 1.21-2.20; $P < 0.01$ vs. Caucasians).⁸ Prevalence rates were lowest among Hispanic-Americans, followed by Chinese-Americans and Japanese-Americans. Other factors that were found to increase a woman's risk for VMS included age, higher body mass index, having less than a college education, smoking, baseline anxiety, and baseline depression.^{7,8} On average, most women experience VMS for 6 months to 2 years; however, approximately 10% of women report experiencing VMS for 10 or more years.^{5,9}

According to U.S. census data, there are more than 48 million American women aged over 50 years, and nearly 60 million women aged 45 years and over.¹⁰ Considering the fact that all these women will go through menopause, 75% of them will experience VMS,⁵ and 60% of them will seek medical attention for their symptoms,⁶ it isn't surprising that the financial burden of VMS is immense. Direct costs incurred by women with menopause-associated VMS include initial and follow-up physician office visits and telephone calls, which may include visits to specialists (e.g., psychologist, psychiatrist, neurologist), as well as primary care physicians or gynecologists, prescription, and over-the-counter (OTC) medications, dietary supplements, and laboratory tests.⁵ Indirect costs include loss of productivity at home or at work, hygiene-related supplies, increased energy usage for air conditioning and laundry, and management of treatment-related adverse events. One cost-effectiveness comparison estimated the yearly cost of VMS management to average \$681 to \$848 per patient per year.¹¹

Pathophysiology

There is currently no consensus on the pathophysiology of menopause-associated VMS; however, many hypotheses have been proposed. One proposed mechanism for hot flashes is a narrowing of the thermoregulatory threshold between sweating and shivering in the hypothalamus.¹² This narrowing is thought to be caused by changes in the levels of circulating serotonin (decreasing concentration), norepinephrine (increasing concentration), or estrogen (decreasing concentration).^{2,9} The postmenopausal decline in ovarian estradiol production results in diminished negative-feedback effects on the anterior pituitary, leading to a compensatory increase in the secretion of luteinizing hormone from the pituitary, a process regulated by gonadotropin-releasing hormone in the hypothalamus.¹³ Pulsatile surges of gonadotropin-releasing hormone due to estrogen deficiency affect the hypothalamic neurons that control central thermoregulation centers.¹⁴

It has also been hypothesized that the ratios of the specific types of estrogen (i.e., estradiol or estrone) may be better correlated



with the occurrence of VMS than the overall circulating level of estrogen.¹⁵ Estrone, which is much lower in potency than estradiol, is the most abundant circulating estrogen in postmenopausal women.¹³ In premenopausal women, estradiol is the more abundant estrogen.¹³ Further, the occurrence of VMS has been found to correlate better with an acute decline in estrogen levels than with the actual measured levels of estrogen.⁹

In addition to the impact of the change in the relative amounts of estradiol and estrone, another hypothesized contributor to VMS is the actual function of the available circulating estrogen. For example, the cytochrome p450 isoenzyme CYP1A1 is responsible for the hydroxylation of estrone and estradiol, forming hydroxyestrone (2HE). 2HE binds very weakly to the estrogen receptor.^{15,16} The relative amounts of the more potent estradiol is also affected by 17 β -hydroxysteroid dehydrogenase (17HSD), the enzyme responsible for the bidirectional conversion of the less potent estrone and the more potent estradiol.^{15,16} Alterations in the estrogen receptors ER α and ER β may also negatively affect the biologic activity of estrogen.¹⁷ It has been shown in one study that single nucleotide polymorphisms (SNPs) in the genes encoding estrogen-metabolizing enzymes (i.e., CYP1A1, CYP1B1, 17HSD) or ERs are associated with prevalence of VMS, and these polymorphisms correlate with ethnic differences in VMS prevalence noted previously.¹⁵ Additional studies are needed to confirm these results and further clarify the pathophysiology of VMS.

Treatment of Vasomotor Symptoms

Treatment guidelines, consensus statements, or position statements for the management of menopausal symptoms have been published by a number of professional societies in the United

TABLE 1 Recommended Dosing Ranges for Commonly Used Oral and Transdermal Hormonal and Nonhormonal Therapies Used to Treat Menopause-Associated Vasomotor Symptoms

Drug	Daily Dose
<i>Herbal Remedies</i>	
Isoflavone	40 mg-80 mg
Black cohosh	40 mg
Vitamin E	800 IU (divided)
<i>Estrogens</i>	
Conjugated equine estrogens	0.3 mg-0.625 mg
Micronized 17 β -estradiol	0.25 mg-1 mg
Transdermal estradiol	14 μ g-100 μ g
Ethinyl estradiol	0.01 mg-0.02 mg
Vaginal estradiol ring	0.05 mg-0.1 mg
<i>Progestins</i>	
Medroxyprogesterone acetate	2.5 mg (or 5 mg for 10-14 days/month)
Micronized progesterone	100 mg (or 200 mg for 10-14 days/month)
Norethindrone	0.35 mg (or 5 mg for 10-14 days/month)
Levonorgestrel	0.075 mg
<i>Antidepressants</i>	
Fluoxetine	20 mg
Paroxetine	12.5 mg-25 mg
Venlafaxine	75 mg
<i>Gabapentin</i>	900 mg (divided)
<i>Clonidine</i>	0.1 mg orally daily or 1 transdermal patch per week (equivalent to 0.1 mg daily)

Data from References 2, 3, and 9.

States, including the North American Menopause Society (NAMS) in 2007,³ with a position statement dedicated specifically to the management of VMS in 2004,⁹ the American Association of Clinical Endocrinologists (AACE) in 2006,² and the American College of Obstetricians and Gynecologists (ACOG) in 2004.¹⁸ This section will focus specifically on the treatment of menopause-associated VMS and will not address treatment of other menopause-associated symptoms, such as vulvovaginal atrophy, sleep disturbances, sexual dysfunction, or mood disturbances.

Lifestyle Changes

Lifestyle changes should be implemented by all women with menopause-associated VMS. Interventions that help regulate core body temperature include wearing lightweight cotton clothing, dressing in layers, using fans or air conditioning, consuming cool or cold foods and drinks, and avoiding hot foods and drinks.^{2,9} Regular physical activity, weight loss, and smoking cessation may also reduce the risk of VMS; however, the efficacy of these endeavors has not been evaluated.⁹ Relaxation techniques may also provide relief of VMS; however, only paced respiration

(i.e., slow, controlled, diaphragmatic breathing) has been proven effective in clinical trials.^{2,9}

Pharmacologic Interventions

Herbal Remedies

According to NAMS, women with mild VMS that are not controlled by lifestyle changes may consider treatment with an herbal remedy, such as isoflavone supplements (i.e., soy, red clover), black cohosh, or vitamin E.⁹ However, it is important to note that this suggestion is not a consensus recommendation as efficacy data are inconclusive. This suggestion is based primarily on the fact that these herbal remedies have not been associated with serious side effects when used for short durations (i.e., ≤ 6 months). The AACE acknowledges that these herbal preparations are used for the management of VMS but does not advocate for or against their use.² They do, however, caution about the lack of standardization and regulation of herbals, and the potential of herbals to interact with other medications and medical conditions. The ACOG does not recommend the use of these herbal remedies, citing lack of significant effects on VMS.¹⁸ The exact mechanism(s) by which herbal remedies reduce the frequency of VMS is unknown.⁹ Dosing recommendations for isoflavones, black cohosh, and vitamin E are listed in Table 1. Other herbal remedies, such as wild yam extract,¹⁸ natural progesterones, dong quai, primrose oil, ginseng, licorice, and Chinese herbal mixture are not recommended because of a lack of efficacy data.⁹

Hormone Replacement Therapy

Hormone replacement therapy (HRT), consisting of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus [to protect against endometrial hyperplasia or cancer]), is the most widely studied and most effective treatment option for relief of menopause-associated VMS and is considered the standard of care for women with moderate-to-severe VMS.^{2,3} The AACE, ACOG, and NAMS recommend the use of HRT at the lowest effective dose and for the shortest duration possible (preferably ≤ 5 years) in women for whom the potential benefits outweigh the potential risks (Table 2).^{2,3,18} The 5-year cut-off for HRT is suggested because most women will experience spontaneous cessation of menopausal symptoms within 5 years of onset.² Use of HRT for longer durations may be appropriate in some women, such as those who judge the benefits of VMS relief to outweigh the potential risks after failing an attempt to discontinue HRT, those with continued VMS who are also at high risk for osteoporotic fractures, and those requiring osteoporosis prevention who cannot take alternate therapies.³ Several weeks may be required to determine the efficacy of HRT in treating VMS.⁹ There is currently no consensus on whether to discontinue HRT abruptly, to gradually taper the dose downward, or to lengthen the time between doses.³ Contraindications to the use of HRT are listed in Table 3.

Estrogen and progestin are both available in various oral, transdermal, vaginal, and injectable preparations, as well as in

combination products. In women with an intact uterus, progestin may be used continuously (daily) or cyclically (10-14 days per month).² Cyclic progestin administration produces monthly menstruation. Although continuous progestin administration does not produce this, women may experience periodic breakthrough bleeding. Administration of estradiol via transdermal patches eliminates first-pass metabolism of estradiol to the less active estrone and maintains more constant blood levels as a result of sustained release. Transdermal administration results in an estrone to estradiol ratio of approximately 1 to 1, which closely resembles the premenopausal state.¹⁹ There is an absence of rigorous evidence from large-scale, prospective, randomized, double-blind clinical trials on differential effects by hormone formulation or route of delivery.^{9,18,20} Women needing VMS suppression and contraception may be effectively treated with low-dose oral contraceptives.⁹ Women who are unwilling to use estrogen but who are willing to use other hormone therapy may be treated with a progestin alone.³ The combination of estrogen plus an androgen should be reserved for women with symptoms of androgen deficiency or those whose VMS persist despite adequate estrogen therapy.⁹ Dosing recommendations for commonly used oral and transdermal estrogen and progestin preparations are listed in Table 1.

Nonhormonal Therapy

Nonhormonal therapies, such as antidepressants, anticonvulsants, and antihypertensives, have been used for relief of VMS; however, these drugs are not FDA-approved for this indication.² Of these agents, AACE, ACOG, and NAMS consider the antidepressants to be the most effective nonhormonal therapy.^{2,9,18} Two advantages of antidepressants are almost immediate reduction in VMS scores and the added benefit of mood enhancement in women suffering from mood disorders.⁹ Nonhormonal treatment alternatives may be used in women who cannot or will not use HRT for relief of VMS, such as those with a history of or at risk for breast cancer.^{2,9,18} The mechanisms by which these nonhormonal therapies reduce the frequency of VMS are unknown.⁹ Recommended agents and doses are listed in Table 1.

Treatment Alternatives: Clinical Overview

The previous section outlined a number of pharmacologic interventions for the treatment of menopause-associated VMS that are recommended by the AACE, ACOG, and NAMS. This section will provide a brief overview of the clinical efficacy of these interventions. Readers are encouraged to consult the treatment guidelines and other cited resources for a more detailed explanation of benefits, risks, and dosing considerations, as a detailed review of available studies for all treatment options is beyond the scope of this review.

Herbal Remedies

ACOG and NAMS, which both published treatment recommendations in 2004, drew contrasting conclusions about the use

TABLE 2 Potential Risks and Benefits of Hormone Replacement Therapy in Perimenopausal Women

Potential Risks	Potential Benefits
<ul style="list-style-type: none"> • Breast cancer • Endometrial cancer^a • Stroke • Venous thromboembolism 	<ul style="list-style-type: none"> • Suppression of vasomotor symptoms • Reduced risks of: <ul style="list-style-type: none"> ◦ Colorectal cancer ◦ Coronary heart disease^b ◦ Dementia ◦ Diabetes mellitus ◦ Osteoporosis and osteoporosis-related fractures

^a In women with an intact uterus treated with estrogen alone.

^b In younger women in the early stages of menopause who do not have pre-existing cardiovascular disease; pertains especially to estrogen alone.

Data from References 2 and 3.

TABLE 3 Contraindications to the Use of Hormone Replacement Therapy (HRT)

<ul style="list-style-type: none"> • Breast or estrogen-sensitive cancers • Undiagnosed vaginal bleeding • Endometrial hyperplasia • Blood clotting disorder • Hypertension • Liver disease • Hypersensitivity to the active or excipient compounds in HRT

Data from the AACE Menopause Guidelines Revision Task Force (2006).²

of herbals for the management of VMS. ACOG, citing a lack of clinical efficacy, does not support their use.¹⁸ NAMS does support their use, despite acknowledging inconclusive efficacy data.⁹ The AACE recommendations, the most recent of the three, took a more neutral approach, neither recommending nor discouraging the use of herbals.²

A recent meta-analysis of 6 trials of soy isoflavones, ranging in doses from 50 mg to 150 mg per day, resulted in mixed results, with numerical reductions in the mean number of daily hot flashes compared with placebo at 4-6 weeks (weighted mean difference, -1.15; 95% CI, -2.33 to 0.03), at 12-16 weeks (weighted mean difference, -0.97; 95% CI, -1.82 to -0.12), and at 6 months (weighted mean difference, -1.22; 95% CI, -2.02 to -0.42).²¹ All 6 of these studies were judged by the authors of the meta-analysis to be of poor-to-fair quality based on a number of factors that reduce the quality of the study design; such factors include a study population of <50 participants, inadequate analysis, or <80% follow-up or follow-up not reported. A meta-analysis of 6 fair-to-good quality trials of 2 types of red clover isoflavones (promensil [40-160 mg per day] and rimostil [57 mg per day]) showed little difference

between red clover isoflavones and placebo in reducing the mean number of daily hot flashes (weighted mean difference, -0.44; 95% CI, -1.47 to 0.58).²¹ Because soy isoflavones and red clover isoflavones are thought to act on estrogen receptors, they should not be used in women with a history of breast cancer.⁹

The AACE, ACOG, and NAMS recommendations on the use of black cohosh are based on the same 2 trials. One of these trials did demonstrate that black cohosh was superior to placebo at reducing VMS,²² while the other showed no significant difference between treatment groups.²³ Because of its purported estrogenic effects, black cohosh should not be used in women with a history of breast cancer.³

Data from 1 clinical trial that evaluated the efficacy of vitamin E for the treatment of VMS found a significant difference compared with placebo; however, this difference equated to 1 less hot flash per day in the women receiving vitamin E.²⁴ Collectively, these data do not provide conclusive support for the use of herbal or vitamin remedies for the relief of menopause-associated VMS.

Hormone Replacement Therapy

HRT is the standard of care for the treatment of moderate-to-severe VMS.^{2,3} This recommendation is based on a plethora of data demonstrating the effectiveness of estrogen or estrogen plus progestin in the reduction of VMS frequency and severity. In fact, a meta-analysis of 24 double-blind, randomized, placebo-controlled trials including a total of 3,329 subjects and ranging in duration from 3 months to 3 years demonstrated a significant 75.3% reduction in the frequency of hot flashes experienced per week (weighted mean difference, -17.92, 95% CI, -22.86 to -12.99) and a significant 87% reduction in the severity of symptoms (OR, 0.13; 95% CI, 0.07 to 0.23) relative to placebo.²⁵ These relative reductions are significant considering that the placebo response rate in this meta-analysis was 57.7%. As previously stated, there are currently no data available to suggest that any 1 formulation of estrogen or estrogen plus progestin is clinically superior to another.^{9,18,20}

Nonhormonal Therapy

Of the nonhormonal agents used for the treatment of VMS, antidepressants have been studied most extensively. In a recent meta-analysis of 6 trials of selective serotonin reuptake inhibitors (SSRIs; paroxetine, fluoxetine, citalopram) or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, antidepressants were found to be significantly more effective than placebo at reducing the mean number of daily hot flashes (weighted mean difference, -1.13; 95% CI, -1.70 to -0.57).²¹ The individual antidepressants had variable efficacy. Paroxetine was evaluated in 2 studies (1 fair and 1 good) and was found to reduce the mean number of daily hot flashes by 1.66 (95% CI, -2.43 to -0.89); fluoxetine was evaluated in 2 fair-quality studies and was found to reduce the mean number of hot flashes by 1.37 (95% CI, -3.03 to 0.29); citalopram was evaluated in 1 fair-quality study and was

found to reduce the mean number of hot flashes by 0.20 (95% CI, -1.45 to 1.05); venlafaxine was evaluated in 2 studies (1 fair and 1 good) and was found to reduce the mean number of hot flashes by 0.49 (95% CI, -2.40 to 1.41).²¹ Meta-analyses of 4 trials of clonidine and 2 trials of gabapentin also demonstrated significant reductions in the mean number of daily hot flashes compared with placebo.²¹ Clonidine reduced the mean number of daily hot flashes by 0.95 (95% CI, -1.44 to -0.47) at 4 weeks (4 trials) and by 1.63 (95% CI, -2.76 to -0.50) at 8 weeks (2 trials). Gabapentin reduced the mean number of daily hot flashes by 2.05 (95% CI, -2.80 to -1.30). Although these nonhormonal agents have been proven significantly more effective at reducing the mean frequency of hot flashes by 1 to 2 per day, they are not as effective as HRT,²⁵ according to reported efficacy rates from separate trials. Although these results are not from head-to-head comparisons, the vast difference in the efficacy rates for hormonal versus nonhormonal therapies is worth noting.

New Drugs in Development

There are several new therapies for the treatment of menopause-associated VMS that are in various stages of clinical development, including 2 antidepressants (low-dose paroxetine mesylate and desvenlafaxine succinate), a serotonin-2 antagonist (Org50081), and an alpha-2 delta receptor binding agent (PD-0299685) (www.clinicaltrials.gov). At this time, no data are available on the efficacy of low-dose paroxetine mesylate or Org50081. Preliminary data suggest that PD-0299685 reduces the mean number of hot flashes relative to placebo.²⁶ Results from a recently completed and presented clinical trial demonstrate that desvenlafaxine (100 mg per day) reduced the frequency of moderate-to-severe hot flashes by 65% at 12 weeks compared with 51% in the placebo group with reductions seen as early as week 1.²⁷ Additional data suggest that these differences may be sustained for 52 weeks.²⁸ Desvenlafaxine also significantly reduced the severity of hot flashes compared with placebo. Adverse events were comparable to placebo, with nausea being the most frequently reported adverse event (25% vs. 7%).²⁷ Additional clinical trial data on these investigational agents are eagerly awaited.

Conclusions

Current treatment of menopause-associated VMS is centered on a foundation of lifestyle changes in all women and HRT in women with moderate-to-severe VMS. Herbal remedies are commonly used for the treatment of VMS; however, the mechanisms by which they reduce the frequency of VMS remains unknown and clinical trial efficacy data are inconsistent and inconclusive. Isoflavones and black cohosh are thought to possess estrogenic properties, and like HRT, should not be used in women with a history of breast cancer. Additional studies are warranted to determine the efficacy and safety of herbal remedies in the treatment of menopause-associated VMS. SSRIs, SNRIs, gabapentin, and clonidine have been proven superior to placebo in reducing the mean number

of hot flashes experienced per day; however, these nonhormonal therapies are less effective than HRT. The mechanisms by which nonhormonal therapies reduce the frequency of hot flashes remain unknown. These nonhormonal alternatives may be appropriate in women who cannot or will not take HRT, such as those with a history of breast cancer. HRT, consisting of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus), remains the standard of care in women with moderate-to-severe VMS. Numerous hormonal and nonhormonal therapies in various stages of clinical development have shown promising results in the treatment of VMS. Efficacy and safety data from ongoing clinical trials are eagerly awaited. Comparative clinical trials and cost-effectiveness analyses will be needed to determine if any of these investigational therapies are capable of replacing HRT as the standard of care in women with moderate-to-severe VMS.

DISCLOSURES

Elena M. Umland discloses that there was no financial relationship or financial interest relating to the topic of this activity. Umland was responsible for the entire study concept and design of this article. She performed all the data collection, data interpretation, writing, and revision of this article.

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