Hormonal and Non-Hormonal Management of Vasomotor Symptoms: A Narrated Review

Orkun Tan1,2*, Anil Pinto2 and Bruce R. Carr1
1Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Texas Southwestern Medical Center, USA
2Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, ReproMed Fertility Center, USA

Abstract

Background: Vasomotor symptoms (VMS; hot flashes, hot flushes) are the most common complaints of peri- and postmenopausal women. Therapies include various estrogens and estrogen-progestogen combinations. However, both physicians and patients became concerned about hormone-related therapies following publication of data by the Women's Health Initiative (WHI) study and have turned to non-hormonal approaches of varying effectiveness and risks.

Objective: Comparison of the efficacy of non-hormonal VMS therapies with estrogen replacement therapy (ERT) or ERT combined with progestogen (Menopausal Hormone Treatment; MHT) and the development of literature-based guidelines for the use of hormonal and non-hormonal VMS therapies.

Methods: PubMed, Cochrane Controlled Clinical Trials Register Database and Scopus were searched for relevant clinical trials that provided data on the treatment of VMS up to June 2013.

Findings: Depending on the dose, ERT using any of several types of estrogen receptor (ER) ligands is unequivocally the most effective treatment for VMS. In most studies, the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), ribonone, clonidine and gabapentin are more effective than placebo. Paroxetine, which is an SSRI, is the only FDA-approved non-hormonal agent for the treatment of VMS. SSRIs must be used with caution in women with breast cancer receiving adjuvant tamoxifen therapy since SSRIs reduce the metabolism of tamoxifen to its most active metabolite, endoxifen. Although gabapentin and some of the SNRIs may be effective in relieving VMS, there are no placebo-controlled trials demonstrating their efficacy. Oral micronized progesterone is effective for treatment of VMS in early postmenopausal women. Bazedoxifene/conjugated estrogen may be a promising alternative to hormone therapy for the treatment of VMS. The effects of phytoestrogens on VMS are similar to placebo. Black cohosh, dong quai, evening primrose oil, ginseng extract, kava kava, vitamin E, red clover leaf, hypnosis, acupuncture are either ineffective or not clinically significantly efficacious in the treatment of VMS.

Conclusions: VMS vary greatly in severity, and women with mild to moderate symptoms may not need to use ERT/MHT, or any treatment at all. However if used, ERT or MHT is effective for the treatment of VMS. Initial one to three month trials for efficacy and tolerance are recommended since relief from VMS is usually substantial within 4 weeks of starting ERT/MHT. As with all treatments, the risks and benefits of estrogen treatments and neurotransmitter-active treatments must be reviewed before they are administered. Randomized double blind controlled trials comparing paroxetine, SNRIs, clonidine, dehydroepiandrosterenedione or stellate ganglion block with ERT/MHT are needed to confirm their efficacy and side effect profiles. So-called “bioidenticals” have no advantage over conventional preparations and are not subject to FDA standards.

INTRODUCTION

In menopausal women, vasomotor symptoms (VMS; hot flashes, hot flushes) are due to decreased estrogen and they are described as waves of feeling hot then cold and sweating, primarily over the “shield area” of the anterior body surfaces [1]. VMS occur in conjunction with decreased estrogen levels/action in women and usually their severity and frequency mirrors the abruptness of the loss of estrogen activity [2,3].

It was for decades the approach to offer FDA- (Food and Drug Administration) approved estrogen combined with progestogen (Menopausal Hormone Treatment, MHT) for menopausal VMS. The Women’s Health Initiative study (WHI) drove most women and their caregivers away from MHT, including its use for VMS [4]. As a result menopausal women have turned to other, non-hormonal means of relieving VMS [5]. Therefore, a comprehensive review of the present state of treatment for VMS was needed.

Evaluation of VMS

There is no need for diagnostic studies in peri- and postmenopausal women who are suffering from VMS unless they do not respond to estrogen or have additional symptoms consistent with infection, hyperthyroidism, narcotic withdrawal, pheochromocytoma, alcohol consumption, cardiac symptoms, dumping syndrome, and medications such as nitrates, niacin, gonadotropin-releasing hormone agonists, and anti-estrogens (see Figure 1 “Useful Tips”). Levels of follicle-stimulating hormone and luteinizing hormone may be within the normal premenopausal range during the menopausal transition [6].

Treatment of menopausal VMS

Placebo effect: Evaluation of the treatment of VMS is
complicated by a strong placebo effect [7]. The following discussion takes the placebo effect into account by specifying whether long-term, placebo-controlled trials are considered. Randomized controlled prospective, single- or double-blinded trials comparing the efficacy of hormonal or nonhormonal options with the gold standard ERT or MHT for the relief of VMS were also included in this review.

Hormonal treatment of VMS

Estrogen plus Progestogen replacement therapy (MHT): Until recently, see above, MHT was the most common treatment for VMS. A systematic review and meta-analysis of 32 treatment trials found that the use of conjugated equine estrogens (CEE), oral or transdermal 17β-estradiol alone has consistent and comparable effects on the treatment of VMS in menopausal women. All estrogen agents significantly reduced the weekly number of VMS compared with placebo (CEE, 1 trial: mean change, 19.1; oral 17β-estradiol, 5 trials: pooled weighted mean difference, 16.8; transdermal 17β-estradiol, 6 trials: pooled weighted mean difference, -22.4) and differences between agents were not significant [8]. A 2009 Cochrane meta-analysis including 24 trials found that ERT or MHT greatly reduces the frequency and severity of VMS compared to placebo. VMS frequency was reduced 75%, and severity decreased as well [9].

There are many MHT preparations with different regimens, routes of administration, and doses (see Figure 2). Currently there is no evidence indicating that one product is superior to another for relief of VMS. Because of the risk of endometrial hyperplasia and endometrial adenocarcinoma with prolonged unopposed estrogen use, all women with an intact uterus should receive systemic progestogen with estrogen [10]. Relief from the frequency and severity of VMS is usually substantial within 4 weeks after starting standard doses (0.625 mg) of estrogens (See Figure 2). An oral tablet of CEE 0.625 mg/day with Medroxyprogesterone acetate (MPA) is the most commonly used MHT in menopausal hot flashes trials. It has been demonstrated that VMS were reduced by 83% using standard-dose conjugated estrogens (0.625 mg) and by 63% with low-dose conjugated estrogens (0.3 or 0.45 mg) [11]. Lower doses may not have maximal effects for 8 to 12 weeks but are associated with fewer side effects, such as breast tenderness [11]. A double blind, randomized trial examined the efficacy and safety of low doses of conjugated estrogens combined with MPA and found that lower doses relieved vasomotor symptoms as effectively as standard doses [12]. Doses of conjugated estrogens at 0.45 and 0.3 mg/d, with and without concurrent MPA, significantly reduced the frequency and severity of VMS compared with placebo by the third week of treatment. There were no significant differences regarding the relief of VMS between conjugated estrogens (0.625 mg) plus MPA (2.5 mg) and any of the lower-dosage conjugated estrogens (0.3 and 0.45 mg) plus MPA groups (1.5 mg), although low-dose conjugated estrogen without MPA was not quite as effective as standard-dose conjugated estrogens (0.625 mg) or low-dose conjugated estrogens/Medroxyprogesterone acetate combinations. This may be because Medroxyprogesterone acetate has an independent effect on VMS reduction [7,13].

Levonorgestrel-containing intrauterine device (LNG-IUD; Mirena, Bayer HealthCare Pharmaceuticals Inc., USA) is approved by FDA for contraception and the treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. However LNG-IUD which delivers 20 µg of levonorgestrel over a 24-hour period is now licensed for use as the progestogen component of continuous estrogen therapy in United Kingdom [14].

Estrogen Replacement Treatment (ERT): Estrogens alone markedly improves the frequency and severity of VMS as demonstrated by many randomized trials [8]. Estrogens, which are available in oral, transdermal, vaginal ring and topical forms, are effective in up to 90% of women with VMS (see Figure 2) [15]. The benefit is dose-related and even low doses of estrogens are often effective [12,16,17]. With standard doses of estrogens (CEE, 0.625 mg; oral micronized 17β-estradiol, 1 mg; transdermal 17β-estradiol, 50 µg/d), relief from VMS is usually seen within 1 month [18]. Lower doses may not have maximal effects for 2-3 months but side effects such as breast tenderness and uterine bleeding are less commonly seen compared to the higher doses [11,18]. Examples for lower doses of estrogens include CE (0.3 mg, 0.45 mg), micronized oral 17β-estradiol (0.5 mg), and
transdermal 17β-estradiol (0.025 mg). ERT is the standard of care for post-hysterectomy patients for the treatment of VMS. Women without a uterus do not require progestogens.

Since the preparations that are presently available for ERT and MHT have been assessed for satisfactory rates of endometrial- and other complications, we suggest starting with an FDA-approved "low dose" regimen by either the oral or parenteral route and assessing the effect on VMS after one to three months. Some studies have shown that low-dose estrogens may be less likely to cause many of the potential risks associated with higher dose estrogens [19]. If the dose is effective it may be continued. However, if the effect is not adequate, higher-dose, FDA-approved formulations may be tested.

Follow-up of patients on MHT/ERT: neither the dose nor length of this period is defined, especially in regards to individual patient needs, the length of therapy should be periodically reviewed with the patient. Consideration should include the likelihood that she no longer needs the MHT/ERT for VMS. It is not necessary to routinely evaluate the endometrium of women with uterine spotting or light uterine bleeding in the first six months of continuous MHT (throughout the month) [20]. Endometrial assessment of such women is recommended if spotting or bleeding persists beyond six months, although there is a very low incidence of endometrial hyperplasia or neoplasia [21].

ERT/MHT has long-term health risks and benefits. In a 2011 randomized controlled trial (RCT), LaCroix et al. investigated health outcomes after stopping conjugated equine estrogens (CEE) among postmenopausal women (between ages 50-79) with prior hysterectomy. In the CEE group, at the time of hysterectomy, 39.8% of patients were <40 years of age, 43.7% between 40-49 years of age, 9.2% between 50-54 years of age and 7% ≥ 55 years of age. CEE use for a median of 5.9 years was not associated with an increased or decreased risk of coronary heart disease (CHD), deep vein thrombosis, stroke, hip fracture, colorectal cancer, or total mortality [22]. A 2009 meta-analysis indicated a reduction in mortality in younger postmenopausal women (aged 50-59 years) taking hormone therapy compared with no treatment [23]. However ERT/MHT use is not without significant risks. Contraindications to MHT use include breast or endometrial cancer, cardiovascular disease, thromboembolic disorders, and active liver disease [7]. Whereas observational studies and WHI clinical trial were at odds regarding coronary heart disease risk, findings regarding breast cancer were extremely consistent. A randomized trial of hormone therapy use in women with a history of breast cancer and bothersome vasomotor symptoms was terminated early, after 2 years of follow-up, when more new breast cancer events were diagnosed in women randomly assigned to hormone therapy [24]. Estrogen-alone therapy was associated with a significantly increased risk of breast cancer after 15 years of current use in the Nurses' Health Study [25] and for current users in the Million Women observational study of United Kingdom women [26]. An increased risk of breast cancer is seen after approximately 5 years of MHT use, with no increased risk seen in short-term or past-users [7]. In 2009, WHI investigators reported that the increased risk of breast cancer associated with MHT declined markedly soon after discontinuation of the therapy suggesting that the incidence of breast cancer among women in certain age groups in the United States is predominantly related to a decrease in the use of MHT [27]. The endocrine society in 2010 reported that MHT increases the risk of invasive breast cancer, which may occur within 3 to 5 yr of initiation and rises progressively beyond that time [28]. In the same statement, congruent trends suggested additional benefit including reduction of overall mortality and coronary artery disease in the subgroup of women starting MHT between ages 50 and 59 or less than 10 yr after onset of menopause [28].

So far, basic science studies and numerous animal models provide biological plausibility for the concept that estrogens can exert atheroprotective effects via both systemic effects on circulating factors and direct effects on the heart and blood vessels [29,30]. Subgroup analyses suggest that the lack of benefit or increase in CHD risk observed in the overall analysis of the WHI resulted from harmful effects of MHT in older women starting therapy many years after onset of menopause [28].

The results of studies regarding the effects of estrogens on cognition have been conflicting [31,32]. As a possible explanation, Henderson and Sherwin suggested that estrogen might have an age-dependent neuroprotective effect on the brain [33,34]. They proposed the "critical window" or "timing" hypothesis, which suggests that estrogen begun later in menopause does not benefit cognitive outcome and, instead, is detrimental. However, early initiation of estrogen might reduce dementia risk [31,33-35].

In conclusion, hormone therapy should not be prescribed to women with a history of breast cancer and should be used by women at high risk only after a careful assessment of potential risks and benefits. These findings should be reassuring to women and their clinicians considering short-duration HRT for bothersome VMS at the time of the menopausal transition. The lowest effective estrogen dose with the shortest duration should be given to the patients since the risks increase with increasing age, time since menopause, and duration of use. Women must be informed of the potential risks and benefits of ERT/MHT, and care should be individualized, based on the medical history, risk factors and expected benefits from hormonal therapy [7].

Progestogens: Different progestogens, such as MPA and megestrol acetate have been used effectively for the treatment of VMS (see Figure 2). Studies of the efficacy of megestrol acetate for the prevention of VMS have been limited to breast cancer survivors. In a double blind, placebo-controlled randomized trial, patients receiving megestrol acetate, at a dose of 40 mg per day, showed an 85% reduction in VMS, as compared to a 21% reduction in the placebo group. In a randomized placebo controlled trial, Goodwin et al. compared megestrol acetate (MA) 20 mg or 40 mg with placebo as treatment for VMS over 6 months in patients with a history of breast cancer [36]. Patients were randomly assigned to placebo, MA 20 mg or 40 mg for 3 months. Success at 3 months was defined as completion of treatment with ≥75% reduction in VMS from baseline. Success at 3 months was 14% on placebo, 65% on 20 mg MA, and 48% on 40 mg MA [36] concluding that MA with either dose is significantly more effective than placebo in controlling VMS.

Treatment with MPA was reported to control VMS as effectively as estrogens in two studies [37]. In one study, 43
women who had undergone a natural (n=8) or surgical menopause (n=35) were randomized to receive either 0.625 mg of CEE or an intramuscular injection of 150 mg of depo-medroxyprogesterone acetate (DMPA) for 25 days each month [38]. VMS decreased significantly in both groups, and this reduction was of a similar magnitude with either treatment after 3 months of therapy. VMS decreased 61.5 ± 7.5% with conjugated estrogens and 69.4 ± 7.7% with DMPA [38]. In the randomized double blind parallel group controlled trial, oral CEE (0.5 mg/day; n=18 patients) and MPA (10 mg/day; n=20 patients) were compared for their effects on VMS for duration of 1 year. Their results showed that MPA and CEE were equivalent and effective in the control of the number of VMS immediately following premenopausal ovariectomy [39].

Micronized progesterone is molecularly identical to human progesterone. A 2012 placebo-controlled randomized clinical trial compared oral micronized progesterone with placebo for the treatment of postmenopausal VMS [40]. Participants (ages between 44 and 62) were randomized to progesterone 300 mg once a day at bedtime (n = 68) or placebo (n = 46) and followed up to 12 weeks and they recorded daily frequency and severity (1-4) of VMS in the Daily Menopause Diary. The VMS scores of women taking progesterone were better than placebo with mean VMS score reductions of 10.0 (95% CI, -12.0 to -8.1) and 4.4 (95% CI, -6.6 to -2.2) in the progesterone and placebo arms, respectively. This study showed that oral micronized progesterone is effective for treatment of VMS in early postmenopausal women [40]. Biodientical progesterone cream was also studied for the treatment of VMS as compared to the placebo but not to the gold standard estrogen. Evidence from these studies does not support the efficacy of bioidentical progesterone cream for the management of VMS [41]..

Whereas progesterone use seems to be effective in alleviating VMS, the risk of breast cancer associated with progesterone use needs to be discussed with the patients. The 2010 endocrine society statement reveals that combined estrogen and progesterone therapy increases the risk of invasive breast cancer, which may occur within 3 to 5 years of initiation and rises progressively beyond that time [28].

Progesterone use may be associated with some side effects such as headache, depression, weight gain and irregular bleeding and sexual dysfunction [42]. The injectable MPA carries a black box warning stating that prolonged use of more than 2 years may cause loss of bone mineral density [42]. Based on the limited available data, the use of other forms of progesterone has not been associated with any significant loss of bone mineral density [37-43].

**Selective Estrogen Receptor Modulators (SERMs) and Tissue-Selective Estrogen Complexes (TSECs):** An ideal hormone therapy would reduce the number and severity of VMS, effectively treat vulvovaginal atrophy and its symptoms, prevent and treat menopausal osteoporosis, and have favorable effects on lipoprotein profiles, while at the same time would not stimulate the endometrium, not cause uterine bleeding, not increase the risk of vascular events, not be associated with breast pain or tenderness, and potentially reduce breast cancer incidence [44].

Femarelle (DT56a) is one of the selective estrogen receptor modulators. Nachtigal et al. recently investigated the effect of Femarelle on platelet function in 25 symptomatic postmenopausal women with normal clotting times and seven symptomatic women with shortened clotting times (<61 s) [45]. Those women were being treated for severe menopausal symptoms with Femarelle. All participants reported improved symptoms during the treatment period (8 weeks and 1 year follow up). Femarelle did not adversely affect platelet reactivity, as measured by Platelet Function Analyzer-100 closure times, in symptomatic thrombophilic postmenopausal women or normal controls therefore it may offer a new clinical choice for therapy of symptomatic postmenopausal women [45].

TSECs are the pairing of estrogen(s) with a selective estrogen receptor modulator (SERM). The goal of developing a TSEC is to provide the clinical benefits of each of its components with improved tolerability. This goal can potentially be achieved by the result of the different molecular and cellular activities of the treatment’s estrogen and SERM components [46]. Both estrogens and SERMs bind to estrogen receptors, eliciting a range of effects in different cell types and exhibiting tissue-dependent estrogen receptor agonist and antagonist activity, both alone and when combined [47-50]. The therapeutic profile of a TSEC would optimally include relief of VMS, treatment of vulvovaginal atrophy and its symptoms, and prevention of bone loss, while providing safety for the endometrium and breast [51].

Bazedoxifene, a SERM studied for the prevention and treatment of postmenopausal osteoporosis, [52] paired with conjugated estrogen (CE) represents a TSEC [46].

In SMART-2 study, 332 postmenopausal women were examined for VMS as a primary endpoint over 12 weeks (with at least 7 moderate-to-severe VMS/day or 50/week). Participants received bazedoxifene (BZA) 20 mg/conjugated estrogen (CE) 0.45 mg or 0.625 mg or placebo. At weeks 4 and 12, women taking BZA/CE had significant reductions from baseline in the mean daily number and severity of moderate to severe VMS compared with placebo at 4 and 12 weeks follow up (\(P < 0.001\)). The number of VMS was reduced by 74% for BZA 20 mg/CE 0.45 mg and 80% for BZA 20/CE 0.625 mg, whereas it was 51% for placebo and significant decreases in VMS frequency and severity with both BZA/CE doses compared with placebo were sustained until week 12 [53].

Overall BZA/CE may be a promising alternative to hormone therapy for the treatment of menopausal symptoms and prevention of osteoporosis in non-hysterectomized postmenopausal women [54]. Bazedoxifene/CE is not FDA approved yet.

**Tibolone:** Tibolone has been commonly used in Asia and Europe for the treatment of vasomotor symptoms, but is not approved by FDA [55]. In one study, after 12 weeks of treatment, around 80% of the women in tibolone group had no or only mild VMS, compared to 40% in the placebo group [56]. In 2010, 11 Asia Pacific countries developed recommendations for its use in Asian postmenopausal women, based on the evidence from clinical studies published since 2005 and the panel agreed that because it has specific effects in different tissues after conversion to three active metabolites (estrogenic, androgenic, progestogenic metabolites) following oral ingestion, there was a need for data
on the possible adverse effects of tibolone on the cardiovascular system and endometrial cancer in treatment patients [57]. In addition tibolone has been shown to increase the risk of stroke by two-fold in older women with osteoporosis [58]. Although the 2010 endocrine society scientific statement reported tibolone as an effective agent in alleviating VMS (level of evidence A), it has been associated with an increased risk of stroke in older women [28] and tibolone increases the risk of breast cancer recurrence in breast cancer survivors [59]. In a 2013 study, authors compared the effects of a continuous-combined regimen of low-dose hormone therapy versus tibolone and supplemental calcium/vitamin D3 (control) on quality of life in postmenopausal women with VMS. The patients were randomised into three groups: (a) daily treatment with 2.5 mg tibolone (n = 64), (b) 50 mg calcium carbonate + 200 IU vitamin D3 (Ca/Vit D3, n = 54) or (c) 1 mg estradiol + 0.5 mg norethindrone acetate (n = 56) for 12 weeks. Low dose hormone therapy was superior to tibolone and Ca/Vit D3 treatment for improvements in vasomotor symptoms [60].

A 2012 Cochrane review by Formoso et al. investigated the efficacy as well as short and long term effects of tibolone in postmenopausal women and concluded that there was evidence that treatment with combined HT is more effective in managing menopausal symptoms than with tibolone. Long-term safety of tibolone is concerning given the increase risk of stroke in women whose mean age is over 60 [61]. Currently, due to safety concerns with tibolone, it should not be used in the postmenopausal women [62]. Tibolone is not FDA-approved.

**Dehydroepiandrosterone (DHEA):** Dehydroepiandrosterone is a pro-hormone produced by the adrenal glands. It furnishes both estrogens and androgens. DHEA levels decrease following puberty. The circulating DHEA decreases dramatically during the perimenopausal period [62,63]. A prospective pilot trial was performed in 22 women and found a decrease in mean VMS scores of 50% and an improvement in quality of life related to VMS after 4 weeks of DHEA therapy [63]. Currently, there are no double blind RCTs comparing DHEA with ERT/MHT therefore its safety and efficacy is limited in the treatment of VMS.

**Isoflavones and other phytoestrogens:** Phytoestrogens include compounds that contain one or more phenolic rings (isoflavones, lignans, coumestanes) [64]. We separate the discussion of the use of phytoestrogens from botanicals because the phytoestrogens preparations available in the US are extracts subjected to manufacturing standards that offer high likelihood of reproducibility compared to other botanical products. Phytoestrogens are rapidly and extensively metabolized in the body, making identification of active compounds difficult; however, the active phytoestrogens and metabolites bind to ER-α [65] and -β [66] and this is considered to be their mechanism of action [65,67]. A substantial number of studies of phytoestrogens and isoflavones have been conducted and have not shown clear benefits over placebo for the treatment of VMS [68-70]. Recently publications have appeared indicating that an over-the-counter phytoestrogens-based preparations containing an ERα-selective compound(s) is effective against VMS but much less than estrogens [45,71]. In our experience, the effect is more strongly the amelioration of VMS than their cessation. Adverse event information provided in studies of phytoestrogens use is limited, and long-term side effects have not been well investigated [18]. Women using these estrogen receptor-active compounds should be followed in the same manner as women using ERT/MHT [62]. A Cochrane meta analysis included 30 RCTs investigating the efficacy of dietary soy, soy extracts, and red clover extracts (promensil) in the treatment of VMS [69]. There was no evidence of a difference in percentage reduction in VMS between study groups and placebo. There was a strong placebo effect in most trial with a reduction in frequency ranging from 1% to 59% with placebo. Although some of the individual studies in the meta analysis found that phytoestrogen treatments alleviated the frequency and severity of VMS when compared to placebo but most of these studies were of low quality and were underpowered [69]. In a single-center, 6-month, randomized, double blind, estrogen-controlled trial, Kaari et al. evaluated the effects of isoflavone on the climacteric symptoms in addition to other parameters in postmenopausal women. Seventy-nine women were randomly assigned to one of the two treatment groups: isoflavone (n=40) 300 mg of the standardized soy extract with a medium dose of 120 mg isoflavones/day as glycoside and aglycone (60 mg twice a day), or estrogen (n=39) one capsule of 0.625 mg CEE and other capsule with glucose 0.625 mg (placebo). After one month, there was a significant decrease in VMS. There was a decrease in the VMS (total score) of 2.8 times (p<0.01 compared to baseline) in estrogen group and 1.8 times (p<0.01 compared to baseline) in isoflavone group. There was also a significant improvement in VMS after the second month of treatment in the isoflavones group compared to the first month (p<0.05). Authors concluded that the daily standardized soy extract with 120 mg isoflavones’ effect on symptoms was similar to that from estrogen [72]. In a recent 2010 meta analysis including 19 studies, Bolanos et al. investigated whether intervention with soy (dietary, extract, or concentrate), as compared with placebo, reduces the incidence of VMS in climacteric women [73]. Although the overall combined results and the results by subgroups (according to the type of supplement used) showed a significant tendency in favor of soy, authors could not establish conclusive results given the high heterogeneity found in the studies [73]. Although one randomized double blind estrogen controlled trial showed that soy extract with 120 mg isoflavones’ effect on VMS was effective and similar to estrogen [72], most of the trials are small, of short duration and poor quality [69]. Some trials found a slight reduction in VMS with phytoestrogen-based treatment [69] but overall there is no strong evidence that phytoestrogens are more effective than placebo. In 2012, Eden et al. performed a systematic literature review and concluded that although the efficacy of isoflavones are slightly superior than placebo in some studies, the magnitude of effect is so small that it is not clinically significant and overall isoflavones are not clinically superior than placebo in the treatment of VMS.

**NONHORMONAL THERAPY**

Hormonal agents have been the predominant therapy for VMS, but their use decreased substantially following the shifts in risk-benefit ratios that were identified in the Women’s Health Initiative Estrogen plus Progestin RCT [74].

Nonhormonal treatment of postmenopausal symptoms is a
subject of great interest today. Although estrogen replacement is the most effective treatment for relief of VMS at present, it is contraindicated in about 10% of women with menopausal symptoms [75]. During the past few decades, several new agents on prescription have been used for the management of VMS such as clonidine, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and gabapentin (see Figure 3 and Table 1-3) for randomized controlled trials comparing the intervention group (nonhormonal) with ERT or MHT for the relief of VMS.

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs have been investigated for VMS treatment with mixed results [76-81]. Commonly used SSRIs are: fluoxetine 20 mg/day, paroxetine 5-12.5 mg/day, citalopram 20 mg/day and escitalopram 10-20 mg/d [80,81].

A large trial of paroxetine [82] showed a significant reduction (approximately 50–60%) in the frequency of VMS when used in the short term. In 2013, FDA approved low-dose mesylate salt of paroxetine (LDMP) at a dose of 7.5 mg/day for the treatment of moderate to severe VMS. Paroxetine mesylate is an orally administered psychotropic drug similar to paroxetine hydrochloride [83]. Paroxetine mesylate is FDA-approved for the treatment of major depressive disorder, obsessive-compulsive disorder, generalized anxiety disorder, and panic disorder at doses of 20 to 60 mg/d, depending on the indication [84]. LDMP was developed specifically for the treatment of moderate to severe VMS associated with menopause, at a dose of 7.5 mg once daily which is lower than that indicated dose for psychiatric disorders. LDMP’s phase 2 and 3 trial results have been presented at the 61st Annual Clinical Meeting of the American College of Obstetricians and Gynecologists (ACOG) in May 6, 2013 but the data has not been published as a manuscript yet. Based on the press release by the manufacturer in 2013, LDMP 7.5 mg once daily is both efficacious and well tolerated for the treatment of moderate to severe VMS and it is the only FDA approved nonhormonal agent for the treatment of moderate to severe VMS [85].

In addition to paroxetine, citalopram and fluoxetine are two other SSRIs and an RCT investigated the efficacy of citalopram and fluoxetine compared to placebo in the treatment of VMS. The initial dose was 10 mg of both fluoxetine and citalopram, and it was increased to 20 mg at 1 month and to 30 mg at the 6-month visit. Compared to placebo, citalopram and fluoxetine have little effects on VMS [77]. A phase III placebo controlled trial of three doses of citalopram for the treatment of VMS revealed that VMS scores and frequencies showed significant improvement citalopram over placebo, with no significant differences among doses. Reductions in mean VMS scores were 23%, 49%, 50% and 55% for placebo and 10, 20 and 30 mg of citalopram, respectively [80]. Kalay et al. evaluated the efficacy of citalopram on VMS and the combined effect of citalopram and hormone therapy (HT) on VMS in women inadequately responsive to MHT alone [78]. One hundred postmenopausal women were equally divided into four groups: 1) citalopram (10-20 mg), 2) placebo, 3) citalopram (10-20 mg) plus MHT (CEE 0.625 mg/d or estradiol 2 mg/d plus MPA 5 mg/d) or 4) placebo plus MHT. After 8 weeks of treatment, mean VMS scores improved significantly in all groups with reduction rates of 37% in group 1, 13% in group 2, 50% in group 3 and 14% in group 4 (group 1 vs. group 2: p=0.001; group 3 vs. group 4: p=0.001). In this study, citalopram was found to be an effective alternative treatment option to MHT [78].

Escitalopram is another commonly used SSRI and 2011 placebo-controlled RCT, evaluated its efficacy and tolerability [81]. Otherwise healthy women received 10 or 20 mg/d of escitalopram or a matching placebo for 8 weeks. 55% of women in the escitalopram group vs 36% in the placebo group reported a decrease of at least 50% in VMS frequency (p=0.09) at the 8-week follow up. These findings suggested that among healthy women, 10 to 20 mg/d of escitalopram provides a nonhormonal, off-label option that is effective and well tolerated in the treatment of VMS [81].

Some of the side effects of SSRIs include cardiovascular side effects (sinus tachycardia, prolonged QT intervals), increased risk of suicidal behavior, weight loss, headache, agitation [86,87].

Serotonin Norepinephrine reuptake inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs; such as venlafaxine, desvenlafaxine) were studied for the treatment of VMS [88]. A randomized, double blind, placebo-controlled trial of desvenlafaxine for the treatment of VMS included 567 postmenopausal women who were assigned to receive desvenlafaxine 100 mg or 150 mg daily or placebo. After 12 weeks, reductions in the number of VMS in the 100 mg, 150 mg, and placebo group were 60%, 66%, and 47%, respectively [28]. A double blind placebo-controlled RCT assessed the efficacy of venlafaxine at doses of 37.5 mg/d, 75 mg/d, 150 mg/d or placebo. After 4 week of treatment, median VMS scores were reduced 37%, 61%, 61% and 27% respectively [89]. Some of the adverse effects of SNRIs include nausea, dry mouth, dizziness and anxiety [90].

A double blind randomized controlled trial compared a single dose intramuscular injection of depomedroxyprogesterone acetate (MPA) 400 mg to oral venlafaxine 37.5 mg for 1 week followed by 75 mg daily (n=109 patients in each arm) [91]. During the sixth week after randomization, VMS scores were reduced by 55% in the venlafaxine arm as compared to 79% reduction on
In a 2012 double-blind, randomized, controlled trial including 35 sites in Europe, two sites in South Africa, and one site in Mexico, Bouchard et al. evaluated the efficacy and safety of desvenlafaxine (100 mg/d) compared to tibolone (2.5 mg/d) or placebo for menopausal vasomotor symptoms [92]. The primary endpoint was the reduction in the average daily number of moderate and severe hot flushes at weeks 4 and 12. At week 12, the reduction of the average daily number of moderate and severe hot flushes for desvenlafaxine was similar to placebo (p=0.92), although time to 50% reduction was significantly less than placebo (13 vs. 26 days, p = 0.006). The placebo effect was high (57%). Nausea was the most common adverse event with desvenlafaxine, was generally mild to moderate, and resolved within the first 2 weeks [92]. I that study, desvenlafaxine was not superior to placebo in relieving mild to moderate VMS during the study period of 12 weeks [92].

In terms of safety concerns, European Medicines Agency cited an increase in cardiovascular events and hepatotoxicity with desvenlafaxine compared to placebo in postmenopausal women [93,94]. Desvenlafaxine is FDA-approved for treating depression but not VMS in postmenopausal women [94].
Table 2: Randomized trials comparing intervention group with the ERT/MHT in the treatment of VMS.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Type of study</th>
<th>Comparison of groups</th>
<th>Main outcome measure</th>
<th>Follow up</th>
<th>Results and magnitude of effect</th>
<th>Author's conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy SY 2006</td>
<td>Randomized, double-blind trial</td>
<td>Conjugated estrogens vs. placebo vs. Gabapentin</td>
<td>0.625 mg/d of conjugated estrogens (n = 20, mean age=51.5±4.9) or Placebo (n = 20, mean age=52.2±4.2), or Gabapentin titrated to 2,400 mg/d (n = 20, mean age=51.2±4.4) for 12 weeks.</td>
<td>VMS composite score, which takes into account both severity and frequency of VMS</td>
<td>12 weeks</td>
<td>Reduction in the VMS composite score for both estrogen (72%, P = 0.016) and gabapentin (71%, P = 0.004) was greater than the reduction associated with placebo (54%)</td>
</tr>
<tr>
<td>Aguirre W 2010</td>
<td>Prospective single blind randomized study</td>
<td>Gabapentin 600 mg/night (n=23, mean age=48.3±2.3) or transdermal 25 μg/day estradiol per week (n=22, mean age=48.7±2.3)</td>
<td>Relief of VMS (percent reduction at the end of treatment)</td>
<td>8 weeks</td>
<td>Percent reduction at the end of treatment compared to baseline Gabapentin: 58.9% Estrogen: 70.1%</td>
<td>Gabapentin 600 mg was as effective as low-dose transdermal estradiol in controlling moderate to severe VMS in postmenopausal women</td>
</tr>
<tr>
<td>Newton KM 2006</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Black cohosh vs. Multibotanical with black cohosh vs. Multibotanical plus dietary counseling vs. CEE with or without MPA vs. placebo</td>
<td>Group 1: Black cohosh, 160 mg daily (mean age=52) Group 2: Multibotanical with black cohosh, 200 mg daily (mean age=52.2) Group 3: Multibotanical plus dietary soy counseling (mean age=52.5) Group 4: conjugated equine estrogen, 0.625 mg daily, with or without medroxyprogesterone acetate, 2.5 mg daily (mean age=52.3) or Group 5: placebo (mean age=52)</td>
<td>Relief of VMS compared to baseline in each group and difference among groups</td>
<td>1 year</td>
<td>Did not differ between the herbal interventions and placebo (P &gt; 0.05 for all comparisons). The difference for hormone therapy versus placebo was ~4.06% for the 6 months treatment period. If no difference was observed between hormone therapy and placebo, P &lt; 0.001.</td>
</tr>
<tr>
<td>Fisk 2008</td>
<td>Prospective single blinded randomized trial</td>
<td>Electroacupuncture (EA) vs hormone therapy</td>
<td>Acupuncture (30 min, 2 times weekly for first 2 weeks and 1 time weekly for 10 weeks, plus electrical stimulation [2 Hz, 4 points used, n = 23, mean age=56.5]) Hormone therapy (HT): sequential estrogen/progestagen, n = 18, mean age=53.4)</td>
<td>Relief of VMS (Mean frequency/day)</td>
<td>24 months</td>
<td>Within-group: P &lt; 0.05 during and after treatment in both groups. Intergroup: HT is more effective than EA, the P-value was not reported</td>
</tr>
</tbody>
</table>

**Table Notes**

- P value not reported. Significance determined by 95% confidence interval. No wash out period and drop-out rate not reported
- • Cal+D: Calcium plus vitamin D
- NS: Not statistically significant

Although some of the placebo controlled randomized trials comparing venlafaxine or desvenlafaxine with placebo showed superior effects of SNRIs, we need prospective randomized trials comparing the efficacy and safety of SNRIs to the gold standard estrogen to better determine the efficacy of these non-hormonal agents in the treatment of VMS.

We were unable to find any double blind randomized controlled trial studies comparing venlafaxine and desvenlafaxine with the gold standard estrogen for the treatment of VMS. Currently a study entitled “comparative efficacy of low-dose estradiol and venlafaxine XR for treatment of menopausal symptoms” is recruiting participants for the comparison of these two groups (clinicalTrials.gov identifier: NCT01418209).

Concerns have been raised regarding the interference of SSRIs with tamoxifen metabolism. Tamoxifen is mainly metabolized by CYP 3A and CYP 2D6 enzymes to the active metabolite endoxifen. Studies have shown that paroxetine and fluoxetine are very potent CYP 2D6 inhibitors, and so reduce endoxifen levels, whereas venlafaxine is the least potent inhibitor [95]. Therefore, at least for tamoxifen users, agents other than paroxetine and fluoxetine may be preferred [96] (See Figure 4 “Warnings”).

**Gabapentin**

Gabapentin is commonly used in the management of neuropathic pain and epilepsy; however, it is not FDA approved for the treatment of menopausal VMS. A RCT involving women...
Table 3: Randomized trials comparing intervention group with the ERT/MHT in the treatment of VMS.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Pinkerton JV 2009</td>
<td>Multicenter double blind Randomized, placebo-controlled trial of 12 week duration</td>
<td>BZA 20 mg / CE 0.45 mg (n=122, mean age:53.5 ) BZA 20 mg / CE 0.625 mg (n=125, mean age:53 ) Placebo (n = 63, mean age: 53.6)</td>
<td>Change from baseline in the average daily number and severity of moderate and severe VMS</td>
<td>At 4 and 12 weeks</td>
<td>At weeks 4 and 12, women taking BZA/CE (74% for BZA 20 mg/CE 0.45 mg and 80% for BZA 20/CE 0.625 mg) had significant reductions from baseline in the mean daily number and severity of moderate to severe VMS compared with placebo at 4 and 12 weeks follow up</td>
<td>E2/NETA 20 mg paired with CE 0.45 mg or 0.625 mg is effective with short term safety for treating VMS in postmenopausal women</td>
</tr>
<tr>
<td>Polisseni AF 2013</td>
<td>Prospective randomized double blind hormone therapy controlled trial of 12 week duration</td>
<td>2.5 mg tibolone (n=42, mean age:51) 50 mg Ca/VitD3 (n=44, mean age:53) 1 mg E2/NETA (n=44, mean age:53)</td>
<td>Quality of life and Improvement of VMS</td>
<td>12 weeks</td>
<td>The tibolone group exhibited better sexual function compared with the E2/NETA and Ca/VitD3 groups. E2/NETA was superior to tibolone and Ca/Vit D3 treatment for improvements in vasomotor symptoms</td>
<td>E2/NETA exhibited a superior response for vasomotor symptoms compared to tibolone</td>
</tr>
</tbody>
</table>

P value not reported. Significance determined by 95% confidence interval. No wash out period and drop-out rate not reported
• Cal+D: Calcium plus vitamin D
NS: Not statistically significant

Possible acute liver disease with black cohosh use.
Paroxetine should be avoided in women receiving tamoxifen because it reduces the formation of one of the major tamoxifen active metabolites .
SSRIs must be used with caution in women with breast cancer receiving adjuvant tamoxifen therapy since SSRIs reduce the metabolism of tamoxifen to its most active metabolite, endoxifen.
MHT increases the risk of invasive breast cancer, which may occur within 3 to 5 yr of initiation and rises progressively beyond that time
Gabapentin may increase the risk of suicidal thoughts or behavior
Desvenlafaxine may be associated with increase in cardiovascular events and hepatotoxicity

Figure 4: Warnings.

without a history of breast cancer examined the efficacy of gabapentin for the treatment of VMS [97]. Gabapentin at 900 mg per day was associated with a 45% reduction in VMS frequency and a 54% reduction in VMS composite score (frequency and severity combined into one score) from baseline compared with 29% for placebo [97]. Reddy et al. performed a randomized, double blind, placebo-controlled trial to assess the efficacy of estrogen and gabapentin in the treatment of moderate-to-severe VMS [98]. Participants were randomly assigned to receive either 0.625 mg/day of CEE (n = 20), placebo (n = 20), or gabapentin titrated to 2,400 mg/day (n = 20) for 12 weeks. The reduction in the VMS composite score for both estrogen (72%, P = .016) and gabapentin (71%, P = .004) was greater than the reduction associated with placebo (54%) at the conclusion of the 12th week. The extent of reduction in VMS composite score, however, was not significantly different between estrogen and gabapentin (P = 0.63). Although this was a small study, gabapentin appeared to be as effective as estrogen in the treatment of postmenopausal VMS at given doses [98].

In 2010, Aguirra et al compared gabapentin versus low-dose transdermal estradiol for treating postmenopausal women with moderate to very severe VMS [99]. A total of 45 postmenopausal women with moderate to very severe VMS were prospectively randomized to receive oral gabapentin (600 mg/d) or transdermal 25 μg/day estradiol per week. VMS intensity and frequency were assessed at baseline and at 1, 4 and 8 weeks. VMS intensity and frequency significantly decreased for both groups at 1, 4 and 8 weeks of treatment as compared to baseline. This decrease was statistically more evident for the transdermal estradiol group. Although the percentage of VMS intensity and frequency reduction at the end of the treatment was higher for estradiol, this was not statistically significant and both treatment options were effective in alleviating VMS (transdermal estradiol vs. gabapentin; 68.2% vs. 60.6% for intensity and 70.1% vs. 58.9% for frequency respectively) [99].

Gabapentin could be considered effective in the treatment of VMS and should be considered as a possible alternative when estrogen therapy is not desired however there are some concerns about its safety. Some of the side effects of gabapentin are dizziness, drowsiness and peripheral edema [100]. In 2008, the FDA issued a Public Health Advisory regarding the potential for any anticonvulsant, including gabapentin, to increase the risk of suicidal thoughts or behavior [94,101]. Therefore prospective clinical trials may be required to investigate not only the efficacy but also the safety of gabapentin in the treatment of VMS in postmenopausal women.

Clonidine

Clonidine is a α-adrenergic agonist agent. It may relieve VMS.
by reducing peripheral vascular reactivity [102]. It is usually given transdermally, starting with a patch that delivers 0.1 mg/day, which is left in place for one week. Clonidine also may be given orally in doses of 0.1 to 0.4 mg three times daily.

In a randomized, double blind, placebo-controlled clinical trial, Pandya et al. evaluated the effectiveness of oral clonidine (0.1 mg/d) compared to placebo for 8 weeks for control of VMS associated with tamoxifen therapy in postmenopausal women with breast cancer. The mean decrease in VMS frequency was greater in the clonidine group than in the placebo group after 4 weeks of treatment (37% compared with 20%). However the available evidence for its efficacy is contradictory. According to a meta-analysis including 10 randomized controlled trials, the severity of VMS was not improved in 6 of the 10 trials with clonidine [103]. Adverse events included dry mouth, insomnia and drowsiness, and occurred more commonly with clonidine, particularly at higher doses [103]. A 2011 double blind placebo-controlled RCT compared the average daily VMS scores among patients treated with venlafaxine 75 mg, clonidine 0.1 mg, or placebo daily for 12 weeks [104]. The reduction in VMS severity scores was similar between venlafaxine and clonidine group (41%) at 12 weeks of treatment and the reduction was significantly higher compared to the placebo group (29%) [104]. To the best of our knowledge, there are no double blind controlled trials comparing clonidine with ERT or MHT regarding its efficacy in the treatment of VMS.

Some of the common side effects of clonidine include difficulty sleeping, mouth dryness, constipation, itchiness (if used as a patch) and drowsiness [105].

**COMPLEMENTARY AND ALTERNATIVE NON-HORMONAL THERAPIES**

**Botanicals**

The findings of WHI study have contributed to the public’s growing interest in complementary and alternative approaches for the management of vasomotor symptoms. In general, research on these approaches is scant and research to date has focused primarily on botanicals, with a few studies of other approaches [103,106].

**Black cohosh (Actaea racemosa or Cimicifuga racemosa)**

In the English-language literature, there is little evidence that black cohosh is an effective treatment for VMS [107,108]. A 2009 randomized, double blind clinical trial compared black cohosh, red clover and placebo for the relief of VMS. 89 women were randomized to receive black cohosh 128 mg/day, red clover 120 mg/day, hormone therapy (625 μg estrogen and 2.5 mg MPA) or placebo. At the end of 12 months the reduction in VMS was 34% in the black cohosh group, 57% in the red clover group, 63% in the placebo group, and 94% in the hormone therapy group. Thus, neither red clover nor black cohosh significantly reduced VMS [109]. In a double blind placebo-controlled trial, Newton et al. tested the efficacy of 4 regimens (1- black cohosh 160 mg/d, 2- multibotanical with dietary soy, 3- multibotanical with black cohosh 200 mg/d, 4- CEE 0.625 mg/d with or without MPA 2.5 mg/d) compared to placebo for the relief of VMS with the follow up duration of 1 year [110]. CEE was associated with significant relief of VMS compared to any of the other groups. There was no difference between placebo and any of the herbal treatments over all of the follow-up points. Some cautions have been raised about possible adverse effects, such as acute liver disease and gastrointestinal side effects with black cohosh use (see Figure 4 “Warnings” box) [103,107].

**Dong quai root, Evening primrose oil, Kava kava, Ginseng root**

have not been shown to have any benefit for VMS relief [111]. The FDA has issued a warning to patients and providers about potential harm with kava kava [103].

**OTHER COMPLEMENTARY THERAPIES**

**Lifestyle changes, mind-body interventions**

Currently, there are limited data from observational studies that lifestyle modifications such as loose clothing, sipping cold drinks, avoiding spicy food, and keeping a lower room temperature can improve mild vasomotor symptoms [112,113]. A recent review of the literature on the efficacy of relaxation techniques such as yoga on VMS control concluded that most trials had positive results. However, the trials were heterogeneous, designed with small sample sizes and included a variety of interventions and outcome measures. Therefore, more large well-designed randomized estrogen-controlled trials are needed to further evaluate the efficacy of these various forms of relaxation techniques on VMS relief [62,114].

**Mind-body therapies; hypnosis, acupuncture**

VMS are often associated with anxiety and stress. Therefore, it has been proposed that hypnosis may act to reduce the frequency and intensity of VMS [62]. In a prospective study including sixty female breast cancer survivors, significant improvements in self-reported anxiety, depression, interference of VMS on daily activities, and sleep were observed for patients who received the hypnosis intervention compared to the no treatment group [115]. Further estrogen-controlled studies are needed to confirm these findings.

Acupuncture involves the use of thin needles inserted into specific points of the body. When electro-acupuncture (EA) was compared with hormone replacement therapy, hormone therapy was more effective than EA [116]. The evidence is not convincing to suggest acupuncture as an effective treatment for VMS in patients with breast cancer [116].

**Exercise**

There was no evidence from randomized controlled trials whether exercise is an effective treatment relative to other interventions or no intervention in reducing VMS in symptomatic women [117]. There are no randomized estrogen-controlled trials examining the efficacy of exercise in managing VMS.

**Stellate ganglion block (SGB)**

The stellate ganglion is present in only 80% of the population. In a recent study, 13 survivors of breast cancer (in remission) with severe VMS were treated with SGB at the anterolateral
aspect of the C6 vertebra. Patients recorded VMS in a daily diary by use of the Hot-Flash Score. The total number of VMS decreased from a mean of 79.4 per week before the procedure to a mean of 49.9 per week during the first 2 weeks after the procedure. This study suggested that SGB might provide survivors of breast cancer with relief from VMS and sleep dysfunction with few or no side effects [118]. We did not find any randomized clinical trials comparing SGB with ERT/MHT for the treatment of VMS.

“Bioidentical” hormone therapy

Bioidentical hormone therapy (BHT) is a confusing marketing term. It is most often used to describe custom-made hormone therapy formulations (called BHT) that are compounded for an individual according to a healthcare provider’s prescription [119]. Custom compounding pharmacies have made claims about the safety and effectiveness of BHT unsupported by clinical trial data and considered to be false and misleading [119]. BHT is not an evidence-based therapy and therefore is not included in detail in this review.

CONCLUSION

ERT/MHT is the most effective treatment for moderate to severe VMS and is a reasonable choice in the absence of contraindications. If the patient has not had a hysterectomy, estrogen with an added progestogen is recommended. The patient should be informed about the potential side effects and risks associated with hormone therapy. The lowest dose of estrogen with the shortest duration that adequately controls symptoms should be used. Given the natural history of vasomotor symptoms, it is reasonable to try discontinuing hormone therapy every 6 to 12 months. If symptoms recur, restarting and then gradually tapering the dose or the number of days per week that hormones are used may be helpful (see Figure 1 “Useful Tips” box) [6].

If estrogen use is not desired or contraindicated, paroxetine 7.5 mg daily is an option as the only FDA approved nonhormonal agent for the treatment of moderate to severe VMS. Several therapeutic agents such as gabapentin, clonidine, SSRIs, SNRIs, have been shown to have a mild to moderate effect on reducing VMS. A 2010 Cochrane review including 16 randomized controlled trials showed that Clonidine, SSRIs, SNRIs, gabapentin and relaxation therapy showed a mild to moderate effect on reducing VMS in women with a history of breast cancer [120]. Evidence for the efficacy of phytoestrogens is limited, because of the small number of trials and their methodological deficiencies, but overall suggests that phytoestrogens were not more effective than placebo in the relief of VMS. Black cohosh is currently not recommended due to the possible side effects such as acute liver failure [109] (see Figure 5 “Key Evidence” box). Although many women prefer these alternative treatments in a belief that they are safe, since they are sold over the counter, data on adverse effects are inadequate to draw conclusions (see Figure 4 “Warnings”). There are safety concerns with gabapentin regarding the increased risk of suicidal thoughts or behavior and desvenlafaxine which might be associated with increased risk of cardiovascular events and hepatotoxicity (see Figure 4, “Warnings”) which require confirmation with future studies. NAMS suggested limited evidence with relaxing therapies such as yoga, massage, mediation, leisure baths, and slow breathing techniques, mind-body therapies such as hypnosis, acupuncture and exercise [8]. A new approach to hormone therapy is combining a SERM with one or more estrogens or TSECs. An optimal TSEC will reduce VMS, increase bone mass density, and have favorable effects on vaginal cytology and symptoms without unfavorable effects on breast and endometrium [44]. Future studies on TSECs may be a promising option for the treatment of VMS in postmenopausal women.

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