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EMAS position statement: Non-hormonal management of menopausal vasomotor symptoms

Gesthimani Mintziori[a], Irene Lambrinoudaki[b], Dimitrios G. Goulis[a,*], Iuliana Ceausu[c], Herman Depypere[d], C. Tamer Erel[e], Faustino R. Pérez-López[f], Karin Schenck-Gustafsson[g], Tommaso Simoncini[h], Florence Tremollieres[i], Margaret Rees[j]

[a] Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Greece
[b] Second Department of Obstetrics and Gynecology, Medical School, National and Capodestrian University of Athens, Greece
[c] Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, and Department of Obstetrics and Gynecology, 'Dr. I. Cantacuzino' Hospital, Bucharest, Romania
[d] Breast Clinic and Menopause Clinic, University Hospital, De Pintelaan 185, 9000 Gent, Belgium
[e] Department of Obstetrics and Gynecology, Istanbul University, Cerrahpasa School of Medicine, Valikonagi Cad. No: 93/4, Nisantasi, 34365 Istanbul, Turkey
[f] Department of Obstetrics and Gynecology, Zaragoza University Facultad de Medicina, Hospital Clínico, Zaragoza 50009, Spain
[g] Department of Medicine, Cardiology Unit and Head Centre for Gender Medicine, Karolinska Institutet and Karolinska University Hospital, Thorax N3:06, SE 17176 Stockholm, Sweden
[h] Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56100 Pisa, Italy
[i] Menopause and Metabolic Bone Disease Unit, Hôpital Paule de Viguier, F-31059 Toulouse cedex 09, France
[j] Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

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ABSTRACT

Aim: To review non-hormonal therapy options for menopausal vasomotor symptoms. The current EMAS position paper aims to provide to provide guidance for managing peri- and postmenopausal women who cannot or do not wish to take menopausal hormone therapy (MHT).
Material and methods: Literature review and consensus of expert opinion.
Results: Non-hormonal management of menopausal symptoms includes lifestyle modifications, diet and food supplements, non-hormonal medications and application of behavioral and alternative medicine therapies. There is insufficient or conflicting evidence to suggest that exercise, supplements or a diet rich in phytoestrogens are effective for vasomotor menopausal symptoms. Selective serotonin-reuptake inhibitors (SSRIs), serotonin norepinephrine-reuptake inhibitors (SNRIs) and gabapentin could be proposed as alternatives to MHT for menopausal symptoms, mainly hot flushes. Behavioral therapies and alternative medicine interventions have been tried, but the available evidence is still limited.
Conclusions: A number of interventions for non-hormonal management of menopausal vasomotor symptoms are now available. For women who cannot or do not wish to take estrogens, non-hormonal management is now a realistic option.

1. Introduction

Menopausal symptoms include vasomotor (hot flushes, night sweats), psychological (anxiety, irritability, depression, sleep disorders, decreased quality of life), urogenital (dryness, dyspareunia, increased urinary frequency), as well as general symptoms (fatigue, headaches, arthralgia). They tend to intensify during the perimenopause and subside within 5 years after the final menstrual period [1]. In some women frequent vasomotor symptoms may last for more than 7 years [2].

Menopausal Hormone Therapy (MHT) for menopausal symptoms includes use of estrogens, alone or in combination with a progestogen, tibolone or a combination of estrogens and selective estrogen receptor modulators (SERMs) [3–6]. While MHT is the most effective treatment for menopausal vasomotor symptoms it is not indicated for all women, such as those with a personal history of breast cancer [3].

The importance of the treatment of hot flashes was underlined by a recent study involving more than 250,000 American women with untreated menopausal vasomotor symptoms [7]. According to

* Corresponding author at: Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, "Papageorgiou" General Hospital, Ring Road, 54601 Nea Efkarpia, Thessaloniki, Greece. Tel.: +30 2310 693131; fax: +30 2310 991510.
E-mail address: dimitrios.goulis@otenet.gr (D.G. Goulis).

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this study, untreated menopausal vasomotor symptoms are associated with significantly higher frequency of outpatient visits and incremental direct and indirect costs. However, women tend not to seek treatment for menopausal vasomotor symptoms, even when symptoms significantly impact their daily function.

The current EMAS position statement reviews non-hormonal therapy options for menopausal symptoms and aims to provide a clinically useful tool for managing peri- and post-menopausal women who cannot or do not wish to take MHT.

2. Non-hormonal management of menopausal symptoms

The options include lifestyle modifications, diet and food supplements, non-hormonal medications, and behavioral and alternative and complementary therapies.

2.1. Lifestyle modifications and diet

Data on the impact of physical exercise on the severity or frequency of menopausal symptoms are conflicting. It has been proposed that exercise can decrease vasomotor menopausal symptoms [8]. However, most of the studies that have reported a positive effect of exercise on menopausal symptoms are observational. According to a recent Cochrane systematic review that only involved randomized control trials (RCTs), there is insufficient evidence to suggest a positive effect of exercise on vasomotor menopausal symptoms, when studied alone or compared with MHT or yoga [9]. This is confirmed by other studies as well [10] and a recent RCT involving 261 women randomized into three groups (two exercise and one control) failed to show effectiveness for hot flushes or night sweats [11]. Well-conducted RCTs are needed to confirm or to refute a positive influence of exercise on menopausal symptoms. On the other hand, moderate exercise in peri- and postmenopausal women has been linked to a better quality of life (QoL), improved cognitive and physical function and a significant reduction in all-cause mortality [12,13].

Soy isoflavones, coumestans and lignans are all phytoestrogen supplements that have been proposed as alternatives to MHT for vasomotor symptoms. Phytoestrogens are found in soybeans (isoflavones), hops (*Humulus lupulus*) [14,15], flaxseed (lignans), fruits, vegetables, whole grains and legumes. All these compounds have been suggested to have estrogenic or anti-estrogenic activity in humans [16]. Extracted or synthesized soybean isoflavones have been found to reduce hot flush frequency and severity [17]. However, a recent meta-analysis found that no there is no conclusive evidence that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats in perimenopausal or postmenopausal women, although benefits derived from concentrates of genistein should be further investigated [16,18]. It has been suggested that *8-pregnylnaringenin* (8-PN), a flavonoid extracted from hops, may improve vasomotor complaints. However, evidence is not conclusive [14,15,19].

Herbs such as black cohosh, St. Johns wort, gingseng, gingko biloba and dong quai have all been studied. However, evidence of efficacy and safety are conflicting [20]. A recent Cochrane review on the use of black cohosh, involving 16 RCTs and 2027 women failed to prove its efficacy in reducing menopausal symptoms, when compared with placebo, hormone therapy, red clover and fluoxetine [21].

2.2. Non-hormonal pharmacological interventions

Selective serotonin-reuptake inhibitors (SSRIs) and serotonin norepinephrine-reuptake inhibitors (SNRIs) have been proposed as alternative to MHT for hot flushes. SSRIs, such as paroxetine, escitalopram, citalopram and sertraline have been studied and are effective in decreasing both frequency and severity of hot flushes [22]. Of the SSRIs, paroxetine seems to have the best evidence base of efficacy [23–25] and was recently approved by Food and Drug Administration (FDA) for the treatment of menopausal hot flushes [26]. SNRIs (venlafaxine, desvenlafaxine) have been used to treat menopausal symptoms, mainly in women in whom MHT is contraindicated [27–29].

Several studies have assessed the use of gabapentin, a gamma-aminobutyric acid (GABA) analog, to improve menopausal symptoms. A meta-analysis found that gabapentin is effective in decreasing hot flushes (menopausal or tamoxifen-induced) [30]. However, there was a high level of heterogeneity across the studies as well as high dropout rates in the gabapentin treatment groups due to adverse events such as dizziness and fatigue. In a randomized, double-blind, placebo-controlled trial involving 197 women, hot flushes were decreased by 51% in women taking gabapentin and adverse effects that were initially observed (dizziness, unsteadiness, drowsiness) returned to baseline levels after 4 weeks of treatment [31]. Another study comparing gabapentin with low-dose transdermal estradiol demonstrated that both therapies decreased hot flushes, with estradiol achieving greater hot flush reductions in the first 8 weeks, though at the end of the study there was no clinical difference between the two interventions [32]. In a phase 3 RCT, Pinkerton et al. assessed 600 women. They showed significant reductions in hot flush frequency and severity in women treated with gastroretentive gabapentin. However 5% more women taking gabapentin withdrew because of adverse events, compared to those receiving placebo [33].

Pregabalin, like gabapentin, is another compound that binds to the $\alpha_2\delta$ (alpha-2-delta) subunit of voltage-dependent calcium channels and has been tested as an option to treat menopausal hot flushes [34,35]. A phase III, double-blind RCT has shown that pregabalin, at a dose of as low as 75 mg twice daily, can decrease hot flushes [34]. Veralipride, a benzamide neuroleptic drug, has been used in some countries to control menopausal vasomotor symptoms and seems to be a safe option [36].

Alpha-2 agonists, mainly clonidine, have been used to treat hot flushes. Clonidine is approved for the treatment of menopausal flushes in some countries, as it seems that it can reduce the occurrence of hot flushes after 3 months of use [37]. Beta-blockers have also been suggested, in an effort to reduce palpitations and anxiety, though their impact on hot flushes or insomnia is limited [38].

It has been suggested that stellate ganglion blockade (SGB) could improve menopausal symptoms. In a small study, SGB was found to be more effective than pregabalin [35]. However, studies have had disparate results [39]. In a randomized sham-controlled trial no significant differences were found between the treatment group and the sham-group regarding vasomotor symptoms frequency [40].

2.3. Behavioral therapies

Cognitive-behavioral, behavioral, and mindfulness-based (CBBMB) therapies have been used to deal with menopausal symptoms, mainly depression [41] though evidence is limited [42]. Telephone-guided self-help cognitive behavioral therapy seems to have a positive influence on menopausal symptoms [43]. Interventions that include relaxation and yoga have also been assessed for the treatment of menopausal symptoms; however the results are inconsistent [44]. A meta-analysis that assessed four studies failed to show that relaxation techniques can be effective in treating menopausal vasomotor symptoms [45].

2.4. Alternative and complementary medicine

A meta-analysis of 12 studies that evaluated the effects of acupuncture on hot flushes, menopausal symptoms, and QoL in

women in natural menopause demonstrated that acupuncture improves menopausal symptoms, the frequency and severity of hot flushes and quality of life [46]. Similarly, an earlier Cochrane review had demonstrated that although less effective than MHT, acupuncture has better results in decreasing menopausal vasomotor symptoms compared with placebo [47]. Paced respiration has been also tried as an intervention for hot flushes, however its efficacy has not been demonstrated [48]. Other alternative medicine technologies, such as chiropractic intervention or hypnosis have also been used in an effort to reduce menopausal symptoms; however, the evidence is limited [49,50].

A randomized control trial assessing the use of individualized oral homeopathic medicine has failed to show significant differences between the groups, though significant improvements were noticed in both groups, perhaps due to the effect of the consultation alone [51].

3. Conclusion

Non-hormonal management of menopausal symptoms includes lifestyle modifications, diet and food supplements, non-hormonal medications, and application of behavioral and alternative medicine therapies. While some are effective, for others the evidence is inconclusive. However, for women who cannot or do not wish to take estrogens, non-hormonal management is now a realistic option.

Contributors

G.M., I.L. and D.G. prepared the initial draft, which was circulated to EMAS board members for comment and approval; production was coordinated by M.R., G.M. and D.G.

Competing interests

The authors have no conflicting interests to declare.

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