Nonpharmacological treatment of postmenopausal symptoms

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Key content
• Menopause is associated with an increase in vasomotor, genitourinary, and musculoskeletal symptoms as well as sleep and mood disturbance.
• Menopause is also associated with an increased risk of cardiovascular disease and osteoporosis.
• While pharmacological agents are available to treat postmenopausal symptoms, many nonpharmacological options are also available.

Learning objectives
• To review the current nonpharmacological agents that are available for the treatment of postmenopausal symptoms.
• To review nonpharmacological options for prevention of diseases that occur at an increased incidence after menopause.

Ethical issues
• While hormone replacement therapy is highly effective in the treatment of postmenopausal symptoms, it is associated with health risks and is not considered first-line treatment.
• Nonpharmacological therapies, including herbal agents, have emerged as options in the treatment of postmenopausal symptoms and are commonly used by postmenopausal women. However, herbal agents are not regulated in many countries, and therefore the contents of a given product varies from sample to sample.

Keywords: atrophic vaginitis / hot flushes / menopause / postmenopausal / vasomotor symptoms

Introduction

Menopause is clinically defined as amenorrhoea of 12 months’ duration after the final menstrual period. Menopause represents complete ovarian follicular depletion and the absence of estrogen secretion by the ovaries. The average age of menopause is 51.4 years. Tobacco use, nulliparity, and family history are associated with earlier menopause. Estrogen deficiency leads to the development of vasomotor, genitourinary, psychological and musculoskeletal symptoms as well as sleep disturbance (Table 1). Estrogen deficiency also leads to longer-term health issues such as a decrease in bone density and an increased risk of cardiovascular disease.

Vasomotor symptoms

The onset of vasomotor symptoms occurs in the perimenopausal state. Hot flushes begin as a sudden sensation of heat centered on the face and upper chest which rapidly becomes generalised. The sensation of heat lasts a few minutes, can be associated with profuse perspiration, and can be followed by chills and shivering. Symptoms result from inappropriate peripheral vasodilatation leading to rapid heat loss and a decrease in core body temperature, and shivering then occurs to restore the core temperature to normal.

Approximately two-thirds of postmenopausal women will experience hot flushes, with 10–20% experiencing severe

Table 1. Clinical manifestations of menopause

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Type of health issue</th>
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<tr>
<td>Vasomotor symptoms</td>
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<td>Memory and attention deficits</td>
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<td>Genitourinary symptoms</td>
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<td>Sexual dysfunction</td>
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symptoms. For most women, symptoms spontaneously resolve within a few years. However, one third of postmenopausal women will experience symptoms for up to 5 years, and 20% will have symptoms for up to 15 years.

Risk factors for developing hot flushes include higher body mass index, tobacco use, African American or Caucasian ethnicity, and surgically-induced menopause. For women with surgically-induced menopause, 90% experience hot flushes during the first year. Vasomotor symptoms appear to be less common in Asian women, which may be secondary to cultural differences with respect to reporting symptoms. Dietary factors may also contribute to the difference in risk as the Asian diet is higher in soy intake, and soy has been shown to be an effective treatment for hot flushes in some studies.

Hot flushes represent thermoregulatory dysfunction, thought to occur at the level of the hypothalamus in response to estrogen withdrawal. However, the exact mechanism of this dysfunction is unknown. Core body temperature is normal at the beginning of a flush but then falls below normal after, indicating rapid heat loss. Premenopausal women initiate mechanisms to dissipate heat when the core body temperature increases by 0.4°C. However, the thermoneutral zone is narrowed in women with vasomotor symptoms, and postmenopausal women initiate mechanisms to dissipate heat at lower increases in body temperature. Hot flushes may be initiated by endogenous central opioid peptide withdrawal, and estrogen has been shown to increase activity of this peptide. In an animal model in which hot flushes are induced by opiate withdrawal, estrogen administration eliminated such temperature changes.

**Pharmacological treatment options**

Hormone replacement therapy (HRT) is the most effective treatment of vasomotor symptoms, improving symptoms in 80–90% of women. The Women’s Health Initiative (WHI), a randomised, placebo-controlled trial evaluating the effects of hormone therapy in postmenopausal women, demonstrated that the risks of hormone replacement therapy outweigh its benefits. In the WHI, over 16000 postmenopausal women were randomised to receive either conjugated equine estrogen (CEE) with progesterone or placebo. The study was stopped early after 5.2 years, secondary to a statistically significant higher number of cardiovascular events, pulmonary embolisms, and breast cancers in the treatment arm. As part of the WHI, over 10000 postmenopausal women who had undergone hysterectomy were randomised to receive either CEE daily or placebo. This trial was also stopped early after 6.8 years secondary to a higher number of cases of stroke in the treatment arm. Given the older age of the WHI participants, the study results may not be valid for younger postmenopausal women. A secondary analysis of the WHI data, published in 2007, suggested that there was not an increased risk of cardiovascular events among menopausal women who were younger or who had recent onset of menopause. Furthermore, Fournier et al. published their study in 2008 which demonstrated that the risk of breast cancer among postmenopausal women receiving combination HRT varied significantly according the type of progestogen used. However, while this study was very large including over 80000 participants, interpretation of its data is limited as it was a prospective cohort study.

Because of its potential risks, HRT is not first-line in the treatment of most postmenopausal symptoms because other treatments that are equally or more effective are currently available. Nevertheless, HRT remains the most effective treatment of vasomotor symptoms, and vasomotor symptoms remain an indication for HRT use according to the Medicines and Healthcare products Regulatory Agency (MHRA) and the United States Food and Drug Administration (FDA). However, both the MHRA and US FDA advise prescribing the lowest dose for the shortest duration possible. Given the potential adverse events associated with HRT, other treatment options for vasomotor symptoms have emerged over recent years, including behavior modification, pharmacological agents, as well as herbal and complementary medicines.

Behaviour modification, when applicable, should be the first-line treatment for women with vasomotor symptoms. For women with mild symptoms, keeping the room temperature cool and dressing in layered clothing may provide adequate relief. Small studies have demonstrated that paced respiration, a relaxation-based method which consists of slow, rhythmic breathing, has a modest effect on hot flushes. Cigarette smoking has been associated with a higher risk of experiencing vasomotor symptoms, and the risk appears to be directly proportional to the number of cigarettes smoked. Exercise, while beneficial in other respects, has not been consistently shown to improve hot flush symptoms. Given the additional health benefits of regular exercise and tobacco cessation, both behavior changes should be encouraged as they may also improve vasomotor symptoms.

Data from randomised, placebo-controlled trials have consistently demonstrated a significant placebo effect of a 20–50% reduction in hot flush symptoms, highlighting the importance of a placebo arm in trials investigating treatment options for vasomotor symptoms. Conclusions from therapy trials that lack a placebo arm may therefore be limited. Several pharmacological agents have been shown to be effective in treating vasomotor symptoms. The most common agents used are clonidine, gabapentin, selective serotonin reuptake inhibitors, and venlafaxine. These agents have been demonstrated to reduce vasomotor symptoms at twice the rate of placebo in randomised, placebo-controlled trials.
Nonpharmacological treatment options
Approximately 50–75% of postmenopausal women will use nonpharmacological agents including vitamins and herbal medicines to treat their hot flushes. A randomised controlled trial of 120 women receiving 800 international units of Vitamin E daily demonstrated a modest benefit over placebo, with an average reduction of one hot flush per day.

Many herbal medicines have been studied in the treatment of vasomotor symptoms, and the degree of regulation of these products varies from country to country. In countries in which there is little or no regulation, the amount of active ingredient in a product may vary from sample to sample and may also include other additional herbal agents. The results of studies investigating the effect of a variety of botanicals on vasomotor symptoms are limited and conflicting. In addition, the use of products that are not chemically identical in different studies make comparisons among studies difficult. There are no consistent data to support the use of dong quai, evening primrose oil, ginseng, gingko biloba, chasteberry, kava kava, or wild yam in the treatment of vasomotor symptoms, and there have been several positive, as well as neutral, studies published on soy, red clover, and black cohosh. Of the complementary therapies, soy, red clover, and black cohosh have been the most heavily investigated.

Soy is the most common plant containing phytoestrogens; plant-based estrogens that bind to estrogen receptors. Newton et al. reviewed 16 randomised controlled trials investigating the effect of soy on hot flush symptoms. Eight trials demonstrated that soy was superior to placebo, and eight demonstrated that soy was comparable to placebo in the treatment of hot flushes. From the positive studies, the average reduction in symptoms with soy ranged from 25–55%, compared to an average reduction of 20–30% with placebo. Interestingly, most of the trials on soy (average length of 12 weeks, with a range of 4–52 weeks) were longer in duration than trials on pharmacological therapies (average length of 4–6 weeks, with a range of 4–36 weeks). Given the natural history of vasomotor symptoms, longer trials are more likely to demonstrate less of a treatment effect, therefore possibly underestimating the effects of soy.

There have been no adverse effects associated with soy. There are data to support the claim that phytoestrogens act like selective estrogen receptor modulators, binding to estrogen receptors and exerting estrogenic and antiestrogenic effects. However, the estrogenic and antiestrogenic effects may depend on the specific tissue and concentration of circulating endogenous estrogen. Therefore, phytoestrogens may cause potential harm in women with estrogen-dependent tumors and may also antagonise the antitumor effect of tamoxifen. Because of this potential harm, phytoestrogens are typically avoided in women who have a personal history of breast cancer, who are at high risk for breast cancer, or who are undergoing treatment with tamoxifen.

Red clover (Trifolium pretense) is a legume that also contains high amounts of phytoestrogens. Two meta-analyses have demonstrated that there is no statistically significant difference between red clover and placebo in treatment of vasomotor symptoms. There have been concerns about red clover altering platelet aggregation; however, a recent randomised controlled trial demonstrated that there were no significant adverse events with red clover taken daily for 1 year.

Black cohosh originates from the plant, Cimicifuga racemosa, which is native to the eastern United States and Canada. It has been used in Europe, particularly in Germany, to treat hot flushes for over 50 years. It is the active ingredient in standardised products which have been used in most clinical studies. Preparations of black cohosh may contain phytoestrogens and therefore should also be avoided in the same patient populations who should avoid soy and red clover. Several small randomised, controlled trials comparing black cohosh to placebo in the treatment of hot flushes have demonstrated conflicting results, but a large randomised, placebo-controlled trial of 1-year duration was published in 2006. A total of 350 women between 45 and 55 years old were randomised to one of five arms: 1) Black cohosh 160 mg daily, 2) a multibotanical containing 200 mg black cohosh daily, 3) the multibotanical plus dietary soy counselling, 4) CEE 0.625 with or without 2.5 mg progesterone daily, or 5) placebo. Fifty-two per cent of the women were perimenopausal. After 1 year of treatment, all three black cohosh treatment arms were comparable to placebo. Women in the hormone therapy arm had a statistically significant reduction in symptoms compared to the other treatment arms and placebo (59.7% vs. 0% reduction in symptoms beyond placebo, respectively). The authors concluded that black cohosh was not superior to placebo in the treatment of hot flushes.

Despite these results, it may still be reasonable to recommend the use of soy, red clover, and black cohosh given that:

- there are no significant adverse side effects associated with these agents as long as they are used in women who do not have a personal history of breast cancer, who do not have high risk of breast cancer, and who are not taking tamoxifen;
- there is a significant placebo effect found in all randomised, placebo-controlled therapy trials for vasomotor symptoms. Women would likely experience a placebo effect of a 20–30% reduction in symptoms with the use of black cohosh or red clover and possibly achieve an even greater reduction in symptoms with the use of soy.
There are limited data on the effect of other complementary therapies such as acupuncture, reflexology and magnetic therapy on vasomotor symptoms. Current, small studies demonstrate that their benefits are no greater than placebo in the treatment of vasomotor symptoms. Additional, larger studies in the future will help determine the efficacy of these complementary therapies in the treatment of hot flushes.

Sleep and mood disturbance

Vasomotor symptoms can disrupt sleep; however, insomnia is also common in postmenopausal women, even in the absence of vasomotor symptoms. Perimenopausal women also have a higher rate of mood symptoms, such as irritability, nervousness, and frequent mood changes, than do premenopausal women. It is also important to recognise that sleep disturbance can often contribute to and result from psychological symptoms.

Behaviour modification, such as regular exercise and decreasing alcohol intake, can improve sleep and mood disturbance. For women with vasomotor symptoms that interrupt sleep, the treatment of hot flush symptoms should be addressed. Psychotherapy has been shown to be effective for mood disturbance and is often underutilised. Studies have shown that the efficacy of antidepressant medications increases with the severity of depression and that antidepressants may have little or no benefit in people with mild to moderate depression. Therefore, psychotherapy, in addition to behaviour modification, should be recommended for psychological symptoms associated with menopause.

Postmenopausal women may also experience difficulties with memory and attention, and whether these symptoms are caused by estrogen deficiency is still unclear. Estrogen receptors are found in many areas of the brain important to cognition, but studies investigating the role of estrogen on cognition are conflicting. Some indicate that estrogen may maintain or enhance cognitive functioning, whereas others have demonstrated that estrogen has either no effect or adverse effects on cognition. Memory and attention difficulties, however, may result from sleep disruption secondary to vasomotor symptoms or from mood disturbance. Therefore, if women experience such cognitive symptoms in menopause, treating sleep and mood disturbance, if present, is an appropriate first-line approach.

Genitourinary symptoms

Estrogen deficiency results in atrophy of the vaginal epithelium. Symptoms of atrophic vaginitis include vaginal dryness, vaginal itching, and dyspareunia. Estrogen deficiency causes an increase in vaginal pH, resulting in an alteration of vaginal flora. These changes predispose postmenopausal women to urinary tract infections (UTIs). In addition, low estrogen levels result in atrophy of the superficial and intermediate layers of the urethral epithelium causing atrophic urethritis, diminished urethral mucosal seal, loss of compliance, and irritation. These changes predispose women to both stress and urge urinary incontinence.

Topical estrogen therapy improves symptoms of atrophic vaginitis and frequent UTIs as it thickens the vaginal epithelium and restores vaginal pH. Non-hormonal therapies, such as vaginal moisturisers and lubricants, may also improve symptoms of atrophic vaginitis. Vaginal moisturisers maintain hydration and relieve dryness; and they should be used on a regular, long-term basis. Moisturisers are available over-the-counter in the form of a gel or cream. Vaginal lubricants, which are also available over-the-counter, moisten the vaginal epithelium and therefore help to relieve dyspareunia. Vaginal lubricants should be used as needed and on a short-term basis. In addition, regular sexual activity increases blood flow to pelvic organs and decreases the symptoms of atrophic vaginitis, and therefore symptomatic women should be encouraged to continue regular sexual activity.

Postmenopausal women report low desire or arousal, which may be in part due to estrogen deficiency, and also in part due to the adverse effects of atrophic vaginitis on sexuality. A woman’s physical and emotional health, as well her relationship with her partner, has been shown to be key determinants of sexual satisfaction. A reasonable first-line approach is to recommend lifestyle changes including stress and fatigue reduction, relaxation techniques, increasing quality time with a woman’s partner, and bringing novelty to the sexual repertoire. Specific psychotherapeutic techniques such as sex therapy, couples therapy, and sensate focus, a series of exercises designed to help couples increase communication and intimacy, may also be helpful for some women.

For women with frequent UTIs, it is reasonable to advise postmenopausal women to consider behaviour changes such as postcoital voiding, increasing fluid intake, and consumption of cranberry juice to prevent UTIs. Despite the lack of efficacy in trials, these measures are often recommended to premenopausal women to prevent urinary tract infections as they are not harmful and may be beneficial to some women.

Pelvic muscle (Kegel) exercises are effective in the treatment of stress, urge, and mixed incontinence. The recommended regimen is three sets of exercises three to four times a week for a minimum of 15–20 weeks, with each set consisting of eight to twelve slow-velocity contractions lasting six to eight seconds each. For urge incontinence, bladder training has been shown to be an effective treatment modality and is often used in conjunction with Kegel
exercises. Biofeedback, in addition to bladder training or Kegel exercises, may also be helpful in some women.

**Musculoskeletal symptoms**

Many women experience musculoskeletal pain at the time of menopause. In some studies, up to 50% of postmenopausal women report joint pain. Estrogen receptors are present in the synovial tissue, and estrogen may play a role in cartilage homeostasis. A higher frequency of joint pain or stiffness in postmenopausal compared with premenopausal women has been demonstrated in some studies, but not in others. In an Australian study which followed over 400 women for 8 years, BMI and negative mood correlated with the severity and frequency of joint symptoms. It is unclear if these musculoskeletal symptoms are secondary to estrogen deficiency, as results of studies investigating the efficacy of HRT in the treatment of joint pain in menopausal women are conflicting. Weight loss may be helpful for symptomatic postmenopausal women who are overweight, and physical therapy may also improve symptoms, particularly in women with underlying osteoarthritis.

**Long-term health effects**

For women who experience postmenopausal symptoms, these symptoms typically begin at the menopausal transition, and some postmenopausal women may experience minimal symptoms. However, all postmenopausal women, regardless of the severity, presence, or absence of symptoms, will have increased risk of certain long-term health issues. Resulting from estrogen deficiency, these health issues primarily consist of an increased risk of cardiovascular disease and osteoporosis.

**Cardiovascular disease**

The risk of coronary artery disease in premenopausal women is low, except in women with significant cardiac risk factors. The postmenopausal state, however, is considered a cardiac risk factor, as the incidence of coronary artery disease increases after menopause. The mortality rate from coronary artery disease in women in their sixth decade equals that in men.

Risk factor modification is the mainstay of prevention of heart disease. Smoking cessation, blood pressure control, maintaining a normal lipid profile and blood sugar level, and regular exercise are essential to lowering the risk of heart disease. The United States Department of Health and Human Services recommends at least 150 minutes of moderate-intensity aerobic activity, such as brisk walking each week and muscle-strengthening exercises involving all major muscle groups on two or more days of the week for health risk reduction.

**Bone health**

Menopausal women are also at increased risk for osteopenia and osteoporosis, which increase the risk of bone fractures. As estrogen inhibits bone resorption, the estrogen-deficient state of menopause results in increased bone resorption and rapid bone loss. Bisphosphonate therapy is the first-line treatment for osteoporosis in most women and can be used for osteoporosis prevention in certain patients. For women with premature ovarian failure, HRT is the medication of choice for the prevention of osteoporosis.

Adequate calcium and vitamin D intake and behaviour modification have been shown to be effective in the prevention of osteoporosis and should be used in conjunction with pharmacological therapy in the treatment of the condition. The recommended intake of calcium and vitamin D is 1200 mg daily and 600–800 IU daily, respectively. A well-balanced diet, including adequate amounts of protein, vitamin K, magnesium, and phytoestrogens, has also been shown to improve bone strength. As bone mass increases in response to activities causing stress on a given bone, weight-bearing and strength-training exercises improve bone strength by increasing muscle mass. Weight-bearing exercises, such as brisk walking, jogging, and running, are beneficial as they provide impact-loading on the skeleton. Strength-training exercises can be done with resistance bands, free weights, and bar bells. Fall prevention is highly important as most osteoporotic fractures are precipitated by a fall. Improving muscle strength and balance, reducing fall hazards at home, and adjusting medication use are effective measures in reducing the risk of falls. Further behaviour modification strategies to improve bone strength include smoking cessation and limiting alcohol intake to seven or less drinks per week.

**Conclusion**

Menopause is associated with vasomotor, neuropsychological, genitourinary, and musculoskeletal symptoms as well as with bone loss and an increase in cardiovascular events. While hormone replacement therapy is very effective in the treatment of most postmenopausal symptoms, it is associated with health risks. Given these potential adverse health risks, many non-hormonal pharmacological agents as well as nonpharmacological agents have emerged as options in the treatment of postmenopausal symptoms. The use of non-pharmacological therapies is very common among postmenopausal women. As many as 50–75% of postmenopausal women use nonpharmacological options to treat vasomotor symptoms, which the majority of postmenopausal women experience, and therefore, it is important for healthcare providers to be aware of and
informed about the nonpharmacological therapies available for women who are experiencing postmenopausal symptoms.

Conflict of interest
None declared.

References