

# Non-hormonal management for menopause

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## ABSTRACT

Menopause is a physiological process, but for many women it is a difficult time due to vasomotor symptoms and symptoms related to the urogenital sphere.

The hormonal changes and biological disorders that occur have a negative influence on women's health and functionality, on their physique and mental health. In addition, many women associate menopause as a transition from middle age to old age, which is psychologically difficult to face.

Disturbing manifestations such as hot flushes, sleep disturbances, dyspareunia and decreased libido affect the quality of life of menopausal women and they must receive optimal therapy to help them get through this period more easily.

The most effective therapy for treating menopausal symptoms is hormone replacement therapy. However, this is contraindicated for some women and avoided by others. That's why efforts are continually being made to find alternative and complementary therapies for menopause. Doctors must also be prepared to offer psychological support to these women.

**Keywords:** menopause, hot flushes, non-hormonal therapy

## INTRODUCTION

Non-hormonal management for menopause includes non-hormonal drug therapy, non-pharmacological therapies, alternative and complementary therapies and topical non-hormonal therapy of vaginal atrophy (1).

Non-hormonal therapy is the treatment for menopausal symptoms that does not contain sex steroid hormones. Doctors should be familiar with safe and effective non-hormonal menopause treatment options, as many women request them. Treatment should focus on the symptoms that are most troublesome and that affect quality of life and may require different approaches to manage vasomotor symptoms, vaginal symptoms, and emotional distress (1,2).

## MENOPAUSAL HORMONE TREATMENT

The most effective therapy for treating menopausal symptoms is hormone therapy (MHT, Menopausal Hormone Treatment), but this is contraindi-

cated for some women and avoided by others. Breast cancer patients have more frequent vasomotor symptoms, and these are also more severe and persistent than in the general population (1). Systemic menopausal therapy has to be avoided after breast cancer, and non-hormonal treatment may be a necessary adjuvant. Most women experience a recurrence of vasomotor symptoms when they discontinue MHT (2), which may require treatment with non-hormonal approaches. Many of these women search for information to the internet or to friends and family for advice on menopausal management and are confused by the wide range of options. Differences between study populations, variations in outcomes, lack of studies directly comparing hormonal and non-hormonal treatments, and contradictions in guidelines regarding the indications and efficacy of non-hormonal treatments have complicated clinical management.

According to the guidelines of the Romanian Society of Obstetrics and Gynaecology, MHT is contraindicated in some cases (3).

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*Article History:*

Received: 9 November 2021

Accepted: 8 December 2021

### Absolute contraindications

Hormonal treatment should be contraindicated, even if women have intolerable hot flushes, for women with unexplained vaginal bleeding, active liver disease, active thrombosis/history of deep vein or pulmonary thrombosis, diagnosed cardiovascular disease, disseminated lupus erythematosus, breast cancer, women with current / history of malignant melanoma, history of stage  $\geq$  II endometrial cancer, or stage I with deep invasion or positive nodes; may be used in women with a history of stage I without endometrial or myometrial invasion.

### Relative contraindications

Since hormone therapy in menopause interferes with cardiovascular and liver pathology and increases the risk of breast neoplasia, the relative contraindications are active gallbladder disease, history of migraines, increased serum triglycerides, strong history of breast cancer (more than one case in first-degree relatives), history of fibroids, atypical ductal mammary hyperplasia.

Alternative medications to MHT for women with climacteric syndrome who do not want or have contraindications to MHT will be discussed below.

## NON-HORMONAL PHARMACOLOGICAL TREATMENT FOR VASOMOTOR SYMPTOMS

The development of new targeted treatments for vasomotor symptoms has been limited by insufficient understanding of the phenomenon underlying the mechanisms of production.

Selective serotonin and norepinephrine reuptake inhibitors, gabapentin, pregabalin and clonidine are drugs studied in randomized, double-blind, controlled clinical trials that have clinical evidence that they work to improve vasomotor effects.

### Serotonin selective reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs)

This class of antidepressant drugs are used in the treatment of major depression, other depressive disorders, anxiety and other psychiatric and psychological conditions.

SSRIs and SNRIs are effective non-hormonal inhibitors, effective alternatives for vasomotor symptoms (4), reducing the intensity and frequency of hot flushes by 20%-65% (5). Since hot flushes are thought to occur due to changes in thermoregulation induced by estrogen deprivation, with a consequent decrease in serotonin levels, SSRI- and SNRI-induced serotonin and noradrenaline receptor blockade may counteract this imbalance (6).

International guidelines and systematic reviews of randomised controlled trials recommend a selec-

tion of SSRIs and SNRIs for the non-hormonal treatment of vasomotor symptoms associated with menopause (7). However, NICE guidelines recommend that these pharmacological treatments should not be offered as first-line treatment for vasomotor symptoms only (8).

Selective serotonin reuptake inhibitors (SSRIs) used for menopausal symptoms are shown in table 1.

TABLE 1. SSRIs used in the treatment of hot flushes (9)

First-line in the treatment of hot flushes	Paroxetine 7.5-20 mg/day
	Escitalopram 10-20 mg/day
	Citalopram 10-20 mg/day
Second-line medication	Sertraline 25-100 mg/day
	Fluoxetine 20 mg/day

Selective serotonin-norepinephrine reuptake inhibitors (SNRIs) used in menopausal therapy are represented by the following, all of them being first-line medicines like Venlafaxine 37.5-150 mg/day, extended release, Desvenlafaxine 100 mg/day and Duloxetine 30-120 mg/day.

The most common complaints of patients with a history of breast cancer are vasomotor symptoms. Those taking tamoxifen as endocrine therapy or high-risk women taking tamoxifen for breast cancer risk reduction should avoid fluoxetine and paroxetine, as they affect the conversion of tamoxifen to its active metabolite, which may decrease its effectiveness (10). A randomised trial comparing venlafaxine (extended-release, 75 mg/day) with  $17\beta$ -estradiol (oral 0.5 mg/day) found that both treatments were associated with a statistically significant decrease of approximately 50% in the frequency of vasomotor symptoms after eight weeks of use (11). Estradiol improved quality of life at menopause (as measured by The Menopause-Specific Quality of Life (MENQOL-64) indicator) more than venlafaxine (12). Neither treatment affected sexual function over an eight-week treatment period and both significantly improved sleep quality compared to placebo. Estradiol, at this dose is effective for at least four years for vasomotor symptoms, but the long-term efficacy of venlafaxine is not known.

Desvenlafaxine is a metabolite of venlafaxine and reduces vasomotor symptoms for up to 12 months.

Side effects of SSRIs and SNRIs may include nausea, dizziness, dry mouth, nervousness, constipation, drowsiness and sexual disturbances.

All antidepressants should be started at the lowest dose for 2 weeks and then the standard dose can be started. To discontinue the drug in the same way, the lowest dose should be taken for 2 weeks before ending treatment (13).

## Gabapentin and pregabalin

Gabapentin and pregabalin are drugs used in epilepsy as anticonvulsants. The mechanism by which these drugs decrease the frequency of hot flashes is by binding to calcium channels located in the hypothalamus and consequently better modulate thermoregulatory activity (9). However, the mechanism of action is incompletely elucidated. These beneficial effects of gabapentin on hot flashes have been observed in healthy postmenopausal women as well as in patients with a history of breast cancer who have survived the disease (14).

Gabapentin is an antiepileptic agent, used as an anticonvulsant drug, but also for peripheral neuropathic pain (long-lasting pain caused by nerve damage) and postherpetic neuralgia. Although considered a gamma-amino butyric acid (GABA) analogue, gabapentin does not bind to GABA receptors nor does it affect neuronal uptake or GABA content. Gabapentin is also effective in the treatment of restless legs syndrome (15), a common menopausal disorder that may be responsible for poor sleep quality.

A systematic review of 13 randomised controlled trials including 1,714 women found that gabapentin (300 mg p.o. three times a day) reduced both frequency and severity of vasomotor symptoms in breast cancer survivors (10). At doses up to 900 mg/day gabapentin is generally well tolerated, but side effects depend on the dose, and may include drowsiness, dizziness and fatigue (16).

Another randomized, double-blind, placebo-controlled study was conducted in 197 postmenopausal women aged 45 to 65 years who experienced at least 14 hot flashes per week. These women received either gabapentin 900 mg per day or placebo for 4 weeks. In the group of women who received gabapentin, the percentage by which hot flashes decreased was 51% from baseline to week 4. Compared to the placebo group the reduction was 26%. In the first week, women receiving gabapentin reported drowsiness and dizziness compared to those taking placebo; however, symptoms improved by week 2 and returned to baseline levels by week 4 (17). No long-term studies are available on the efficacy of gabapentin on hot flashes.

Pregabalin is an anticonvulsant also used in neuropathic pain (pain in peripheral neuropathy), in the treatment of generalised anxiety disorder in adults and in restless legs syndrome (18).

Pregabalin is similar in structure to the neurotransmitter gamma aminobutyric acid (GABA) but has very different biological effects. Neurotransmitters are chemicals that allow communication between nerve cells. Exactly how pregabalin works is not fully understood, but it is thought to affect the way calcium enters nerve cells. It reduces the activ-

ity of some nerve cells in the brain and spinal cord, reducing the release of other neurotransmitters that play a role in pain transmission, epilepsy and anxiety states. A randomised controlled trial in 163 breast cancer survivors found that pregabalin (75 mg p.o. twice daily) contributed to a significant reduction in the severity and frequency of vasomotor symptoms (19).

## Clonidine

Clonidine is a centrally active  $\alpha$ -2 adrenergic agonist. It is an antihypertensive agent. Studies using doses of clonidine from 0.025 mg twice daily to 0.075 mg twice daily for oral dosing and 0.1 mg daily for transdermal dosing have reported significant results in reducing the frequency or severity of hot flashes.

A double-blind, randomized, placebo-controlled trial of clonidine (0.1 mg/day) versus venlafaxine (75 mg/day extended-release) versus placebo in 102 breast cancer survivors over a 12-week period showed that both clonidine and venlafaxine were superior to placebo in reducing vasomotor symptoms, and although venlafaxine worked faster, clonidine was more effective at 12 weeks (20). Side effects of clonidine include dizziness, orthostatic hypotension, headache, constipation, dry mouth and skin reactions to the transdermal patch (21).

## DIET AND FOOD SUPPLEMENTS/ NON-PHARMACOLOGICAL THERAPIES

Nature provides us with variants of phytoestrogens, the so-called natural estrogens. Examples are soy derivatives, black cohosh or cimifuga racemosa, maca or red raspberry leaf.

Randomised controlled trials of food supplement therapies reviewed concluded that phytoestrogens have a modest effect in relieving hot flashes and vaginal dryness, and no effect in improving night sweats (22). There is also some limited evidence from randomised controlled trials showing that isoflavones (soy) or black cohosh can relieve vasomotor symptoms, even night sweats (23). A recent 2017 study of 63 women showed that a combination of probiotics and isoflavones from red clover was superior to placebo and reduced the frequency of vasomotor symptoms by 4.3 hot flashes per day on average, compared to <1 per day with placebo (24). NICE guidelines recommend avoiding black cohosh and other isoflavones in breast cancer patients (25).

## Phytoestrogens

Phytoestrogens, due to their chemical structure, can exert estrogen-like actions in the body. Phytoes-

trogens are found in most plants, vegetables and fruit. Three main types of phytoestrogens are known: soy isoflavones (the strongest), coumarins and lignans. In the intestinal tract these substances are metabolised into compounds with weak estrogenic action.

In soybeans the two representative isoflavones are genistein and daidzein. Red clover (*Trifolium pratense*) is also rich in phytoestrogens. It contains at least four oestrogenic isoflavones. It appears that their mechanism of action is by binding to oestrogen receptors. However, the exact mechanism of action is not fully understood. Even so, these dietary supplements should be avoided by patients with estrogen-dependent cancers. In addition, the efficacy of isoflavones in the treatment of hot flushes is controversial.

Most studies have included isoflavones. Nelson conducted a meta-analysis of 17 randomised controlled trials. Six of these studies used an isoflavone from red clover versus placebo. Of the six studies, only one found a reduction in the frequency of hot flushes, but none of the studies found a reduction in the severity of hot flushes.

In the other 11, the substance studied was a soy-free isoflavone, also compared with placebo. Four studies showed an improvement in hot flushes after 3-4 months, two studies after 6 months, but after a short use interval of only 4-6 weeks the decrease was insignificant (26).

Other studies were also reviewed that could not demonstrate the role of phytoestrogens in significantly decreasing the frequency of phytoestrogen flushing (27). It should also be mentioned that placebo response varied widely in the studies reviewed, from one percent to 59%. The quality of these studies was low and therefore the results are implausible.

### **Black cohosh**

Black cohosh (*Cimifuga racemosa*) is a plant native to eastern North America. Although the active ingredients are unknown, it has estrogenic effects. Several studies using black cohosh versus placebo have been conducted and analysed and in none has it been conclusively confirmed to be effective in improvement vasomotor symptoms. However, many women, including breast cancer survivors, use black cohosh.

Some studies reviewed that used a daily dose of 40 mg with oral administration of black cohosh showed no significant difference between it and placebo in relieving hot flushes (28).

Others have shown a trend towards a reduction in vasomotor symptoms, but only in mild to moderate symptoms (29).

And another recent Herbal Alternatives for Menopause Trial (HALT) study, which compared black cohosh with placebo and estrogen replacement over a 12-month period, suggested that black co-

hosh was ineffective in relieving vasomotor symptoms (30).

### **Dong Quai/Angelica sinensis**

It has been used for thousands of years in traditional Chinese medicine as the most common herb used for “women’s problems“. It is considered the most effective female tonic with multi-purpose action. No evidence of estrogenic activity was found in the studies reviewed and it has a possibly carcinogenic, especially for skin cancers in relation to sun exposure (31).

### **Vitamin E**

Is known for its antioxidant properties, and recently it has also been shown that vitamin E can relieve both vasomotor symptoms and vaginal dryness specific to menopause. In a study that included 50 postmenopausal women who received a 4-week treatment with vitamin E (400 IU) followed by placebo, and vice versa, placebo followed by vitamin E, it was shown that hot flashes were reduced by two per day and a reduction in their severity in vitamin E patients (32).

### **Evening primrose oil**

It is a plant known for its multiple health benefits for women. Even though the exact mechanism of action is not fully understood evening primrose is a widely used product for the treatment of menopausal symptoms. It has proven effective in reducing depression, irritability, pain or tension in the breasts.

A study of 56 postmenopausal women compared a combination of evening primrose oil (2,000 mg/day) with vitamin E (10 mg/day) versus placebo and surprisingly showed a significantly greater reduction in daytime hot flushes in the placebo group than in the treatment group (33).

A detailed classification of over the counter and herbal therapies can be found in the North American Menopause Society’s 2015 position statement on non-hormonal management of vasomotor symptoms associated with menopause (34). The problem is that they are difficult to dose, product quantity, quality, safety and purity can vary from brand to brand or even from batch to batch of the same brand and there is no known maximum dose that increases the risk of breast and endometrial cancer.

## **ALTERNATIVE AND COMPLEMENTARY THERAPIES**

### **Cognitive-behavioural therapy (CBT)**

Cognitive-behavioural therapy is designed to help understand emotional and physical states, to manage feelings more effectively and to alleviate distressing symptoms.

It is based on the most recent studies in the field of health, which have shown that weekly sessions of cognitive-behavioural therapy help to reduce discomfort and manage emotions during the transition to menopause, without the risk of any negative effects as with drug treatment. Cognitive behavioural therapy (CBT) effectively reduced the impact of vasomotor symptoms in women with and without a history of breast cancer (35,36). The British Menopause Society and the North American Menopause Society recommend cognitive behavioural therapy as a highly effective non-hormonal treatment for menopausal symptoms (34).

### Lifestyle changes

One of the most important factors in combating menopausal symptoms is diet. Fruit and vegetables, which are rich in dietary fibre, play an important role in relieving menopausal symptoms. Weight loss may be also beneficial. Coffee should be replaced with green or black tea. Smoking should also be stopped to relieve hot flushes. It is also recommended to follow a number of rules concerning lifestyle changes: limiting alcohol consumption, dress appropriately in light, light-coloured cotton or silk clothing, maintaining a cool environment at home and at work and exercising regularly.

### Exercise

Exercise has a beneficial influence on the health of postmenopausal women, although the studies reviewed concluded that exercise does not improve vasomotor symptoms (37). Exercise however confers other health benefits. Women included in these studies had better sleep, fewer migraines, less depression and significantly lower blood fat levels.

### Acupuncture

Acupuncture is a traditional component of Chinese medicine in which thin needles are inserted into the skin at key points in the body to balance the flow of energy. Acupuncture is useful during menopause, especially in the treatment of emotional states: anxiety, withdrawal and depression, by producing endorphins, which may be responsible for the beneficial effects felt. A preliminary study has shown a significant reduction of more than 50% in hot flushes in healthy women treated with acupuncture or electroacupuncture (38). But a Cochrane review failed to confirm its effectiveness in reducing hot flushes in breast cancer patients (39).

### Aromatherapy

Essential oils frequently relieve menopausal symptoms. Essential oils of valerian, linden bloss-

om, jasmine or lavender are recommended to combat sleep disorders caused by menopause. Mint or thyme essences are recommended against hot flushes. They can be used in aromatherapy lamps or dissolved in bath water (40).

## OSTEOPOROSIS PREVENTION AND TREATMENT THERAPY

In the first period of menopause, loss of bone mass is marked by disturbances in the calcium balance. Thus, using measurements to determine total body calcium, it has been estimated that daily calcium loss is 200 mg in the first 3-4 years, after which it decreases to 45 mg per day in the next 5-10 years post menopause. Synthesis of the active metabolite 1,25-dihydroxyvitamin D decreases with declining renal function (at a glomerular filtration rate of 50-60 ml/min there is a 50% decrease in metabolite formation). Decreased calcium absorption with advancing age, associated with vitamin D deficiency, also induces secondary hyperparathyroidism, which increases bone resorption. Bone mass loss is high in the first year before onset of menopause and continues at a high level for another three years after onset (41).

MHT is not recommended as first-line therapy in the prevention and therapy of osteoporosis. Non-hormonal therapy for the prevention and treatment of osteoporosis in menopause includes selective estrogen-receptor modulators (SERMs) and bisphosphonates.

SERMs are orally administered non-hormonal substances that bind to estrogen receptors and can induce various estrogenic responses in tissues where receptors are present. SERM preparations include Raloxifene, 60 mg/day, oral. It acts on receptors in the bone, but not in the uterus or breast. An RTC study found that SERM derivatives increase vertebral and hip bone density by 2-3% and decrease vertebral (but not non-vertebral) fractures by 30-50% (3).

Bisphosphonates (alendronic acid, ibandronic acid, risedronic acid, zoledronic acid). These are associated with increased bone density and decreased risk of hip and vertebral fractures (by 40-50%) (3). Bisphosphonates inhibit bone resorption by decreasing osteoclast numbers, inhibiting osteoclast maturation and recruitment, their adhesion to bone and their lifespan.

Along with pharmacological treatment, risk factors can be reduced by diet and lifestyle modification like calcium supplementation (1,200 mg per day), vitamin D (800 IU per day) and protein – 1 g/ kg of body weight/day are recommended. Stop smoking and reduce alcohol consumption are also recommended.

## TOPICAL NON-HORMONAL THERAPY OF VAGINAL ATROPHY

Non-hormonal options for vaginal dryness are limited. Moisturisers contain mainly water and there is little evidence that these products lead to clinically significant improvements in vaginal symptoms. Moisturisers may cause local irritation, and this may be more pronounced with preparations where the osmolarity and pH differ from normal vaginal secretions. Non-hormonal vaginal preparations may also be recommended to increase vaginal trophicity, which include sodium hyaluronate, hyaluronic acid, bismuth, glycerin, collagen.

The treatment of coital vaginal dryness also has a wide range of vaginal lubricants. These are used during sexual activity to reduce friction. Lubricating gels can be water, silicone or vegetable oil-based (for example olive oil).

## CONCLUSIONS

Even though hormone replacement therapy is the most effective method for treating menopausal symptoms, for some women it is not a solution. Therefore, non-hormonal alternatives must be found that are effective and focus on the most upsetting symptoms. But their effectiveness must be based on serious and credible clinical studies. The following have proven effective: selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin and clonidine. Dietary supplements are less effective, although they are widely used. Complementary therapies play a positive role in the management of menopausal symptoms: cognitive-behavioural therapy, acupuncture and physical exercises.

*Conflict of interest:* none declared

*Financial support:* none declared

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