

Systematic Review

Hormone Therapy for Relieving Postmenopausal Vasomotor Symptoms: A Systematic Review

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Abstract

Background: Menopause is a critical phenomenon in women's life. After cardiac diseases, menopause is the second major cause of living with a disability in 45–60 year old women. The majority of women will experience bothersome vasomotor symptoms (VMS). Menopausal hormone therapy (MHT) is the most effective treatment for these symptoms. The objective of this review is to focus on hormone therapy for relieving postmenopausal vasomotor symptoms.

Methods: For this systematic review, we primarily explored 125 papers published about hormone therapy for VMS from 2001 to 2015 by searching with combinations of the keywords in various databases. Among those, 59 papers met the initial search criteria and among them, 9 papers were potentially retrievable and reviewed. All included studies used estrogen formulations in the management of VMS.

Results: Nine studies met all inclusion criteria. All studies assessed the effects of hormone replacement therapy on VSM. The results showed that low-dose oral and transdermal estrogen in all dose ranges were more likely than placebo to decrease the frequency of VMS. Indeed, the nanostructured formulation was safe and effective in relieving the symptoms of menopause. The mean daily decrease in the number of hot flashes from baseline was found in the studies.

Conclusion: MHT has a complex pattern. Understanding the natural history of VMS, and the risks and benefits of both hormonal therapies, helps to individualize management plans. Low-dose estrogen-based therapies can be the most effective regimens to relieve VMS. These medications can be used by different administration routes and formulations.

Key words: hormone therapy, menopause, vasomotor symptoms,

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Introduction

Menopause is a critical phenomenon in every woman's life.¹ Despite its categorization as a developmental process, the specific conditions of menopause turn women into a vulnerable group.² Menopause is commonly regarded as a women's second adulthood. The complexity of menopause is believed to affect the quality of life in women.³ According to the increasing trend, the aging population is growing in both developed and developing countries.⁴ Following medical advances and the consequent increase in life expectancy during the recent decades, more women reach menopause each year. Moreover, life expectancy has extended from 40 years at the beginning of the 20th century to 80–84 years in the third millennium.⁵ However, since such increases in life expectancy have not changed the average age of menopause, i.e. 51.5 years in the world and 48.2 years in Iran,⁶

women spend about one-third of their lives in pre- and postmenopausal stages.⁷ Therefore, from the beginning of the third millennium, researchers have paid growing attention to menopausal women.⁸ After cardiac diseases, menopause is the second major cause of living with a disability in 45–60-year-old women. As the ovaries stop working and estrogen levels decline, a woman will experience several complaints such as vasomotor instability, hot flashes, night sweats, mood swings, and sleep disorders. Long-term estrogen deficiency will also lead to life-threatening conditions including cardiovascular diseases and osteoporosis.⁷ The incidence of irritating vasomotor symptoms (VMS) is 60%–80% in postmenopausal women. Such symptoms are known to exert negative effects on women's quality of life.⁹ As VMS are caused by sudden discontinuation of estrogen provision, hormone replacement therapy (HRT) seems to be the most relevant treatment option.⁷

As women constantly seek appropriate pharmaceutical treatments for VMS, various methods have been developed to relieve such problems. While hormone therapy (HT) with either estrogen or progesterone is commonly considered as the most effective treatment for vasomotor symptoms,⁹ estrogenic therapy is useful in reducing menopausal symptoms like hot flashes, night sweats, insomnia and sexual disorder.¹⁰ Moreover, estrogens are effective in preventing the acceleration of bone turnover associated with menopause, and in reducing cardiovascular accident.^{11,12}

The Women's Health Initiative (WHI) was designed to determine the benefits and risks of HT taken for chronic disease prevention by predominantly healthy postmenopausal women. The study ended early, due to findings of increased risk of coronary

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heart disease, breast cancer and stroke in women receiving HT.¹³ Given the persistent confusion about the risks and benefits of hormone therapy since 2002 and the first publication from the WHI primary findings, women are increasingly motivated to find effective approaches to treat menopause symptoms.¹⁴ With publication of “Updated International Menopause Society recommendations on menopausal hormone therapy (MHT) and preventive strategies for midlife health”, a general consensus has been reached on HRT.¹⁵ Nowadays, women’s inability to adapt with menopausal symptoms are the most common cause for their visits to health centers.¹⁶ Therefore, it is necessary to develop effective interventions and treatments for vasomotor symptoms. The objective of this review is to focus on hormone therapy for relieving postmenopausal vasomotor symptoms.

Materials and Methods

Search strategy

For this systematic review, we primarily explored 125 papers published about hormone therapy for relieving vasomotor symptoms in postmenopausal women from June 2001 to May 2015, fulfilling eligibility criteria by searching in reliable databases such as Web of science, MEDLINE, Scopus, EmMBASE, CINAHL, Cochrane database, Google Scholar and the Iranian databases. Our research was restricted to material in either English or Persian. The main keywords used for the search included: menopause, vasomotor symptoms and hormone therapy. The search used Boolean operators OR, AND between main phrase. A search

strategy was built applying advanced search capability of the search engine.

Article selection

Studies were considered eligible and included if they dealt with steroidal hormone therapy for vasomotor symptoms. Only those articles were retrieved that had one of the first 3 keywords either in the title or the abstract. Results were restricted to observational studies, clinical guidelines, systematic reviews, and randomized control trials. Case reports and manuscripts without full text were excluded.

Quality assessment

These criteria included: method of sampling, definition of disease status, age range, possible correlates of disease and complications, study setting specification, inclusion and exclusion items specification, and data collection description.

Literature identified

Among 125 articles published on the study’s aim, 59 papers met the initial search criteria and among them, 9 papers were potentially retrievable and remained to be reviewed (Figure 1).

Results

After massive search with the selected key words, nine studies met all inclusion criteria. We excluded all papers without full texts or required details of study goals in the review. All studies assessed the effects of hormone replacement therapy on VSM.

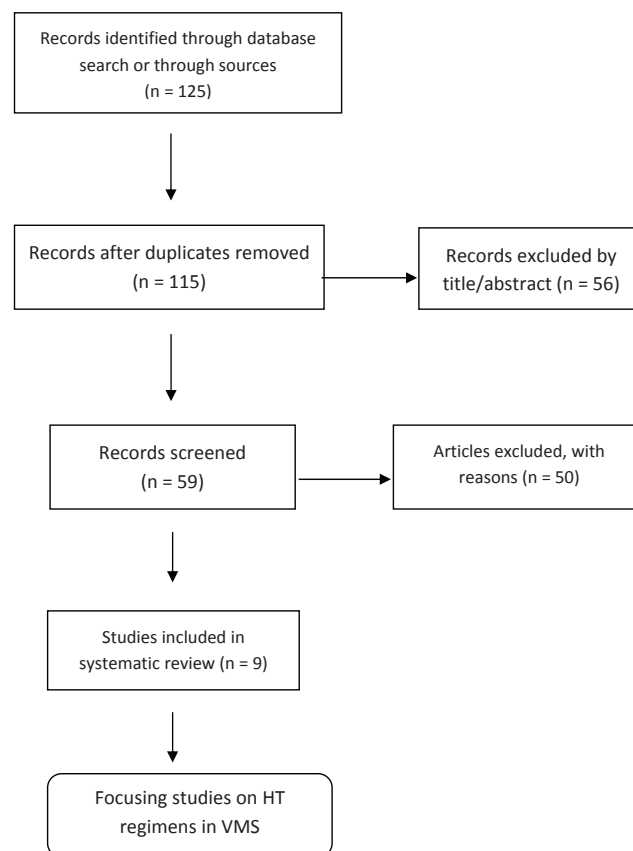


Figure 1. The algorithm of including studies in the systematic review.

The results showed that low-dose oral and transdermal estrogen in all dose ranges were more likely than placebo to decrease the frequency of VMS. Indeed, the nanostructured formulation was safe and effective in relieving the symptoms of menopause. The mean daily decrease in the number of hot flashes from baseline was found in the studies (all were significant at $P < 0.05$). Table 1 summarizes the characteristics of included studies separately.

Menopausal vasomotor symptom

The biological definition of menopause involves the absence of ovarian activity and menstrual cycles for 12 months.¹⁷ Vasomotor symptom commonly characterized by hot flashing is common among women worldwide with an incidence rate of 62% to 83%.^{18,19} This manifestation is a collection of several symptoms such as intense heat sensation, and sweating especially at night that may last from 5 to 10 minutes and can even lead to mood and sleeping disorders needing medical attention.^{20,21} Despite its uncertain cause, it seems that the change in the endocrine function, especially in endogenous estrogen concentration, is a major underlying cause for this syndrome.²² Although vasomotor symptom frequently appears to be a short-term, temporary and transient phenomenon, in some rare cases it can be prolonged for even more than 10 years.²³ Besides estrogen reduction (as the main reason for vasomotor symptom), reduction of circulating serotonin as well as increased norepinephrine levels have also been identified as related pathophysiological causes for this symptom.¹⁸ In addition to the role of estrogen deficiency in the onset of vasomotor symptom, the ratio of different types of estrogens such as estradiol or estrone is more related to the pathophysiological fundament of VMS.²⁴ In fact, in the premenopausal period, the potent active form of estrogen is estradiol; however, during the postmenopausal period, the most abundant estrogen may shift to estrone that has considerably lower potency explaining the central role of the ratio of these estrogens subtypes in the onset of vasomotor symptom.²⁵

Risk factors for vasomotor symptom

Several risk factors have been introduced for VMS such as obesity, smoking, and specific racial tendencies.^{26,27} Regarding the association between obesity and VMS, it has been shown that non-obese women seldom suffer from this symptom, while the symptom is common in women with a body mass index higher than or equal to 31 kg/m².²³ Some studies have demonstrated a sevenfold increased risk for VMS in obese women compared to the non-obese.²⁶ Regarding the association between vasomotor symptom and ethnic variations, a higher prevalence rate of VMS has been shown in African-Americans compared with other ethnicities such as Southeast Asian races.²⁸ Although the difference in racial tendency for VMS has been uncertain, it may be indirectly mediated by the higher prevalence of obesity or smoking in African-Americans compared to other races. Furthermore, the association between smoking and severity of VMS can be linked to the anti-estrogenic effect of tobacco leading to the double risk of VMS in smokers than non-smokers.^{26,27} Both chemical and alternative medicines have been applied to relieve VMS.²⁹ The overall evidence supporting these treatments is variable.³⁰ Complementary and alternative medicine has grown increasingly popular in the last decade. Although no evident statistics are available in the rate of using alternative medicines to relieve VMS, it seems that a considerable number of individuals in these areas benefit from these methods.^{31,32}

Steroid hormone therapies for VMS

Because of reduced sex steroid hormones as a result of aging and also experiencing menopause in healthy women, the appearance of vasomotor symptoms is frequently expected. For this reason, the use of steroid supplements has been hypothesized to be effective in preventing the onset of these symptoms.³³ Besides complementary medications, hormonal-based treatments are now considered as a standard option for the treatment of VMS.³⁴ Estrogen reduces the severity and frequency of VMS by more than 70%, usually within one month.³⁵ In recent decades, the combination of estrogen and progestin has been used as an appropriate therapeutic method for this syndrome. However, considering the increased risk of breast cancer, cerebral vascular accident, thrombotic events, and also heart diseases, using these drugs for treating hot flashes is now questioned.³⁶

The Women's Health Initiative was a set of long-term studies initiated by the National Health Organization in 1993. It aimed to assess long-term effects of hormone replacement therapy with estrogen and progesterone, as a method to prevent osteoporosis and cardiovascular diseases, in 50–79-year-old postmenopausal women. Although the study was planned to last for 15 years, it was ceased in 2002 when the higher risk of breast cancer, thromboembolic complications, stroke, and coronary disease in women undergoing hormone replacement therapy (compared to those receiving placebo) was revealed.^{13,37} A recent analysis of the long-term outcomes of women from the WHI indicates that short-term use of hormones is associated with little increased overall risk, and they remain an appropriate option for symptom management.³⁸

Other large prospective clinical trials have addressed the role of hormone replacement therapy in increased risk of thromboembolic complications, breast cancer, and dementia. Negative effects of medroxyprogesterone acetate and conjugated estrogens on hemostatic balance and immune and inflammatory factors can be held responsible for such side effects before and after menopause.³⁹ The use of steroid, especially megestrol acetate, has been introduced as a novel treatment option.³³ In a randomized trial on 71 menopausal women treated with oral megestrol acetate, about two-thirds of the women had a 50% reduction in vasomotor symptoms. Despite the considerable efficacy of this steroid drug on VMS, serious side effects of this drug should be considered.⁴⁰

Currently, estrogen therapy particularly in combination with progestin is the most common therapeutic strategy to relieve vasomotor symptom worldwide.⁴¹ Several clinical trials have shown the clinical efficacy of estrogen plus progestin medication for relieving VMS. A meta-analysis on 24 clinical trials with a total sample size of 3329 patients showed a 75.3% reduction in the rate of hot flashes and also 87% reduction in symptom severity following the use of oral estradiol or ethinyl estradiol, with or without a 19-nor testosterone.⁴² Various formulations and routes of estrogen plus progestin can be used for treating VMS such as transdermal, vaginal, oral, or intravenous.⁴³ However, the different doses and durations considered for this aim result in different rates of efficacy. On the other hand, the main endpoint for proper outcome of this medication is achieving the highest drug efficacy with minimized drug side effects such as hyperlipidemia, thrombotic events, or liver and gallbladder disorders.⁴⁴ Thus, it is preferred to use topical emulsions or transdermal sprays instead of oral or intravenous administration of these drugs.⁴⁵ Besides the combination of estrogen plus progestin, the combination of selective estrogen receptor modulator (SERM) with estrogen has been

Table 1. Characteristics of included studies.

Author	Year	Study duration	Sample size	Route of HT administration	Main outcome mean standard error	Main side effects
Botelho ⁴⁷	2014	60 month	66	Transdermal (Emulsion)	Improvement in climacteric symptoms in 92.5% of women	No adverse health-related events
Buster ⁴⁸	2008	12 week	454	Transdermal (spray)	Significant decrease in hot flashes at weeks 4 and 12	Not reported
Bertelli ⁴⁰	2002	6 week	71	Intramuscular - Oral	50% reduction in VMS in two-third of women	Not reported
Simon ⁴⁹	2006	12 week	200	Transdermal (gel)	Reduction in the frequency of VMS	No serious adverse events
Ruiz ⁵⁰	2014	follow-up: 1-3 months, 3-6 months	40	Sublingual	Improvement in VMS	Not reported
Bachmann ⁵¹	2007	12 week	425	Transdermal (patche)	Reduction in frequency and severity of hot flashes	Not reported
Joffe ⁵²	2014	8 week	339	Oral	Mean VMS frequency decreased by 53%	Not reported
Shulman ⁵³	2002	12 week	293	Transdermal (patche)	Improvement in VMS	Application-site reactions, vaginal hemorrhage, breast pain
Hedrick ⁵⁴	2009	12 week	488	Transdermal (gel)	Reductions in frequency and severity of VMS	Not reported

recently taken into consideration.³⁰ SERMs can act as agonists or antagonists in different tissues leading to a distinct action profile. Also, by using them, the adverse effects of estrogen such as increased risk for malignancies in some tissues such as breast or uterine are potentially blocked.⁴⁶ This recent medication allows us to minimize hot flashes as well as the risk for cancerous changes in estrogen target tissues.

Discussion

This is a systematic review of hormone therapy in the treatment of postmenopausal VMS. The most notable finding of this review is that low-dose oral and transdermal estradiol are effective treatments for VMS in midlife women. These findings are consistent with recommendations from other studies.⁵² In a study by Bachmann *et al.*, the micro-dose E2 (0.014 mg/d) was more effective than placebo in reducing the number of moderate and severe hot flashes, with a 41% response rate.⁵¹ Indeed in another study in this review, we observed that the compounded sublingual HRT is effective in reducing vasomotor symptoms experienced in menopausal women. Topical therapy does not appear to improve symptoms as extensively or rapidly as sublingual therapy.⁵⁰

Menopausal hormone therapy has a complex pattern of risks and benefits and the management depends on a variety of factors, such as the woman's health and the severity of symptoms.⁵⁵ HT may be very helpful in relieving hot flashes because it has been well demonstrated that serum steroid levels correlate with multiple aspects of hot flashes including duration, frequency, episode, timing and intensity.⁵⁶ One study in our review showed that nanostructured formulation is safe and effective in re-establishing optimal serum levels of estradiol and relieving the symptoms of menopause.⁴⁷

Nowadays, estrogen therapy particularly in combination with progestin is the most common therapeutic strategy to relieve VMS worldwide.⁴¹ In this regard, a low dose of these drugs for a

short-term administration is recommended by the American Association of Clinical Endocrinologists and the American College of Obstetricians and Gynecologists.⁵⁷ Occasionally, higher dosages of estrogen plus progestin medication may be required for administration over a longer period (>5 years) for women at increased risk of osteoporosis or osteoporotic fractures.⁵⁸ However, this effective medication is partially contraindicated in those women with women specific cancers, vaginal bleeding with unknown origin, endometrial hyperplasia, coagulative disorders, or sensitivity to these hormonal drugs.⁵⁹

Overall, low-dose estrogen-based therapies, especially in combination with progestin can be the most effective regimens to relieve VMS. These medications can be successfully used by different administration routes and formulations. However, it should be strongly noted that because of the negative effects of estrogen derivatives on their targeted tissues such as breasts or the uterus, the risk of hyperplasia or even malignant cellular behaviors may increase with these medications. Therefore, two main points should be considered for administering these drugs. First, the use of HT should be intended for the lowest effective dose and with the shortest duration. Second, the use of transdermal route of administration can be considered with minimized side-effects related to hormone therapy.

Author Contribution

All of the authors had the same contribution in various process performed in this project.

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Conflict of interests

Authors have no conflict of interests.

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