EXPERT VIEW/REVIEW PAPER

Emerging Trends in Treatment of Hot Flashes at Menopause: A Review

Deepthy Balakrishnan[1], Ruchika Garg[2]

Abstract

Hot flashes represent a prevalent symptom prompting menopausal women to seek assistance. The utilization of treatment among these women is notably low, particularly in countries such as India, where women may display hesitancy toward regular follow-up. Hormone replacement therapy (HRT) has been identified as the standard treatment for addressing hot flashes in menopausal women. Notably, several guidelines have advocated for the safe use of HRT in healthy women under the age of 60 who have entered menopause within the past decade. It is recommended that women with comorbidities undergo assessment and receive personalized treatment plans. Non-hormonal treatments and complementary therapies should be considered for women unable to undergo HRT. Additionally, emerging pharmaceuticals may serve as viable substitutes for traditional HRT. This review provides insight into both current and forthcoming treatments for hot flashes.

Keywords: Hot flashes, Menopause, Menopausal hormone replacement therapy, Menopausal transition.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2501

Introduction

The menstrual transition encompasses perimenopause and the initial 12 months following the final menstrual period. This is a phase characterized by an ambiguous duration, with a median period of 4 years, persisting until menopause or for a year following amenorrhea.[1] It is further categorized into early and late stages. The early menopausal transition is defined by a consistent variance of 7 days or more in the length of consecutive cycles or the occurrence of one or more skipped cycles. Late menopausal transition is denoted by a period of amenorrhea lasting 60 days or more. The late menopausal transition is particularly significant as it heralds the onset of novel symptoms of hypoestrogenism, including but not limited to hot flashes, joint pain, mood swings, sleep disturbances, decreased libido, increased adiposity, as well as vaginal and sexual changes alongside alterations in the menstrual cycle pattern.[1]

As of 2021, the global population of postmenopausal women stood at 1.02 billion, with projections indicating an increase to 1.65 billion by 2050.[2] While the average age of menopause is 51 years, a systematic review revealed a lower average of 46.6 years in India.[3] According to the National Family Health Survey 2019–2021, India had 96 million women aged over 45 years, a number anticipated to reach approximately 400 million by 2026.[4] This demographic, often called the sandwich generation, assumes the dual responsibility of caring for elderly parents and children. Notably, numerous women in this group hold senior positions in diverse organizations.[5] Given the substantial population of women entering the perimenopausal to the menopausal stage, providing comprehensive medical support tailored to address their specific symptomatic needs is imperative.

The primary concern among perimenopausal and menopausal women is the occurrence of hot flashes, a prevalent vasomotor symptom (VMS). Hot flashes are characterized by episodic sensations of heat, flushing, and sweating, primarily affecting the upper part of the body, including the face and chest, before spreading to the rest of the body. These episodes, often accompanied by palpitations, perspiration, and anxiety, can vary in frequency, occurring hourly, daily, or occasionally among different individuals, each lasting between 2 and 4 minutes.[6,7] This condition affects approximately one-third of women in the perimenopausal–postmenopausal age group, with most enduring it for around a year. In contrast, others may experience symptoms for a decade or longer.[8] Factors impacting prevalence and treatment effectiveness include ethnicity, with African–American and Native American women exhibiting the highest rates of occurrence, while Asian ethnicities, particularly Japanese and Chinese, report the lowest rates.[2,6,9] Notably, although Japanese women experience a shorter duration of symptoms, their quality of life is significantly affected.[2,6] Women with higher BMI experience severe hot flashes during perimenopause, whereas the frequency diminishes after reaching the postmenopausal stage. Additionally, early onset of hot flashes during perimenopause may lead to an extended duration of symptoms. Socioeconomic status, smoking, and negative baseline mood are among the factors influencing the duration of hot flashes. However, clinicians can reasonably predict the likelihood of long-term symptoms requiring treatment. Approximately 20% of women in their late 50s, 10% in their 60s, and 5% in their 70s experience persistent hot flashes, necessitating prolonged treatment to preserve their quality of life.[10] Furthermore, women experiencing

[1]Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, Odisha, India

[2]Department of Obstetrics and Gynaecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India

Corresponding Author: Deepthy Balakrishnan, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, Odisha, India, Phone: +91 9446439373, e-mail: balakrishnandeepthy@gmail.com

How to cite this article: Balakrishnan D, Garg R. Emerging Trends in Treatment of Hot Flashes at Menopause: A Review. J South Asian Feder Obst Gynae 2024;16(5):595–601.

Source of support: Nil

Conflict of interest: Dr Deepthy Balakrishnan and Dr Ruchika Garg are associated as the Editorial board members of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of these Editorial board members and their research group.

hot flashes exhibit reduced heart rate variability, correlating with an increased cardiovascular risk.[11]

Notably, women with breast carcinoma treated with antiestrogenic drugs, chemotherapy, or oophorectomy have a heightened incidence of hot flashes. Studies have indicated a greater incidence of hot flashes among women prescribed tamoxifen compared with first-line hormonal therapy drugs for metastatic breast cancer, particularly among postmenopausal women. This heightened incidence is also notable among women experiencing premature menopause due to chemotherapy.[12]

Androgen deprivation therapy and surgical intervention for prostate cancer are known to induce hot flashes in men. This phenomenon has been documented extensively.[13]

Physiology of Hot Flashes

Understanding the pathophysiology that causes hot flashes is essential for effective symptom management. The precise mechanisms are not wholly elucidated, but it is postulated that dysfunction of the thermoregulatory nucleus, governing core body temperature, may precipitate hot flashes. Notably, the narrowing of the thermoregulatory zone in women experiencing hot flashes often results in frequent threshold crossings and subsequent symptom manifestation. Moreover, the reduction in estrogen in a post-menopausal woman is linked to an increase in norepinephrine, potentially leading to heightened hypothalamic serotonin receptor activity and a consequent decrease in the upper threshold of the thermoregulatory zone.[14] Recent research underscores the pivotal role of hypothalamic neuropeptide signaling pathways in centrally regulating reproductive and thermoregulatory pathways following menopause. Evidently, upregulated neurokinin B (NKB) neurons, arising from low estrogen levels, project into the medial preoptic area of the hypothalamus, thereby precipitating hot flashes. Additionally, compelling evidence implicates NKB neurons in enhancing VMS by promoting increased skin blood flow and cutaneous vasodilation, thereby contributing to estrogenic modulation of temperature.[15,16]

Management of Hot Flashes

Menopausal HRT

The standard therapy that is most beneficial for women experiencing hot flashes is menopausal hormone replacement therapy (MHRT). Recommended hormone therapies include oral or transdermal estrogen with or without LNG-IUS, estrogen–progestogen therapy, and low-dose oral contraceptive pills (OCPs). In estrogen–progesterone treatment, the hormone dose is low and contains 1/4th of the estrogen in OCPs.[6] A meta-analysis of randomized controlled trials (RCTs) has shown that oral conjugated equine estrogen and transdermal estradiol can reduce hot flashes by 70–95% within 1 month of treatment initiation.[17] For women with premature or early menopause, hormone therapy can be continued until the average age of menopause, which is around 50–52 years. The HRT through the oral route is mostly the method of administration but has an effect on SHBG, blood pressure, neutral fat, and C-reactive protein levels compared with non-oral methods.[6]

The North American Menopause Society's 2022 guidelines recommend hormone therapy for menopausal symptoms, prevention of bone loss, premature hypoestrogenism, and genitourinary symptoms of menopause. Various guidelines suggest initiating hormone therapy before the age of 60 or within 10 years of menopause, as HRT in this age group might have a protective effect on coronary artery disease.[18–22] The lowest possible dose for the shortest time is recommended. The 2017 recommendations from the American College of Endocrinology and the American Association of Clinical Endocrinologists suggest hormonal treatment for menopausal symptoms after considering factors such as age, time since menopause, lipid profile, and chronic illnesses like diabetes, smoking, and cardiovascular risk for a maximum duration of 5 years.[20]

Before starting MHRT, a relevant medical history should be obtained, and a basic examination should be conducted. Factors such as smoking, alcohol consumption, mental illness like depression, family history of Alzheimer's disease, diabetes, osteoporosis, cardiovascular disease, venous thromboembolism (VTE), or cancers of the endometrium, breast, or liver should be noted.[6] Height, weight, BMI, blood pressure, and examinations of the thyroid and breast, along with various investigations such as liver function tests, blood sugar tests, renal function tests, complete blood count, lipid profile, mammography, DEXA scan, pelvic ultrasound, and Pap smear should be performed. Thyroid function tests, endometrial biopsy, and breast ultrasound can be done in selective cases considering the risk factors.[6] Since a few symptoms mimic VMS, ruling out diabetes and thyroid dysfunction are essential for all patients.

The HRT is contraindicated in the active liver, uncontrolled hypertension, peripheral artery disease, unprovoked VTE, any clotting disorders, myocardial infarction, stroke, carcinomas of breast and endometrium, and undiagnosed vaginal bleeding. Caution should be exerted for conditions like controlled hypertension, hyperlipidemia, smoking, HIV patients, gall bladder diseases, and ovarian and cervical cancers in response to hormones.

Research indicates that women who begin MHRT before the age of 60 and within 10 years of menopause can safely continue treatment if they do not develop any new health issues.[6] All women should be evaluated for VTE 8–12 months after starting HRT because the highest incidence occurs during the first year. If VTE develops, HRT should be stopped immediately.[6] Estrogen therapy alone can be given to women without a uterus, as it has a lower risk of VTE compared with combined estrogen–progestogen therapy. The incidence of VTE is lower in the Asian population compared with the Western population.[6] Using lower doses of estrogen or transdermal estrogen with micronized progesterone or dydrogesterone may further reduce the risk of VTE.

If gallstones develop, oral HRT can be switched to transdermal therapy. Women should be evaluated annually for cardiovascular and cerebrovascular risk factors, as well as the risk of bone and colorectal cancer, breast cancer, genitourinary cancers, and gall bladder disease if they are undergoing HRT.[6] Guidelines recommend discontinuing treatment after symptom relief and considering an extension of treatment only if symptoms recur after evaluating the risks of breast cancer and cardiovascular disease.

Long-term HRT with estrogen has been linked to a higher risk of breast cancer. A meta-analysis of 58 prospective and retrospective studies conducted by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHBC) revealed an additional 1.4–2 cases per 100 individuals and a 20-year follow-up of the Women's Health Initiative (WHI) randomized controlled trials showed an extra 1.8 cases per 100 individuals over 20 years in estrogen–progestogen users.[23] Estrogen users had fewer breast cancers, according to WHI, while CGHBC estimated an increase of an additional 0.5 cases per 100 individuals.[24]

Table 1: Estrogens recommended for systemic hormone therapy

	Drug	*Mode of administration*	*Dose*
1	17-β estradiol	Oral/transdermal patch/gel pouch/gel/pump	1 mg daily/0.05 mg once or twice weekly/1 mg daily/1–2 pumps daily, respectively
2	Conjugated equine estrogen	Daily oral	0.625 mg (can be used in post-hysterectomy)
3	Ethinyl estradiol	Daily oral	0.01–0.015 mg
4	Esterified estrogen	Daily oral	0.625 mg
5	Estradiol acetate	Vaginal ring	0.05 mg

Table 2: Progestogens recommended for systemic hormone therapy

	Drug	*Mode of administration*	*Dose*
1	Micronized progesterone	Oral or vaginal capsule	100–300 mg (100 mg/day if given daily or 200 mg/day given for 12 days cyclical with estrogen
2	Levonorgestrel IUS	Intrauterine system	For 5 years
3	Drospirenone	Oral daily	4 mg
4	Medroxyprogesterone acetate	Oral daily	2.5–5 mg/day if daily or 5–10 mg/day for 10–14 days in a 30–day cycle, cyclical with estrogen
5	Norethindrone	Oral daily	0.7 mg
6	Norethindrone acetate	Oral daily	2.5 mg or 5 mg/day if combined with estrogen
7	Megestrol acetate	Oral daily	20–40 mg
8	Dydrogesterone	Oral daily	2.5 mg/day or 10 mg/day given cyclical with estrogen in a 28-day cycle

The estimated risks may be overstated, as the risk is lower with newer progestogens such as micronized progesterone or dydrogesterone.[2] A cohort study using micronized dydrogesterone did not show an increased risk of breast cancer with usage for up to 5 years.[25]

A study indicated a higher risk of breast cancer with all progestogens, though dydrogesterone was linked to the lowest risk.[26] One meta-analysis found that LNG-IUS does not increase the risk of breast cancer, while another suggested an increased risk with IUS.[27,28] The HRT is not recommended for women who have been diagnosed with breast cancer because it may increase the risk of recurrence.[29]

Exercise caution when initiating MHRT in women aged over 60 who have been menopausal for more than 10 years due to the pronounced elevated risk of VTE and stroke in this cohort.[30] Observational studies have indicated that transdermal estrogen carries a diminished risk of VTE and stroke, making it the preferred choice for women with decreased libido. Oral estrogen diminishes the bioavailability of testosterone by augmenting sex hormone-binding globulin levels. The incidence of VTE is lower in transdermal estrogen users' women with diabetes, hypertension, hyperlipidemia, and other risk factors for cardiovascular disease; it is recommended to consider this option.[31,32] Transdermal estrogen did not show any advantage over oral estrogen in reducing breast cancer risk.[25]

It is advisable to exercise caution when considering MHRT for women over 60 years of age and those who have been menopausal for more than 10 years due to the notably heightened absolute risk of VTE and stroke within this demographic.[30] According to observational studies, the use of transdermal estrogen demonstrates a lower risk of VTE and stroke, making it a preferred option, especially for women exhibiting low libido. Oral administration of estrogen reduces testosterone bioavailability by elevating sex hormone-binding globulin levels. Significantly, transdermal estrogen usage is associated with a decreased incidence of VTE and is particularly favored in individuals with diabetes, hypertension, hyperlipidemia, and other cardiovascular disease risk factors.[31,32] While transdermal estrogen did not demonstrate a clear advantage over oral estrogen in reducing the risk of breast cancer, these observations need to be thoughtfully considered in clinical decision-making processes (Table 1).[25]

Progestogens

Progestogens are frequently prescribed in conjunction with estrogen to mitigate menopausal symptoms in women with a uterus, as well as to avert endometrial hyperplasia. Oral micronized progesterone as a standalone therapy has demonstrated efficacy. Notably, a dosage of 300 mg per day over 12 weeks yielded a 55% reduction in symptoms compared with a 29% reduction with a placebo.[33] Furthermore, another clinical trial revealed that oral micronized progesterone at a 300 mg daily dose substantially lessened VMS and enhanced sleep quality without eliciting an increase in depression, in contrast to its placebo counterpart.[34,35] However, it should be noted that this high dosage may lead to heightened side effects in comparison to estrogen. Progestational agents like oral megestrol and intramuscular medroxyprogesterone acetate are effective in reducing hot flashes in menopausal women. However, they should not be used in women with breast cancer due to an increased risk of breast cancer. When estrogen is combined with progestins, such as medroxyprogesterone acetate, higher rates of stroke, coronary heart disease (CHD), and VTE have been observed. On the other hand, oral micronized progesterone, low-dose norethindrone acetate, and dydrogesterone do not seem to have the same negative effects (Table 2).[7,36–38]

In women with a uterus, the combination of estrogen and progestins helps reduce the risk of endometrial hyperplasia and carcinoma. This therapeutic regimen may be administered continuously or cyclically, with the latter entailing a 12–14 days

progestogen administration in the latter phase of a 28-day cycle. Repeated cyclical treatment, termed sequential combined HRT, does not involve intermissions. Notably, withdrawal bleeding is to be expected upon cessation of progestogen. In the event of a missed HRT dose, a recommendation is for the individual to promptly take the missed dose if it has been within 12 hours of the scheduled administration or to resume the regular dosing schedule after this timeframe without doubling the subsequent dose to compensate for the omission. Prolonged progestogen use may occasion irregular bleeding, particularly during the initial 6 months. In cases where the uterus is absent, estrogen monotherapy suffices, although progestins are indicated for patients with endometriosis or those with endometrioid ovarian cancer.[2] The optimal method for discontinuing drugs for VMS lacks consensus, as both abrupt and gradual cessation demonstrate no influence on the recurrence rate. Notably, women with stage III or IV endometrial cancer necessitate non-hormonal treatments for symptom management.[2]

Women who exhibit menopausal symptoms despite not being in menopause may require specific hormonal interventions. In instances where women under MHRT experience breakthrough bleeding or necessitate contraceptive measures, it is advisable to consider hormonal treatments such as oral contraceptives or hormonal patches or rings until they reach the age of menopause.[7] Continuous oral contraceptives (OCPs) with 30 µg of ethinylestradiol or combined oral contraceptives like Qlaira, with a reduced pill-free interval, are preferred for alleviating symptoms, particularly as symptoms tend to exacerbate during the 7-day pill-free period. This therapeutic approach is applicable for women aged 40–55 without obesity, hypertension, smoking habits, or cardiovascular conditions. However, women at increased risk of cardiovascular ailments should be cautious, as hormonal contraception may elevate the relative risk of stroke and myocardial infarction. In such cases, the provision of an intrauterine device (IUD) with or without progestin can be considered to mitigate VMS.[7]

Other Formulations

Tissue Selective Estrogen Complex

The tissue-selective estrogen complex (TSEC) comprises selective estrogen receptor modulators (SERMs) and estrogens. The use of individual SERMs is suboptimal due to the imbalance in their agonist and antagonist effects in treating menopausal symptoms. The TSEC specifically refers to a combination of conjugated estrogen and bazedoxifene, which is a selective estrogen receptor agonist-antagonist (ERAA) and functions as an agonist to estrogen receptors in bone, thereby reducing the risk of osteoporosis. Conversely, it is an antagonist to estrogen receptors in the breast and uterus.[39] This combination can be prescribed for women with a uterus experiencing breast pain, increased breast density, and vaginal bleeding due to estrogen–progesterone therapy as part of the treatment for menopausal symptoms.[39,40] Limited data exist regarding the associated risk of developing breast carcinoma with this combination.[41] Furthermore, SERMs and their combination with estrogens can alleviate genital symptoms, increase bone density, and improve sleep quality and overall quality of life without adversely affecting lipid metabolism and hemostasis.[41–43] Endorsed by the American Endocrine Society and the North American Menopause Society, the recommended daily dosage is 20 mg bazedoxifene + 0.45 mg conjugated estrogen/20 mg bazedoxifene + 0.625 mg conjugated estrogen.[19,44]

Synthetic Steroids

Tibolone, a synthetic steroid derived from 19-nortestosterone, exhibits estrogen-like properties by binding to estrogen receptors alongside androgenic and progestogenic effects. Its use has shown effectiveness in alleviating VMS and improving mood disorders, bone mineral density, sexual function, and genitourinary symptoms. Administration of tibolone at a daily dose of 2.5 mg yields noticeable relief from VMS after 4 weeks, with maximal effect achieved after 12 weeks.[45] This regimen is well-suited for menopausal women without a natural period for a minimum of 1 year; however, administering tibolone within 1 year of menopause may result in irregular bleeding. Notably, it can be prescribed to hysterectomized post-menopausal women and is associated with a lower incidence of breast pain, vaginal bleeding, and reduced breast density compared with estrogen–progestin combinations used in HRT.

Tibolone use does not present an increased risk of VTE, coronary artery heart disease (CAHD), breast cancer, or endometrial cancer. Nevertheless, its use is contraindicated in older women and those with a history of breast cancer due to the elevated risk of recurrent breast cancer and stroke, particularly in women over 60 years of age.[46] Regular mammograms and breast examinations are advised for women undergoing tibolone therapy. Although uncommon, side effects may include headache, dizziness, abdominal pain, nausea, edema, and irregular spotting.[6]

Nonhormonal Therapy

As per the 2019 treatment guidelines issued by the National Institute for Health and Care Excellence, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and clonidine are recommended as second-line treatments for VMS.[47] These medications are particularly beneficial when VMS co-occurs with other morbidities. Clonidine, an α adrenergic agonist, exhibited effectiveness in less than 50% of trials and was associated with dry mouth and constipation. It is considered particularly suitable for women with coexisting hypertension. Among SSRIs, only paroxetine is FDA-approved for this use; however, it was found to be linked to higher mortality in breast cancer patients using tamoxifen. Other SSRIs, including fluoxetine, venlafaxine, and citalopram, demonstrated significantly reduced hot flashes but require cautious use. Clinical trials revealed that gabapentin reduced hot flashes by 35%. Oxybutynin is an additional viable option for women experiencing urge incontinence and vasomotor symptoms (Table 3).[48]

Complementary Therapies

Lifestyle modifications, such as hypnosis, cognitive behavioral therapy, weight loss, exercise, and stress reduction, may aid in mitigating hot flashes.[49–52] Management of mild hot flashes can involve the reduction of body temperature by wearing loose clothing, consuming cold food or drinks, avoiding spicy food, and utilizing fans as needed.[53] Non-pharmacological treatments like black cohosh, yoga, omega-3 fatty acids, and vitamin E lack evidence to substantiate their effectiveness.[54] Stellate ganglion block, entailing the injection of local anesthetic into a cluster of sympathetic nerves in the lower cervical and upper thoracic region, has been utilized for hot flash management; however, its clinical application is hindered by cost and limited availability.[48,55,56] Isoflavones in soy products, such as genistein and daidzein, have shown conflicting data regarding their effectiveness in treating VMS,

Table 3: Non-hormonal drugs

	Drug	*Mode of administration*	*Dose*
1	Gabapentin	Oral (associated sleep disorders/migraine)	100–300 mg/day
2	Paroxetine mesylate	Oral (associated mood disorders)	7.5 mg/day
3	Paroxetine HCL	Oral	10–20 mg/day
4	Venlafaxine	Oral (may be given in women with ca breast on tamoxifen)	37.5–150 mg/day
5	Oxybutynin	Oral (associated urge incontinence)	2.5–5 mg. max to 15 mg/day
6	Clonidine	Oral (associated hypertension)	0.05–0.15 mg/day

accompanied by side effects like bloating, flatulence, and diarrhea.[48] Acupuncture has emerged as an alternative treatment for VMS, with numerous clinical trials indicating its efficacy compared with no treatment; however, meta-analyses evaluating its effectiveness have yielded inconclusive results. Cognitive behavioral therapy has reduced VMS, and internet-delivered CBT has been identified as a viable option for hot flash management.[57] Women undergoing hypnosis have exhibited high satisfaction levels.[58]

Newer Treatment Modalities

Estetrol is a fetal human estrogen that demonstrates potential synergistic activity with endogenous estrogen and may offer a prospective treatment approach for managing vasomotor symptoms.[59]

The neurokinin-3 receptor (NK3R) antagonists encompass fezolinetant, elinzanetant, and Q-122. Recently sanctioned by the FDA at a 30 mg dose, fezolinetant, an oral NK3R antagonist, exhibited noteworthy efficacy in Phase III trials, resulting in a 93% reduction in severity after 12 weeks. The drug exhibited a rapid onset of action, ranging from 2.2 to 8.4 days for doses of 90 and 15 mg BID, respectively. Notable side effects included upper respiratory tract infection, diarrhea, UTI, headache, nausea, and cough.[60]

Elinzanetant, an oral neurokinin-1 and neurokinin-3 receptor antagonist, is currently undergoing Phase III trials. In Phase II trials, the 160 mg dose proved most effective in mitigating vasomotor symptoms after 12 weeks of treatment.

The Q-122 is an oral medication that targets the C–X–C chemokine receptor type 4 in KNDy neurons. Encouraging results from Phase II clinical trials in women undergoing treatment with aromatase inhibitors or tamoxifen for breast cancer included significant improvements with twice-daily dosage following 28 days of treatment.[2]

The NK-814, a selective antagonist of the neurokinin pathway targeting NK1 and NK3 receptors, demonstrated substantial efficacy. In the RELENT-1 Phase II RCT, a 150 mg dose of the medication led to an 84% decrease in hot flashes, while the placebo group experienced a 37% reduction. Furthermore, a 12-week double-blinded RCT identified the drug's 120 and 160 mg dosages as the most effective in managing vasomotor symptoms with no adverse effects.[61,62]

Conclusion

While an array of treatment options exists for VMS, clinicians in developing countries may exhibit hesitance in addressing menopausal symptoms due to concerns regarding potential drug side effects, diagnostic complexities, and patient adherence. Initiating pharmacological therapy in women under 60 years of age who have experienced menopause within the last decade and continuing treatment for 5 years has been deemed safe. Nonpharmacological interventions may be considered for those with contraindications to MHRT. The forthcoming introduction of experimental drugs holds promise for enhancing VMS management shortly.

Orcid

Deepthy Balakrishnan https://orcid.org/0000-0001-6646-261X
Ruchika Garg https://orcid.org/0000-0002-4416-4993

References

1. Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. BMJ 2023;382:e072612. DOI: 10.1136/bmj-2022-072612.
2. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2024: Summary of Results 2024; UN DESA/POP/2024. Available from: http://population.un.org/wpp/Publications/Files/WPP2024_Key-Messages.pdf.
3. Ambikairajah A, Walsh E, Cherbuin N. A review of menopause nomenclature. Reprod Health 2022;14(1):1–15. DOI: 10.1186/s12978022-01336-7.
4. Kundu S, Acharya SS. Exploring the triggers of premature and early menopause in India: A comprehensive analysis based on National Family Health Survey, 2019–2021. Sci Rep 2024;14(1):1–15. DOI: 10.1038/s41598-024-53536-9.
5. Evans KL, Millsteed J, Richmond JE, et al. Working sandwich generation women utilize strategies within and between roles to achieve role balance. PLoS One 2016 Jun 15;11(6):e0157469. DOI: 10.1371/journal.pone.0157469.
6. Lee SR, Cho MK, Cho YJ, et al. The 2020 menopausal hormone therapy guidelines. J Menopausal Med 2020;26(2):69–98. DOI: 10.6118/jmm.20000.
7. Delamater L, Santoro N. Management of the perimenopause. Clin Obstet Gynecol 2018;61(3):419–432. DOI: 10.1097/GRF.0000000000000389.
8. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med 2015;175(4):531–539. DOI: 10.1001/jamainternmed.2014.8063.
9. Harlow SD, Burnett-Bowie SM, Greendale GA, et al. Disparities in reproductive aging and midlife health between black and white women: The study of women's health across the nation (SWAN). Womens Midlife Health 2022;8(1):3. DOI: 10.1186/s40695-022-00073-y.
10. Brunner RL, Aragaki A, Barnabei V, et al. Menopausal symptom experience before and after stopping oestrogen therapy in the Women's Health Initiative randomized, placebo-controlled trial. Menopause 2010;17(5):946–954. DOI: 10.1097/gme.0b013e3181d76953.
11. Thurston RC, Christie IC, Matthews KA. Hot flashes and cardiac vagal control: A link to cardiovascular risk? Menopause 2010;17(3):456–461. DOI: 10.1097/gme.0b013e3181c7dea7.

12. Kligman L, Younus J. Management of hot flashes in women with breast cancer. Curr Oncol 2010;17(1):81–86. DOI: 10.3747/co.v17i1.473.
13. Richard W, Walker LM, Robinson JW Androgen Deprivation Therapy: An Essential Guide for Prostate Cancer Patients and Their Loved Ones. 2023. DOI: 10.1891/9780826184030.
14. Morrow PK, Mattair DN, Hortobagyi GN. Hot flashes: A review of pathophysiology and treatment modalities. Oncologist 2011;16(11):1658–1664. DOI: 10.1634/theoncologist.2011-0174.
15. Rance NE, Dacks PA, Mittelman-Smith MA, et al. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: A novel hypothesis on the mechanism of hot flushes. Front Neuroendocrinol 2013;34(3):211–127. DOI: 10.1016/j.yfrne.2013.07.003.
16. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): A phase 3 randomised controlled study. Lancet 2023;401(10382):1091–1102. DOI: 10.1016/S0140-6736(23)00085-5.
17. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: Scientific review. JAMA 2004;291(13):1610–1620. DOI: 10.1001/jama.291.13.1610.
18. Faubion SS, Crandall CJ, Davis L, et al. The 2022 hormone therapy position statement of the North American Menopause Society. Menopause 2022;29(7):767–794. DOI: 10.1097/GME.0000000000002028.
19. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2015;100(11):3975–4011. DOI: 10.1210/jc.2015-2236.
20. Cobin RH, Goodman NF, AACE Reproductive Endocrinology Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause–2017 update. Endocr Prac 2017;23(7):869–881. DOI: 10.4158/EP171828.PS.
21. Hamoda H, Panay N, Pedder H, et al. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. Post Reprod Health 2020;26(4):181–209. DOI: 10.1177/2053369120957514.
22. Schnatz, Peter F. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause (New York, NY) 24.7 (2017): 728.
23. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: Individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019;394(10204):1159–1168. DOI: 10.1016/S0140-6736(19)31709-X.
24. Chlebowski RT, Anderson GL, Aragaki AK. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. JAMA 2020;324(4):369–380. DOI: 10.1001/jama.2020.9482.
25. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort study. Breast Cancer Res Treat 2008;107(1):103–111. DOI: 10.1007/s10549-007-9523-x.
26. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: Nested case-control studies using the Q Research and CPRD databases. BMJ 2020;371:m3873. DOI: 10.1136/bmj.m3873.
27. Silva FR, Grande AJ, Lacerda Macedo AC, et al. Meta-analysis of breast cancer risk in levonorgestrel-releasing intrauterine system users. Clin Breast Cancer 2021;21(6):497–508. DOI: 10.1016/j.clbc.2021.03.013.
28. Conz L, Mota BS, Bahamondes L, et al. Levonorgestrel-releasing intrauterine system and breast cancer risk: A systematic review and meta-analysis. Acta Obstet Gynecol Scand 2020;99(8):970–982. DOI: 10.1111/aogs.13817.
29. Liotta M, Escobar PF. Hormone replacement after breast cancer: Is it safe? Clin Obstet Gynecol 2011;54(1):173–179. DOI: 10.1097/GRF.0b013e3182083cbb.
30. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 2015;2015(3):CD002229. DOI: 10.1002/14651858.CD002229.pub4.
31. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: Impact of the route of estrogen administration and progestogens: The ESTHER study. Circulation 2007;115(7):840–845. DOI: 10.1161/CIRCULATIONAHA.106.642280.
32. Hirsch H, Manson JE. Menopausal symptom management in women with cardiovascular disease or vascular risk factors. Maturitas 2022;161:1–6. DOI: 10.1016/j.maturitas.2022.01.016. Epub: 29 Jan 2022.
33. Prior JC. Progesterone for treatment of symptomatic menopausal women. Climacteric 2018;21(4):358–365. DOI: 10.1080/13697137.2018.1472567.
34. Prior JC, Cameron A, Fung M, et al. Oral micronized progesterone for perimenopausal night sweats and hot flushes a Phase III Canada-wide randomized placebo-controlled 4 month trial. Sci Rep 2023;13(1):9082. DOI: 10.1038/s41598-023-35826-w. Erratum in: Sci Rep 2024 Jul 27;14(1):17229.
35. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288(3):321–333. DOI: 10.1001/jama.288.3.321.
36. Anagnostis P, Lambrinoudaki I, Stevenson JC, et al. Menopause-associated risk of cardiovascular disease. Endocr Connect 2022;11(4):e210537. DOI: 10.1530/EC-21-0537.
37. Kaemmle LM, Stadler A, Janka H, et al. The impact of micronized progesterone on cardiovascular events–a systematic review. Climacteric 2022;25(4):327–336. DOI: 10.1080/13697137.2021.2022644.
38. Tremollieres F, Brincat M, Erel CT, et al. EMAS position statement: Managing menopausal women with a personal or family history of VTE. Maturitas 2011;69(2):195–198. DOI: 10.1016/j.maturitas.2011.03.011.
39. Pickar JH, Boucher M, Morgenstern D. Tissue selective estrogen complex (TSEC): A review. Menopause 2018;25(9):1033–1045. DOI: 10.1097/GME.0000000000001095.
40. The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel: Faubion SS, Crandall CJ, Davis L, et al. The 2022 Hormone Therapy Position Statement of the North American Menopause Society. Menopause 2022;29(7):767–794. DOI: 10.1097/GME.0000000000002028.
41. Pickar JH, Yeh IT, Bachmann G, et al. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil Steril 2009;92(3):1018–1024. DOI: 10.1016/j.fertnstert.2009.05.094.
42. Pinkerton JV, Harvey JA, Pan K, et al. Breast effects of bazedoxifene-conjugated estrogens: A randomized controlled trial. Obstet Gynecol 2013;121(5):959–968. DOI: 10.1097/AOG.0b013e31828c5974.
43. Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: A randomized trial. J Clin Endocrinol Metab 2014;99(2):E189–E198. DOI: 10.1210/jc.2013-1707.
44. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2017;24(7):728–753. DOI: 10.1097/GME.0000000000000921.
45. Landgren MB, Helmond FA, Engelen S. Tibolone relieves climacteric symptoms in highly symptomatic women with at least seven hot flushes and sweats per day. Maturitas 2005;50(3):222–230. DOI: 10.1016/j.maturitas.2004.06.001.
46. Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. N Engl J Med 2008;359(7):697–708. DOI: 10.1056/NEJMoa0800743.
47. Lumsden MA, Davies M, Sarri G. Diagnosis and management of menopause: the National Institute of Health and Care Excellence (NICE) guideline. JAMA Intern Med 2016;176(8):1205–1206. DOI:10.1001/jamainternmed.2016.2761.

48. Khan SJ, Kapoor E, Faubion SS, et al. Vasomotor symptoms during menopause: A practical guide on current treatments and future perspectives. Int J Womens Health 2023;15:273–287. DOI: 10.2147/IJWH.S365808.
49. Nappi RE, Kroll R, Siddiqui E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: Prevalence and quality of life burden. Menopause. 2021;28(8):875–882. DOI: 10.1097/GME.0000000000001793.
50. Lee MS, Kim JI, Ha JY, et al. Yoga for menopausal symptoms: A systematic review. Menopause 2009;16(3):602–608. DOI: 10.1097/gme.0b013e31818ffe39.
51. Lindh-Astrand L, Nedstrand E, Wyon Y, et al. Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy. Maturitas 2004;48(2):97–105. DOI: 10.1016/S0378-5122(03)00187-7.
52. Tremblay A, Sheeran L, Aranda SK. Psychoeducational interventions to alleviate hot flashes: A systematic review. Menopause 2008;15(1):193–202. DOI: 10.1097/gme.0b013e31805c08dc.
53. North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: Position statement of The North American Menopause Society. Menopause 2004;11(1):11–33. DOI: 10.1097/01.GME.0000108177.85442.71.
54. Loprinzi CL, Barton DL, Sloan JA, et al. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: A 20-year experience. Menopause 2008;15(4 Pt 1):655–660. DOI: 10.1097/gme.0b013e3181679150.
55. Piraccini E, Munakomi S, Chang KV. Stellate Ganglion Blocks. [Updated 2023 Aug 13]. In: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2024.
56. Cho SH, Whang WW. Acupuncture for vasomotor menopausal symptoms: A systematic review. Menopause 2009;16(5):1065–1073. DOI: 10.1097/gme.0b013e3181a48abd.
57. Duijts SF, van Beurden M, Oldenburg HS, et al. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized, controlled, multicenter trial. J Clin Oncol 2012;30(33):4124–4133. DOI: 10.1200/JCO.2012.41.8525.
58. Elkins GR, Fisher WI, Johnson AK, et al. Clinical hypnosis in the treatment of postmenopausal hot flashes: A randomized controlled trial. Menopause 2013;20(3):291–298. DOI 10.1097/gme.0b013e31826ce3ed.
59. Gaspard U, Taziaux M, Mawet M, et al. A multicenter, randomized study to select the minimum effective dose of estetrol (E4) in postmenopausal women (E4Relief): Part 1. Vasomotor symptoms and overall safety. Menopause 2020;27(8):848–857. DOI: 10.1097/GME.0000000000001561.
60. Santoro N, Waldbaum A, Lederman S, et al. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: Results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). Menopause 2020;27(12):1350–1356. DOI: 10.1097/GME.0000000000001621.
61. Simon J, Anderson RA, Ballantyne E, et al. OR11-03 NT-814, a non-hormonal dual neurokinin 1,3 receptor antagonist markedly improves vasomotor symptoms in post-menopausal women; results of a randomised, double-blind, placebo-controlled, dose-finding study (SWITCH-1). J Endocr Soc 2020;4(Supplement_1):OR11-03. DOI: 10.1210/jendso/bvaa046.2071.
62. Trower M, Anderson RA, Ballantyne E, et al. Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: A placebo-controlled, randomized trial. Menopause 2020;27(5):498–505. DOI: 10.1097/GME.0000000000001500.