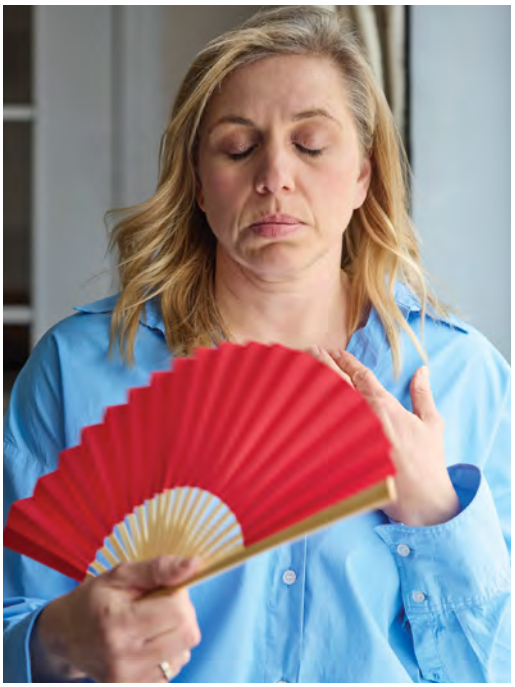
An update on the use of non-hormonal therapies for vasomotor symptoms of menopause



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Background
A significant number of women with severe menopause vasomotor symptoms (VMS) have contraindications or are averse to the use of menopause hormone therapy (MHT).

Objective
To review the various methods of non-hormonal therapies available to treat women with severe menopause hot flushes and sweats.

Discussion
Several non-hormonal therapies have been shown to reduce menopause hot flushes and sweats. Many of these are prescriptive medications used 'off label', however more recently a new class of drugs (neurokinin 3 receptor antagonists) have been developed specifically to treat menopause vasomotor symptoms. Complementary medicines and non-drug therapies can also be used.

MORE THAN 50% OF WOMEN at midlife experience frequent vasomotor symptoms (VMS) such as hot flushes and sweats. These usually last up to 7–8 years and persist approximately 4.5 years after the final menstrual period.[1,2]

Many women do not require treatment for VMS, but if they do, menopause hormone therapy (MHT) is recommended as the most effective first line treatment.[3] However, some women have contraindications to MHT (Box 1) or choose not to use it.

In women with a history of breast cancer, especially younger women, menopause symptoms are more severe than in those without a breast cancer history.[4] Surgical menopause following a bilateral salpingo-oophorectomy is associated with the sudden onset of severe menopause symptoms, especially hot flushes and sweats.

In addition, an Australian cross-sectional study showed that 42% of women aged 60–64 years were still experiencing VMS, with 6.5% experiencing moderate to severe symptoms.[5]

In a large survey study of women, performed across Europe, UK, US and Japan, of whom 3500 had VMS, MHT was contraindicated in 11%.[6]

In women who have contraindications or are averse to MHT, non-hormonal therapies are recommended. These primarily treat the VMS of hot flushes and sweating. Choice of agent may be directed by the additional effects or benefits of a particular class of drug.

Pharmacological therapies, including antidepressants, gabapentinoids and oxybutynin, are used 'off label', that is, they are registered for treatment of other conditions, but have been found to reduce VMS. Fezolinetant is a new agent specifically developed and registered for treatment of VMS. Clonidine is also registered for

Box 1. Contraindications to menopausal hormone therapy (MHT)

- Oestrogen-dependent cancers
  - Current, past or suspected breast cancer
  - Endometrial cancer (current evidence suggests MHT is safe to use in early-stage treatment of the disease, evidence is lacking for higher grade cancer)[27]
- Undiagnosed vaginal bleeding
  - Untreated endometrial hyperplasia
- Active thromboembolic disease
  - Past history requires further investigation
- Active severe liver disease
- Acute myocardial infarction
- Porphyria cutanea tarda
- Untreated hypertension
  - treated hypertension is not a contraindication
- Known sensitivity to active substances or excipients

use but is less effective than other agents. Non-pharmacological therapies include cognitive behavioural therapy (CBT), hypnotherapy, stellate ganglion block and some herbal remedies.

History and examination

A careful history and examination are required, as not all hot flushes and sweating are due to menopause. Chronic infections, medications, thyroid disease, diabetes, anxiety and panic attacks, obesity, certain rare cancers such as carcinoid tumours, and mast cell disorders can all cause flushes and sweating. Hyperhidrosis, a condition of excess sweating, occurs in 1% of the population.

Some medications cause flushing and sweating as side effects, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), vasodilators and calcium channel blockers. Others may exacerbate flushing and sweating, including aromatase inhibitors (eg letrozole, anastrozole, exemestane) and selective oestrogen receptor modulators (eg tamoxifen, raloxifene and clomiphene). The gonadotrophin-releasing hormonal analogues such as goserelin also induce vasomotor symptoms.

Management

Lifestyle

Attention to healthy nutrition, exercise and weight management may improve wellbeing, coping capacity and quality of life. Weight loss in overweight and obese women may lead to a reduction in flushing and sweating.[7]

Treatment options

Prescriptive and non-prescriptive therapies have been listed in Box 2.

Prescriptive therapies

Non-hormonal medications vary in efficacy, and several agents might need to be trialled to find one that is effective for that patient. It is important to consider additional drug effects, side effects, cost and dose complexity.

Box 2. Treatment options

Prescriptive therapies (off label)

- Antidepressants – SSRIs (eg escitalopram), SNRIs (eg venlafaxine)
- Gabapentinoids – gabapentin, pregabalin
- Antispasmodics – oxybutynin

Prescriptive therapies (registered for hot flushes)

- Neurokinin 3 receptor antagonist – fezolinetant
- Antihypertensive – clonidine

Non-prescriptive therapies

- Cognitive behavioural therapy
- Hypnotherapy
- Herbal remedies – black cohosh
- Stellate ganglion blockade

SNRI, serotonin/noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

'Off label'

Antidepressants

These include SRNIs and SSRIs. Various antidepressants have been studied in postmenopausal women to reduce hot flushes and sweats, including women who are breast cancer survivors. Antidepressants may be beneficial where a patient has co-existing mood symptoms, such as anxiety or depression.

Venlafaxine and desvenlafaxine have both been shown to reduce flushing and sweating, usually within the first 4 weeks. The starting dose of venlafaxine is 37.5 mg daily, increasing up to 75 mg as the pre-eminent dose. Above 75 mg side effects increase. Desvenlafaxine is started at 50 mg a day increasing to 100 mg. Discontinuation of either therapy should be gradual over a number of weeks.[8,9] Side effects include headache, nausea, insomnia, dizziness, somnolence, sweating and dry mouth.

SNRIs should not be used in women with uncontrolled hypertension and ischaemic heart disease. SSRIs include escitalopram, citalopram, paroxetine, fluoxetine, sertraline and fluvoxamine. In women on tamoxifen for adjuvant breast cancer treatment, paroxetine or fluoxetine should not be prescribed as they compete for the same liver enzymes and may reduce the effect of tamoxifen. Escitalopram 10–20 mg has been shown to be equivalent to venlafaxine 75 mg and gabapentin 900 mg in treatment of VMS.[10,11]

Gabapentenoids

These include gabapentin and pregabalin. These medicines are registered for neuropathic pain and seizures. Gabapentin is more widely prescribed than pregabalin for hot flushes. These might be beneficial in patients suffering from insomnia and poor sleep. Research has shown that gabapentin 900 mg per day reduces hot flushes compared to placebo. Higher doses have comparable symptom relief to low dose oestrogen.[11,12] Dosage regimens vary, but starting doses are recommended between 100 mg and 300 mg in divided doses or at night because of the somnolent effect. Taking the therapy some hours before bedtime helps to reduce morning drowsiness. Side effects include drowsiness, dizziness, rash, weight gain and lower limb swelling might also occur. Gradual discontinuation of gabapentin is recommended.

Antispasmodic

This medicine is oxybutynin, which is registered for use in overactive bladder and urinary urge incontinence. It is effective in reducing moderate to severe hot flushes within the first 4 weeks.[13] Initiate with a low dosage, 2.5 mg–5 mg twice daily, and increase if tolerated. Side effects include dry mouth, headache, dizziness, urinary retention, and confusion.

Registered for hot flushes

Neurokinin 3 receptor antagonist

Fezolinetant 45 mg is a newly registered daily medication for the treatment of menopausal hot flushes and sweats. Neurokinin 3 (NK3) receptor antagonists reduce the production of neurokinin B in the kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the hypothalamus. Neurokinin B production increases after menopause and acts on the thermoregulatory centre, leading to an increase in flushing and sweating. Fezolinetant reduces hot flushes and sweats rapidly within the first week and overall reduces these symptoms up to 60–70%.[14] Side effects include insomnia, headache and diarrhoea in about 3% of patients. Up to 2.3% of women taking fezolinetant experience elevated liver transaminases. This is typically asymptomatic and resolves on discontinuation.[15]

It is recommended that liver function tests be performed at baseline, then at 1, 2, 3, 6 and 9 months and subsequently as clinically indicated. Discontinue fezolinetant if signs or symptoms suggest hepatotoxicity; transaminase elevation >5 times upper limit of normal; or transaminase elevation >3 times upper limit of normal and bilirubin >2 times upper limit of normal.[16] Contraindications include concomitant use of medications that are CYP1A2 (cytochrome P450 1A2) inhibitors, which include all oestrogens and progestogens. Fezolinetant should not be used in combination with MHT.

All the studies published are in well postmenopausal women without contraindications to MHT. A study in women after breast cancer is in progress. Fezolinetant is not currently listed on the Pharmaceutical Benefits Scheme (PBS) and cost might be a barrier to access for some patients. A PBS application is in progress. Other NK3 receptor antagonists are in clinical trials and might become available in the future.

Antihypertensive/migraine therapy

Clonidine has been widely used in the past for the treatment of flushes and sweats. Reduction in symptoms is less than with other non-hormonal preparations, thus it is now less frequently recommended. The starting dose is 25 mcg daily; however, the lowest available formulation currently available is 100 mcg. Start with lowest available dose, either at night or twice per day, maximum daily dose recommended is 150 mcg. The benefit of clonidine will be seen within 4 weeks of use. Discontinue if ineffective. Side effects include dizziness, hypotension, drowsiness, insomnia and constipation.

Non-prescriptive therapies

Cognitive behavioural therapy (CBT)

A validated CBT program has been developed to reduce bothersome hot flushes and sweats as well as improving sleep and quality of life.[17,18] Patients might be able to access group or individual CBT therapy in person, or via self-help books or online programs.

Clinical hypnotherapy

A validated hypnotherapy program over five sessions followed by self-help maintenance significantly reduced flushes and sweats, consequently improving sleep and mood.[19] A review of studies treating menopause hot flushes by either CBT or hypnotherapy, showed that hypnotherapy was superior to CBT in reducing severity and frequency of flushes, but both improve sleep quality.[20]

Complementary medicines

Complementary medicines and therapies (CMT) are widely used by women in perimenopause and postmenopause. Studies of complementary therapies for menopause have used small numbers and short (less than 3 months) duration and are therefore inadequate to conclude a clinical improvement.

Some therapies included are black cohosh, phytoestrogens including red clover, ashwagandha, evening primrose oil, flaxseed, vitamin E and omega 3 preparations.[21]

Black cohosh (Cimicifuga racemosa)

A plant with known serotoninergic, dopaminergic, gamma-aminobutyric acid (GABAergic) rather than oestrogenic actions with no direct effects on hormone receptors.[22] Its main effect is to reduce VMS of flushing and sweating, with no effect on mood or anxiety. There are two standard black cohosh only products available in Australia. A recent meta-analysis compared the effects of black cohosh only with combination products and found both compounds reduced flushing, sweating and some somatic symptoms compared to placebo.[23] Side effects include headaches, dizziness, nausea and vomiting, which are mild.[24]

Phytoestrogens

Phytoestrogen foods such as soy products, flax seeds and legumes are considered safe to eat and are not contraindicated in women with hormone sensitive cancers.

Red clover

Contains phytoestrogens that, in higher doses, have been shown to reduce hot flushes. In this study, triglyceride levels decreased, significantly lower compared with placebo.[25]

Stellate ganglion block

The stellate ganglion in the sympathetic nerve chain is a fusion of the inferior cervical and first thoracic ganglions at the level of the cervical spine C7 transverse process. An anaesthetic agent is injected to block the ganglion and reduce moderate to severe hot flushes. This therapy is rarely used as there is a lack of data demonstrating efficacy and it can be difficult to access.[26]

Conclusion

Women may have contraindications to taking MHT or choose not to. The options available to treat hot flushes and sweats range from pharmaceutical therapies used 'off label' and others registered for menopause VMS. Non-prescriptive therapies include; herbal remedies, hypnotherapy, CBT and stellate ganglion block. Each woman's prescribed therapy is a discussion between her and her health professional.

Key points

- In 50% of women with menopause, VMS are experienced for more than 7–8 years, with about 10% of women continuing to experience them for more than 10 years.
- MHT is the first-line treatment for VMS; however, many women have contraindications to MHT, particularly hormone-dependent cancers.
- Licensed and off-label pharmaceutical treatments for VMS are available. Choice should be dictated by efficacy, additional drug effects, side effects, cost, tolerance and patient preference.
- Fezolinetant is a new medication specifically developed to treat VMS. It is effective and well tolerated, but expensive in comparison to 'off label' options. It can affect liver function in around 2% of patients.
- CBT and hypnotherapy might be options for women who have not tolerated pharmaceutical treatment or found it effective.

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