AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Non-hormonal Treatments for Menopausal Symptoms

KEY POINTS

- Most non-hormonal treatments only treat hot flushes and night sweats.
- There is a substantial placebo effect.
- Non-prescription remedies have generally shown no or minimal benefit.
- Fezolinetant is a neurokinin 3 receptor antagonist and treats the mechanism underlying hot flushes
- There is evidence that some antidepressants, gabapentin, and oxybutinin all reduce hot flushes.
- Clonidine is no longer recommended for the treatment of vasomotor symptoms.

Many women seek non-hormonal treatments for menopausal symptoms. This information sheet addresses the evidence concerning safety and efficacy of currently available non-hormonal treatments for menopausal symptoms. These treatments are largely prescribed "off-label". Off-label means use outside the specific purpose for which the drug was approved by Australia's medicines regulator, the Therapeutic Goods Administration. Doctors prescribing off-label have a responsibility to be well-informed about the product and to base its use on scientific evidence.

Most non-hormonal treatments only treat hot flushes and night sweats. There are also topical non-hormonal treatments for vaginal dryness. (Please refer to AMS information sheets Vulvovaginal symptoms after menopause and Vaginal health after breast cancer: A guide for patients) .

Hot Flushes and Night Sweats (Vasomotor Symptoms)

A hot flush is a sensation of heat involving the whole body and may be associated with redness and sweating. Night sweats are episodes of profuse sweating at night, either alone or just after a hot flush. These symptoms range in severity from minor irritation to a major disruption in quality of life.

Causes:

- *Oestrogen withdrawal*. The cause of hot flushes is not completely understood but is related to oestrogen withdrawal. Declining estrogen levels are thought to impact on the brain temperature regulatory centre, making both sweating and shivering more common. Centrally acting neurotransmitters including noradrenaline and serotonin are believed to be involved.
- *Other conditions.* Not all hot flushes are due to menopause. Other associated conditions include thyroid disease, diabetes, hyperhidrosis (a condition of excessive sweating which affects 1% of people), anxiety and panic disorders, obesity, hormonally active tumors, chronic infections and neurological disorders.
- *Medications*. Some medicines can cause hot flushes or make them worse. These include anti-oestrogens: tamoxifen, aromatase inhibitors, toremifene, raloxifene and clomiphene, and the gonadotrophin-releasing hormone analogues i.e. goserelin, leuprorelin and nafarelin[1] . Some non-hormonal treatments for hot flushes, such as SSRIs or venlafaxine, can also cause sweating at higher doses.

Non-Hormonal Treatments for Vasomotor Symptoms:

PLEASE NOTE:

- Some studies on these medications have involved survivors of breast cancer, including those taking anti-estrogens such as tamoxifen. The results might not apply to all women.
- Trial results on hot flushes have to be interpreted cautiously as the so-called placebo effect can be higher than 50% and may persist for more than three months.
- The long-term safety of non-prescription remedies including black cohosh, soy isoflavones and red clover is unknown, particularly for women diagnosed with hormone-dependent cancers. Overall, studies have shown either no benefit or minimal benefit for these products in treating hot flushes[2]. (Please refer to AMS Information Sheet Complementary and Herbal Therapies for Hot Flushes).
- Other than hormonal preparations, only fezolinetant and clonidine have been TGA approved for treatment of flushes.

Lifestyle Changes

Many women will benefit from lifestyle changes, stopping smoking, improving diet, losing weight if overweight, and regular exercise. These do not necessarily reduce symptoms but improve overall wellbeing and can make symptoms easier to tolerate. (Please refer to AMS Information Sheet Lifestyle and behavioural modifications for menopausal symptoms). Dressing in layers, wearing breathable fabrics, avoiding spicy food and avoiding excess alcohol and caffeine may also assist.

Exercise and yoga

There is little evidence to support exercise or yoga for the management of menopausal symptoms, although they are associated with general health benefits in mid-life women[3].

Psychological therapies

Cognitive behavioral therapy (CBT)

Cognitive behavioural therapy has been demonstrated to improve sleep, mood and bother of vasomotor symptoms, and in some studies to reduce the frequency of vasomotor symptoms[4].

Hypnosis

Hypnosis has been shown to reduce vasomotor symptoms severity and frequency, and has been useful for reducing anxiety and improving sleep[5].

Mindfulness, paced respiration and relaxation therapies have been studied in the management of menopausal symptoms, but do not have sufficient evidence to support their use[6].

Complementary, "Alternative" or Herbal Therapies

(Please also refer to AMS Information Sheet Complementary And Herbal Therapies for Hot Flushes).

- These may include herbal or plant supplements and have been marketed as skin creams and foods
- Little solid scientific evidence exists to support claims for alternative therapy benefiting menopausal health.
- Whilst some studies support a benefit for soy foods or extracts to reduce vasomotor symptoms, the evidence is inconsistent, and a meta-analysis reported no overall benefit in treating menopausal symptoms[7].
- Black cohosh has been shown in some trials to reduce hot flushes and improve mood in menopausal women. A meta-analysis has reported a comparable effect to low dose hormone therapy, with a good safety profile[8].

Antidepressants

Several types of antidepressants (SNRI and SSRIs explained below) have been noted in small, short-term studies to reduce hot flushes. Four weeks is sufficient to establish whether these will be effective in reducing hot flushes. These medications should not be taken with any other antidepressants or any substance containing St. John's Wort. Discontinuation should be tapered.

- *Venlafaxine and Desvenlafaxine* are serotonin-noradrenaline reuptake inhibitors (SNRIs). Serotonin and noradrenaline, known to affect mood, may also impact thermoregulation
    - The optimum results have been with venlafaxine 75mg SR and desvenlafaxine 100mg.
    - *Side-effects* include dry mouth, nausea, sleep disturbances, loss of appetite and constipation. Venlafaxine should not be used in women with heart disease, electrolyte imbalance or uncontrolled high blood pressure. Blood pressure should be monitored while taking it and discontinuation should be tapered.
    - 75mg of SR venlafaxine is equivalent to low dose oestrogen (25 mcg) for the treatment of hot flushes[9]
- *SSRIs (Selective Serotonin Reuptake Inhibitors)*. This class of antidepressants includes paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram, and escitalopram. There is limited information about how different non-hormonal agents compare with each other for efficacy due to a lack of head to head studies. In selecting first line treatment using non-hormonal methods, a systematic review has reported that Venlafaxine 75mg CR, Escitalopram 10-20mg and gabapentin 900mg have all been shown to be effective for hot flushes after breast cancer[10, 11].
    - *What we don't know*: There are very few studies comparing antidepressants for hot flushes with other therapies such as average dose hormone therapy. The long-term effects of these medications in healthy women are not known.
    - *Side-effects*: The dosage for treatment of hot flushes is generally lower than that used for treatment of depression. Very low doses at the start of therapy may minimise side effects. If this is not effective, the dose can be increased after a week. Women experiencing drowsiness should take the medication at night. Dry mouth is the most common side-effect. Others include nausea, diarrhoea, headaches, insomnia, jitteriness, fatigue and sexual difficulties. Sudden withdrawal can bring on headaches and anxiety, so discontinuation should be tapered.
    - *Use of SSRIs in women with breast cancer using tamoxifen*. There have been concerns that certain SSRIs (paroxetine and fluoxetine) may reduce the active metabolite of tamoxifen. However, it is uncertain whether this is of clinical relevance[12]. It may be safer to use other SSRIs first line in this situation.

Fezolinetant

Fezolinetant is a neurokinin 3 receptor antagonist, specifically designed to treat vasomotor symptoms, and is TGA approved in Australia for this purpose. Fezolinetant targets the neural pathways (KNDy neurons) involved in the hypothalamic thermoregulatory centre. Compared with placebo it has been shown to reduce the frequency and severity of moderate to severe vasomotor symptoms, and improved quality of life and reduced sleep disturbance[13].

- *Dosage:* This is a fixed dose in the form of a daily 45mg tablet.
- *Side effects* may include headache, nausea, fatigue and insomnia. Rarely liver function can be affected, and it is recommended to check liver function tests within the first 3 months of treatment, and then periodically thereafter.

NB: Fezolinetant has not been studied in patients with current or previous breast cancer or with other oestrogen-dependent tumours. A decision to treat these patients with fezolinetant should be based on an individual benefit-risk assessment

Gabapentin

Gabapentin is an anticonvulsant (an analogue of gamma-aminobutyric acid). It is approved to treat neurological disorders such as seizures and neuropathic pain.

- *Research*: A systematic review has confirmed that Gabapentin 900mg per day reduces hot flushes more effectively than placebo[11]. The most common side effect of gabapentin is somnolence, and women may prefer to take it at night.
- A randomized controlled trial of 12-weeks duration compared a higher dose of gabapentin (2400mg daily) and oestrogen (Premarin 0.625mg daily) against a placebo. There was a significant placebo effect (54% reduction in severity and frequency of hot flushes) and gabapentin appeared to be as effective as oestrogen (71% and 72% respectively)[14].
- *What we don't know*: Higher doses may be more effective but may cause more side effects. There have been no long-term studies.
- *Dosage*: The recommended treatment is to start at a low dose (100mg three times a day for three days) and build up to taking one 300mg tablet three times a day. Women typically report reduced hot flushes within days.
- *Side effects:* Rash, dizziness and excessive sleepiness which tends to improve over time. The drug can also cause swelling of the lower limbs and weight gain. Discontinuation should be gradual over a week.

Oxybutynin

This anticholinergic and antimuscarinic medication is used for management of urinary urge incontinence and overactive bladder. It has been shown to reduce moderate to severe vasomotor symptoms in a number of studies[15].
Dosages have varied from 2.5mg-5mg twice daily, up to 15 mg of an extended-release preparation used daily.

- *Side effects* may include dry eyes or mouth, confusion, urinary symptoms, and caution should be used in the elderly, due to the risk of cognitive decline.

Clonidine

Clonidine is a centrally-acting alpha adrenergic agonist which stimulates particular brain receptors and has been used for many years to lower blood pressure and prevent migraine as well as treat hot flushes. In studies it has proved to be less useful than other non-hormonal medications for reducing vasomotor symptoms. Due to the side effect profile and other agents being more effective, clonidine is no longer recommended to treat vasomotor symptoms[6].

- *Dosage*: Oral doses are started low e.g. 25micrograms (mcg) twice a day and built up to 75 mcg twice a day, although some women may need 150 mcg twice a day.
- *Side-effects* include dry mouth, drowsiness, dizziness, constipation and difficulty in sleeping. Advice is to stop clonidine if there is no benefit after four weeks. High doses should be tapered gradually to avoid side-effects like raised blood pressure.

Other strategies

Acupuncture

The evidence for acupuncture significantly reducing menopausal symptoms is mixed[6].

Stellate ganglion block

This treatment involves injection of anaesthetic agent to block the sympathetic nervous chain, via a lower cervical or upper thoracic approach. It has been useful for reducing moderate to severe vasomotor symptoms in some studies[16].

Ongoing treatment and follow-up

Any treatment for hot flushes needs to be evaluated periodically. Before switching from one treatment to another there may need to be a gradual tapering of medication.

Content updated September 2024

Additional reading – Position Statements.

https://www.menopause.org.au/hp/position-statements/emas-position-statement-non-hormonal-management-of-menopausal-vasomotor-symptoms

https://www.menopause.org/docs/default-source/professional/2023-nonhormone-therapy-position-statement.pdf

References

1. Hickey M et al. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. Lancet Oncol 2005;6:687-95.
2. Franco OH et al. Use of Plant-Based Therapies and Menopausal Symptoms: A Systematic Review and Meta-analysis. JAMA 2016;315:2554-63.
3. N Barnard et al. A dietary intervention for vasomotor symptoms of menopause: a randomized, controlled trial. Menopause 2023;30:80-87.
4. Hunter MS. Cognitive behavioral therapy for menopausal symptoms. Climacteric. 2021 Feb;24(1):51-56.
5. Elkins GR et al. Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. Menopause 2013;20:291-8.
6. Advisory panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. Menopause. 2023 Jun1;30(6):573-590.
7. Gençtürk N et al. The effect of soy isoflavones given to women in the climacteric period on menopausal symptoms and quality of life: Systemic review and meta-analysis of randomized controlled trials. Explore (NY). 2024 May 22;20(6):103012
8. Castelo-Branco C et al. Review & meta-analysis: isopropanolic black cohosh extract iCR for menopausal symptoms - an update on the evidence. Climacteric. 2021 Apr;24(2):109-119
9. Joffe H et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. JAMA Intern Med 2014;174:1058-66.
10. Rada G et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev 2011;Sept 8:CD004923.
11. Johns C et al. Informing hot flash treatment decisions for breast cancer survivors: a systematic review of randomized trials comparing active interventions. Breast Cancer Res Treat. 2016;156(3):415-26.
12. Haque R, Shi J, Schottinger JE, et al. Tamoxifen and Antidepressant Drug Interaction in a Cohort of 16,887 Breast Cancer Survivors. J Natl Cancer Inst 2016;108.
13. Chavez MP et al. Fezolinetant for the treatment of vasomotor symptoms associated with menopause: a meta-analysis. Climacteric. 2024 Jun;27(3):245-254.
14. Reddy SY et al. Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. Obstet Gynecol. 2006 Jul;108(1):41-8.
15. David PS et al A Clinical Review on Paroxetine and Emerging Therapies for the Treatment of Vasomotor symptoms. Int J Womens Health. 2022 Mar 10:14:353-361.
16. Walega DR et al. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. Menopause 2014;21:807-14.