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.
- There is evidence that some antidepressants, gabapentin and clonidine all reduce hot flushes.

Many women request 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 base its use on scientific evidence. Most non-hormonal treatments only treat hot flushes and night sweats. There are also non-hormonal treatments for vaginal dryness. (Please refer to AMS information sheets Genito-urinary syndrome of menopause 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 venlafaxine, can also cause hot flushes at higher doses. Some men who undergo treatments for prostate cancer experience hot flushes.

Non-Hormonal Treatments for Vasomotor Symptoms:

Some cautions:

- 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 clonidine has been TGA approved for treatment of flushes.

Lifestyle Changes

Many women will benefit from lifestyle changes, stopping smoking, improving diet 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 advice for healthy ageing). Dressing in layers, avoiding spicy food and avoiding excess alcohol and caffeine may also assist.

"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 with the key ingredient being phytoestrogens.
- Little solid scientific evidence exists to support claims for alternative therapy benefiting menopausal health.
- Black Cohosh has been shown in some trials to reduce hot flushes in peri-menopausal women[3]. However there have been reports of liver damage with its use which is likely to be due to contaminants in certain products.

Vitamin E

Vitamin E is a non-prescription fat-soluble vitamin.

- *Vitamin E shows very marginal efficacy in reducing* hot flushes (average reduction of one hot flush per day)[4].
- *Dosage/side-effects*: 800 to 1000 international units (IU) per day in divided doses, taken with food. Although safety has not been established there was no toxicity in one study of 120 people.

Antidepressants

Several types of antidepressants (SNRI and SSRIs explained below) have been noted in small, short-term studies to reduce hot flushes. Relief, if any, is rapid, unlike for depression where the effect of the medication is often not observed for six to eight weeks. Four weeks is sufficient to establish whether these products 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 and 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 ultra-low dose oestrogen (25 mcg) for the treatment of hot flushes*[5]
- *SSRIs (Selective Serotonin Reuptake Inhibitors).* This class of antidepressants includes paroxetine, fluoxetine, fluvoxamine, sertraline and citalopram, 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 recent systematic review has reported that Venlafaxine 75mg CR, Escitalopram 10-20mg and gabapentin 900ng have all been and shown to be effective for hot flushes after breast cancer.
    - *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[7].

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[6]. The most common side effect of gabapentin is somnolence, and women may prefer to take it at night.
- A recent 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).
- *What we don't know*: Higher doses may be more effective but may cause more side-effects. There have been no long-term studies. The interaction of gabapentin with breast cancer treatments such as tamoxifen has not been studied, but it is thought unlikely because gabapentin does not interfere with other anti-seizure medications.
- *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 300 mg tablet three times a day. Women typically report reduced hot flushes within days.
- *Side-effects* include 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.

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.

- *Research*: Several randomized controlled trials have shown that clonidine is more effective than placebo for hot flushes, but side effects may limit tolerability. Both tablets and transdermal (skin patches) have been tested. Several small studies showed reduced hot flushes at eight weeks (38% for clonidine versus 24% for placebo). Patches reduced flushes by 80% compared to 46% for oral clonidine, however the patches are not available in Australia. Two larger studies of breast cancer survivors taking tamoxifen showed reduced frequency of flushes with oral and transdermal clonidine compared to placebo.
- One recent study comparing clonidine to venlafaxine in breast cancer patients has shown equal efficacy but better tolerability for clonidine[8].
- *Dosage*: Oral doses are started low eg. 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.

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.

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Additional reading – Position Statements.

www.menopause.org.au/health-professionals/position-statements/996-emas-position-statement-non-hormonal-management-of-menopausal-vasomotor-symptoms

www.menopause.org.au/health-professionals/position-statements/1045-nonhormonal-management-of-menopause-associated-vasomotor-symptoms-2015

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3. Laakmann E, Grajecki D, Doege K, zu Eulenburg C, Buhling KJ. Efficacy of Cimicifuga racemosa, Hypericum perforatum and Agnus castus in the treatment of climacteric complaints: a systematic review. Gynecol Endocrinol 2012;28:703-9.
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