



NonHormonal Treatments for Menopausal Symptoms

This sheet is different to other AMS sheets in that it is intended for medical practitioners and nurses to help provide information to their patients.

There is a second consumer/patient pamphlet about the same topic in production.

Women sometimes seek alternative treatments for the symptoms of menopause if they have not found relief with lifestyle changes or their hormone replacement therapy does not work. Some may be advised against hormones because of a medical condition and others want to avoid them after hearing about health risks.

This pamphlet includes summaries of studies of treatments prescribed by doctors "off-label" for relief of menopausal symptoms. (The main symptom treated by these medications is hot flushes/night sweats.) 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.

Hot Flushes and Night Sweats (Vasomotor Symptoms)

A hot flush (or hot flash) 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. It is thought to involve destabilisation of the part of the brain (the hypothalamus) which regulates body temperature. Hot flushes may occur because the woman's threshold for sweating has been lowered. 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, toremifene, raloxifene and clomiphene and the gonadotrophin-releasing hormone analogues i.e. goserelin, leuprorelin and nafarelin. Some men who undergo treatments for prostate cancer experience hot flushes.

Treatment for Vasomotor Symptoms

Some cautions:

- Many studies on these medications have involved survivors of breast cancer, including those taking tamoxifen and anti-oestrogen medication. 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 as high as 54%.
- 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. Small trials have not shown much benefit and we do not yet have the results of some large trials still underway.
- A meta-analysis of randomized controlled-trials indicated that oestrogen reduces the frequency of hot flushes by 77% or by approximately 2.5 - 3 hot flushes per day
- Other than hormonal preparations, only clonidine has been approved for flushes.



Lifestyle Changes

Many women will benefit from lifestyle changes, stopping smoking, improving diet and regular exercise. These do not necessarily reduce symptoms but feeling more healthy can make symptoms easier to tolerate. (See AMS Healthy Ageing and Lifestyle sheet)

Hormone Replacement Therapy (HRT)

Hormone therapy is known to decrease hot flushes by up to 80 to 90%. (See AMS pamphlets on HRT)

"Alternative" or Herbal therapies

- These may include herbal or plant supplements and have been marketed as skin creams and foods with the key ingredient being phyto-oestrogens.
- 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 perimenopausal women. However there have been reports of liver damage with its use.

Vitamin E

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

- Research: in one study, vitamin E was marginally effective in the treatment of hot flushes following breast cancer, demonstrating a reduction by an average of one hot flush per day.
- Dosage/side-effects: 800 to 1000 international units (IU) per day in divided doses, taken with food. Effects, if any, may take weeks. Although safety has not been established there was no toxicity in one study of 120 people.

Antidepressants

Several types of antidepressants (venlafaxine 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. So a trial of one week might be enough to determine if they are going to work for 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: is a serotonin-noradrenaline reuptake inhibitor (SNRI). Serotonin and noradrenaline, known to affect mood, are also believed to be involved separately in setting body temperature.

- Research: Initial results from small studies suggested that venlafaxine 75mg SR was effective and well-tolerated. In a study in breast cancer survivors, venlafaxine reduced vasomotor symptoms by up to 75% compared to only 27% for those taking placebo. However no benefit was shown in a recent 12 week randomized controlled trial of venlafaxine 75mg over placebo.
- 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 high blood pressure. Blood pressure should be monitored while taking it and discontinuation should be tapered.

SSRIs (Selective Serotonin Reuptake Inhibitors). This class of antidepressants includes paroxetine, fluoxetine, fluvoxamine, sertraline and citalopram.

- Research: One study showed women taking paroxetine had up to 65% reduced flushes compared to 38% reduction in women taking placebo. In a study of breast cancer survivors fluoxetine reduced hot flushes 20% more than placebo. However long-term use for hot flushes is questionable following a nine month trial in healthy women showing no benefit of citalopram or fluoxetine over placebo aside from quality of sleep improvement with citalopram.



- What we don't know: There are very few studies comparing antidepressants for hot flushes with other therapies such as 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. The results of one study have suggested that paroxetine reduced the active metabolite of tamoxifen raising concern that the effectiveness of the cancer drug could be reduced.

Mirtazapine

Mirtazapine is an anti-depressant. Only two small studies have looked at its effect on hot flushes but they did not compare the drug to placebo. In one study of four women all reported hot flushes disappeared with a week of taking 15 to 30 mg of mirtazapine daily. The other study in 16 women found hot flushes more than halved.

Gabapentin

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

- Research: In two studies, women taking 900mg gabapentin a day experienced a reduction in hot flushes but 300mg daily dose was no better than placebo. Half of the users had at least one side-effect.
- 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. Gabapentin is expensive (about \$90 a month).
- 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: 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.



- 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.

Antihistamines

The antihistamine cetirizine (Zyrtec) has been reported by researchers as showing promise for reducing hot flushes. Further studies are awaited.

Ongoing treatment and follow-up

Any treatment for hot flushes needs to be evaluated periodically. One reason is to determine if it is still needed as in many women menopause-related vasomotor symptoms will improve over time. New research and changing ideas about treatments may have an impact on health decisions. Before switching from one treatment to another there may need to be a gradual tapering of medication.

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