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Women's Health & Research
INSTITUTE OF AUSTRALIA

MANAGING HOT FLUSHES

In Western societies, the most common menopause symptom is the hot flush. This typically begins as a feeling of heat in the chest or upper body which then spreads all over the body, lasting a few minutes. It is often associated with facial redness, drenching sweats, palpitations and dizziness. Some have 1 or 2 a day; others can have 20 an hour, day and night.

WHAT CAUSES A HOT FLUSH?

The menopausal flush

The menopause flush is caused by a disruption to the thermoregulatory system in the anterior hypothalamus. Basically, there are two 'thermostats'; if core temperature goes above the high one, flushes occur; and if core temperature goes below the lower thermostat, shivering happens. For those with severe vasomotor symptoms, the two thermostats are close together, thus these women are more easily triggered to sweating and shivering. During the flush, central temp does not rise, but skin temperature goes up by 5-7 degrees C. Neurotrans-mitters such as serotonin and noradrenaline are involved, which as we shall see shortly has implications for therapy.

In Australia, most women will have mild flushes for a couple of years, and then the temperature centre adapts and the flushes settle. In a significant minority (10-20%), flushes continue forever.

OTHER CAUSES OF FLUSHING

Not all flushing is due to menopause and so it is important to ask the woman to describe her hot sensation. The differential diagnosis includes:

1. **Fever.**
   If the woman takes her central (mouth) temperature during a flush, it will be less than 37oC. If her temperature is more than 37.5oC then she has a fever and that will need to be investigated.

2. **Hyperhydrosis.**
   These patients sweat all the time. It often especially affects the upper body and can be confused with hot flushes.

3. **Acne rosacea**
   Acne rosacea is a skin condition that causes facial flushing and can co-exist with menopausal flushing.

4. **Hyperthyroidism.**
   Hyperthyroidism causes an increase in sweating, not flushes as such.

5. **Phaeochromocytoma.**

   Phaeochromocytoma is a rare tumour that usually releases noradrenaline into the circulation and so the sufferer will go pale and white because of vasoconstriction. During an attack they will be hypertensive and feel dreadful ('like they are going to die'). It is usually diagnosed by finding raised levels of adrenaline or noradrenaline in a 24-hour urine collection.

6. **Carcinoid tumours.**

   Carcinoid tumours secrete serotonin and the usual primary site is the bowel. During an attack, the patient may turn red, but they often have diarrhoea too and the attack usually lasts longer than a few minutes.

7. **Some drugs.**

   High-doses of SSRIs, SNRIs and vasodilators can cause sweating and flushing

8. **Very rare causes.**

   Mast-cell tumours secrete histamine (producing urticaria) and some rare parathyroid tumours secreting calcitonin can also elicit flushes.

TREATMENT OF HOT FLUSHES

Lifestyle modifications

Avoidance of triggers can be helpful for some. Such triggers include – stress, hot drinks, spicy foods, alcohol, over-heating, and hot weather. There is some evidence that a diet high in soy and cereal can help those with mild flushes. Exercise makes flushes worse by overheating the body.

Herbals

Most of the herbal therapies sold over-the-counter in Australia have been either shown not to be more effective than placebo or haven't been formally tested. Nelson and colleagues performed a meta-analysis (a statistical review) of non-hormonal therapies for menopausal symptoms. They found that red clover extracts were no more effective than placebo but that there was some evidence that some soy extracts are effective (e.g. Phytosoya®, Arkopharma Pty Ltd).

By far the most effective and tested herbal, currently being sold in Australia is Remifemin®, which is an extract of black cohosh. This German herbal therapy for relieving menopausal symptoms has shown to relieve sweats, flushes and mood swings (better than placebo) in a dose of 1 twice a day (see Remifemin® Clinical Studies). A "dose-finding study" showed that 2 twice a day was better than 1 twice a day (but 8 a day was not superior to 4/day). It helps about 7 out of 10 women within 4-6 weeks. It is not oestrogenic and so is safe for women who should not be exposed to oestrogen (e.g. after breast cancer). It can occasionally cause nausea. Rarely, there

have been case-reports of severe liver problems associated with Remifemin® usage. It is not clear if the herb is the cause or it is co-incidental. It has been submitted to several randomised controlled trials (RCTs). Osmers and colleagues performed a RCT of 304 women randomised to 2 tablets a day versus placebo. The active treatment was statistically significant for a global menopause score and specifically for vasomotor, mood and vaginal symptoms, despite the fact that the exact is not oestrogenic. The recommended maximum dose is 4 tablets a day.

Uebelhack and colleagues performed a RCT of Remifemin® and St John's Wort extract (14) amongst 301 women. Again the active compound was superior to placebo for vasomotor and mood symptoms. Unfortunately, the combination product is not available in Australia. Remotiv® (made by Flordis) is a clinical tested extract of St John's Wort that can be combined with Remifemin®.

Trials with black cohosh extracts have largely found no greater risk of side effects than placebo. However, there has been some case reports of hepatic failure, probably autoimmune and idiosyncratic associated with black cohosh. The incidence appears to be less than 1 in 100,000 cases.

OTHER COMPLEMENTARY AND ALTERNATIVE THERAPIES (CAMS)

Nedrow and colleagues have systematically reviewed CAMs used for menopausal symptoms (15). It can be quite challenging to design placebo for physical CAMs such as reflexology and acupuncture – but some researchers managed to do it. One trial compared reflexology and 'routine' foot massage; and 4 trials used sham acupuncture needles. None of these treatments was superior to sham-treatment for the relief of menopausal symptoms. They also reviewed 6 RCTs of Chinese herbal mixtures; all the RCTs were negative. Slow deep breathing – 'paced respiration' – can reduce the severity of a hot flush (1).

Hormone therapy (HT)

For the interested reader, Blake and Grady have recently reviewed the evidence-base for managing meno-pause. HT has been around for a very long time – oestradiol implants since the mid-thirties and Premarin® since 1942.

In Grady's review, she demonstrates that 0.625mg Premarin® and 1-2mg E2 orally reduce hot flushes by around 90-95% with a placebo effect of 45% (9). Relief is usually substantial within 4 weeks. Lower doses (e.g. 1mg E2 daily) take longer to work but have a lower rate of side effects. Progestins are added to prevent endometrial hyperplasia, which can progress to endometrial cancer. These combined hormones are given either cyclically for 10-14 days, or continuously on a daily basis.

Using HT

The healthy perimenopausal woman seeking HT usually begins with a cyclical HT such as Trisequens. Continuous HT does not suppress the cycle and so break-through bleeding is common and can be troublesome. A short course of a low dose contraceptive Pill (e.g. Zoely®) might be considered for a healthy, non-smoking, normotensive under-50 year-old woman. If heavy menstrual periods need treatment, a Mirena

device could be used to both control the menstrual problem and give endometrial-protection, whilst giving a tablet or patch of oestrogen to control flushes and sweats.

No matter the regimen, initial breast soreness and irregular vaginal bleeding are common, and usually settle with time. Around 10-15% will have progestin side-effects such as bloating, mood swings, even depression. Dydrogesterone is the best tolerated oral progestin, and for some, the Mirena® device might suit.

Postmenopausal women are usually offered continuous HT, to help minimize bleeding. Even with low-dose regimens, around 1/3 to ½ will have spotting and bleeding, at least for a month or two.

There are surprisingly few trials on stopping HT. Most clinicians would treat initially for 2 years and then wean the women slowly off the HT over 3-6 months; although there is no evidence to support this practice. If flushes return, some will go back on HT – often on a lower dose than initially. There is a significant minority who have great trouble coming off their HT and they are probably the same women who 'flush-forever.'

Risks and benefits of long-term HT

In the 1990's there was a hope that HT might be a useful long-term preventive agent for women over 50 years of age – reducing heart and fracture risks. However, since 2002, the Women's Health Initiative (WHI) study has had high media profile, and has caused enormous fear in the community because of a perceived link with HT and breast cancer.

The Women's Health Initiative (WHI) was an NIH-funded (USA government) study into strategies to help older women. It had 2 HT arms, both tested in women average-aged late 60's. The combined HT arm (Premarin®-Provera®) has been admirably summarised by MacLennan.

After 5 years of combined HT (compared with placebo), there were the following risks and benefits. All rates are per 10,000 women per year.

Adverse Effects	Benefits
8 extra breast cancers	6 fewer bowel cancers
7 extra episodes of cardiovascular disease*	2 fewer uterine cancers
8 extra cases of pulmonary embolism	10 fewer hip & spine fractures
8 Extra strokes	

Table 1: Risks and benefits of combined HT in older women

*Not statistically significant

When the WHI data were re-analysed in 2007, to examine risks in the usual age group who take HT - those under 60 years – no increased risks were found. It was disappointing that the authors chose to take 5 years to

release these data and unfortunately this important message has not made it out into the general community. MacLennan also points out that there are emerging data that side effects are reduced by using lower HT doses, minimizing systemic progestin exposure by using a Mirena device (or natural progesterone), using non-oral HT in some women (patches or gels) and initiating HT near menopause. Women under 60 years of age who took HRT in WHI actually had a lower risk of death than the placebo group.

The woman who has had a hysterectomy

These women should be treated with oestrogen only medication. The oestrogen-only arm of WHI (Premarin® 0.625mg daily versus placebo) enrolled 10,739 women aged 50-79 years and continued the trial for 7 years. The risk of breast cancer was significantly decreased in the Premarin®-arm and a non-significant increased risk of stroke was demonstrated. There is evidence of decreased risk of thrombosis with transdermal oestrogen.

Long-term issues

HT remains a valid treatment option for some women (under 60 years of age) with osteopenia or osteoporosis. The medical trials to date would suggest that HT has no role in the prevention of heart disease or dementia.

Tibolone

Tibolone is not a traditional HT, but is a hormonal treatment with oestrogenic, progestational and androgenic actions. Its effect on a target tissue depends upon its final metabolism. For example the endometrium converts Tibolone to a progestational metabolite. When given to postmenopausal women, it has a lower rate of breakthrough bleeding and breast pain than standard HT and appears to have no impact on mammographic density unlike HT which usually increases breast density. It probably should be avoided by women over the age of 60 years because of a slightly increased risk of stroke.

Natural Progesterone

Australia is one of the few countries that does not have access to natural progesterone on a normal (PBS) script. Progesterone is used in Europe as a capsule (100mg daily or 200mg cyclically) or vaginally. Oral progesterone is usually well tolerated, although a small number of women seem to develop mood swings (probably from progesterone by-products made by the liver).

Progesterone is variably absorbed as a troche/lozenge or cream. However, the upper vagina absorbs some drugs and hormones directly to the uterus and so vaginal use of progesterone could be useful for some women. Studies have shown that doses of 45-100mg given twice weekly can protect the lining of the uterus with few (if any) side effects. In one Spanish study they combined the vaginal progesterone (100mg) with an oestradiol patch. As the patch is changed twice weekly, the women were asked to insert the progesterone pessary on the day they changed the patch. This seems to be a convenient, safe, bio-identical method of using HRT.

It is important to realise that at the moment, compounding chemists are not regulated and so seek out a very experienced chemist. At WHRIA, we recommend Stenlake pharmacy **(http://www.stenlake.com.au/).** We have had long relationship with this group and often conduct research together.

Non-hormonal drugs for flushes

An increasing number of 'brain-drugs' is being used to treat menopausal symptoms. Intuitively, this makes sense, since the vasomotor and mood symptoms are brain-in-origin. Currently, the most popular non-hormonal drugs for managing menopausal brain-symptoms are listed below:

SSRIs and SNRIs.

Nelson's review examined seven randomised controlled trials (RCTs) and clearly showed evidence of efficacy. Typically the lowest tablet size was the most effective for treating hot flushes. High doses of these agents can actually cause hot flushes and sweats as a side-effect. This is not unusual for hormonal agents. Many hormones in low pulsatile doses stimulate the target receptor, in contrast to high-continuous doses which often down-regulate the receptor. Typical doses used to treat flushes and mood swings of menopause include venlafaxine 75XR and citalopram 20mg daily. The side-effects of these agents are discussed in detail elsewhere.

Clonidine.

This is an old blood pressure medication. Most of the clonidine RCTs used doses between 0.05-0.15mg daily. These doses were more effective than placebo. Side-effects include hypotension, dry mouth, sedation and in high doses – depression. Clonidine might be useful to manage both hypertension and flushes. It can also be used as a prophylactic migraine drug. It is not unusual for migraine frequency to increase around the time of the perimenopause; to then settle after the last period.

Gabapentin.

Two RCTs trials of gabapentin, used doses 300-900mg daily; the higher dose being statistically better than placebo. The main side effects can be headache, drowsiness, dizziness, nausea, disturbed sleep, fluid retention and weight gain. When coming off gabapentin, the dose should be reduced by 300mg at a time every 3-4 days.

It is certainly helpful to have these options available to the clinician and the patient. For example, consider a woman who has just completed chemotherapy for breast cancer and is now rendered menopausal. Her oncologist starts her on tamoxifen or an aromatase-inhibitor and not surprisingly, her flushes increase dramatically. Remifemin®, perhaps even combined with an SNRI will help around 70-80%. These women are often grateful for a reduction in symptom severity, rather than complete resolution of their symptoms. It can be clinically useful to temporarily cease the endocrine therapy for 2-4 weeks to examine the impact of the drug on flushing severity.

A migrainous, hypertensive peri-menopausal woman might choose to try clonidine. A patient suffering from trigeminal neuralgia or epilepsy and significant flushing, might like to try gabapentin – for both problems.

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Managing the woman who flushes forever

If a woman is still having significant flushes after 5-6 years, then she is probably in that small group who flush forever. Properly counselled, some of these women will choose to stay on low dose HT, at least until a better choice is available, and accept the small risks. Theoretically, it may be appropriate to treat these women with transdermal oestrogen (e.g. a dot-patch) to minimize the risk of thrombosis and consideration should be given to fitting her with a Mirena® device or vaginal progesterone to minimize systemic progestin exposure.

CONCLUSIONS

For many women menopause will not present any great difficulties. Most women with mild-moderate symptoms will be content in the knowledge that menopause is another natural stage in their life, perhaps combined with some lifestyle changes and a herbal therapy such as Remifemin. For some however, severe flushes and sweats completely disrupt their lives and these women should be offered medical treatment – usually HT. For a small number, menopause symptoms will continue forever. The long-term management of these problems remains a challenge, but the key is quality medical information and presenting the women with well informed choices.

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More Information

Australasian Menopause Society https://www.menopause.org.au/