Introduction

Research of women’s views confirms that many women will look for non-hormonal or alternative treatments to help manage menopause symptoms, rather than seek medical help.1 Some women cannot take hormonal therapies and greater experience working with women who have had breast cancer2-4 provides better evidence as to how best to manage these patients with an individualised holistic treatment plan.5-7 There are increasing numbers of women preparing for risk reducing surgery or other treatments which will impose a sudden menopause, many of whom will not be recommended to take hormonal therapies or who will be recommended to take hormone replacement therapy (HRT) only to age 50.8 National Institute of Clinical Excellence (NICE) quality standard 143 recommends that women are given information before they have treatment which will precipitate menopause.9

This consensus statement incorporates recommendations for best practice from both national and international guidelines. Hot flushes and night sweats are the most common menopausal symptoms and there is evidence they may last for several years, with an average duration of seven years shown in some studies.11, 12
Most alternative therapies are evaluated in respect to vasomotor symptoms, and some will also have effect on mood. Placebo effect may be as great as 30-50% in many studies (and might itself be considered a treatment option).\textsuperscript{13,14} Much of the most recent information comes from studies involving women who have had breast cancer.\textsuperscript{15} Urogenital problems due to estrogen deficiency are covered in a separate consensus statement.\textsuperscript{16}

Several non-hormonal therapies have been used for symptom control although no treatment is as effective as estrogen.\textsuperscript{17,18} Prescribable non-hormonal therapies that have been tested in randomised placebo-controlled trials and shown to be effective include Paroxetine, Fluoxetine, Citalopram and Escitalopram, Venlafaxine and Desvenlafaxine, Gabapentin and Pregabalin, and clonidine. Self-help options which include Isoflavones and soya products, herbal therapies such as Black Cohosh and St John’s Wort, cognitive behaviour therapy with targeted self-hypnosis, acupuncture and nerve block have also been used for vasomotor symptom control.\textsuperscript{5, 19, 20}

1. **Clonidine: alpha adrenergic receptor agonist/licence class anti-hypertensive and menopause symptom control**

Clonidine is the only non-hormonal drug with a licenced indication for control of hot flushes in the UK.\textsuperscript{21} Clonidine 25 mcg is prescribed twice daily for 2 weeks, increased up to a maximum of 50 mcg three times a day. The evidence base is contradictory, although one study shows significant reduction in the numbers of hot flushes and improved quality of life compared with placebo in women who have had breast cancer using 100 mcg daily.\textsuperscript{22,23,24} Side effects of Clonidine are dose related and at higher doses clonidine causes sleep disturbance in at least 50 percent of users. It must be withdrawn gradually as abrupt cessation can cause rebound hypertension.\textsuperscript{21} Clonidine obviously may not be suitable for patients with a baseline low blood pressure.

2. **Selective Serotonin re-uptake inhibitors (SSRI) (fluoxetine, paroxetine, citalopram, sertraline) and Serotonin Noradrenaline re-uptake inhibitors/ selective Serotonin re-uptake inhibitors (SSRI-SNRI) (Venlafaxine and Desvenlafaxine)**

Historically, SSRI and SNRIs are recognised for their effects on depression and anxiety, but for the purposes of this review the effect on vasomotor symptoms will be considered.\textsuperscript{4} In the USA, FDA approval was granted in 2015 for Paroxetine for menopausal hot flushes.\textsuperscript{25} Most studies compare SSRI or SSRI/SNRI with that of placebo and some with Clonidine or Gabapentin but not with each other.\textsuperscript{26} Overall, studies demonstrate that Venlafaxine 37.5 mg titrated up to 150 mg per day, Paroxetine 10 mg daily or Citalopram 10 mg - 30 mg are the most effective.\textsuperscript{27, 28} Paroxetine has the best evidence and at 10 mg is as effective as at higher doses and associated therefore with a lower incidence of side effects.\textsuperscript{18, 22} Fluoxetine has evidence of efficacy and lower incidence of side effects.\textsuperscript{4, 26} Sertraline seems least effective and escitalopram improves flushes and has significant benefits and improvement in wellbeing but some side effects.\textsuperscript{29-31} Many recent studies are with Venlafaxine which consistently seems effective.\textsuperscript{4, 26, 32, 34, 35} Desvenlafaxine has also been studied for hot flush control but is not available in the UK.\textsuperscript{36}

SSRIs and SSRI/SNRIs induce significant adverse events (SAEs) such as dry mouth, nausea, constipation and appetite problems, which are directly dose related.\textsuperscript{4, 26, 33} Nausea can be reduced by using a long-acting formulation, using a once daily dose with food. Reduction in libido is another class effect.
Some SSRIs inhibit cytochrome P450 activity\(^6,37\), an enzyme involved in tamoxifen metabolism and consequently most guidelines recommend that SSRIs such as Fluoxetine and Paroxetine must not be prescribed concomitantly with tamoxifen.\(^26,38\) The Comité de l'évolution des pratiques en oncologie (CEPO) guidance is less prescriptive in referencing the Arimidex, Tamoxifen Alone, or in Combination Study (ATAK), suggesting there is no strong evidence to avoid.\(^4\) We know too that the impact on cytochrome P450 is dependent on genotype and thus any SSRI may potentially inhibit tamoxifen efficacy for some patients.\(^39\)

Paroxetine is the SSRI with the best evidence for efficacy\(^16,22\), effective at 10 mg daily, although the more usual dose of 20 mg may be used if an antidepressant effect is also required. It is the SSRI of choice for patients not taking tamoxifen. Venlafaxine is the preferred treatment for women who have had breast cancer taking tamoxifen and at 75 mg there is significant reduction in hot flushes with concomitant improvement in fatigue, mental health and sleep disturbance.\(^26\)

3. Gamma aminobutyric acid: class anti-epileptics
Gabapentin at 300 mg daily increasing to 300 mg maximum three times a day (tds) or Pregabalin 75-150 mg twice daily shows statistically significant improvement in hot flushes as compared with placebo.\(^4,22,40,41,43\) Dose dependent side effects limit compliance, the most common side effects being somnolence, dizziness, weight gain and dry mouth.\(^42\) Gabapentin may be as effective as Venlafaxine\(^44\) but most patients prefer Venlafaxine. There is no evidence of further benefit with Gabapentin given concurrently with anti-depressants.\(^4\) Most studies are of short duration with little evidence on long term data. Since April 2019, both Pregabalin and Gabapentin are Schedule 2 controlled medicines.

4. Oxybutinin
Oxybutinin, which is usually used to treat overactive bladder, has been shown to reduce the incidence of hot flushes. It is being used off licence by some menopause specialists for this purpose. Side effects may include stomach pain, diarrhoea, nausea, headaches, dry mouth and dry eyes. The usual dose is 2.5 mg twice daily, with the option of increasing to 5 mg twice daily.\(^54\)

5. Isoflavones and soya products
Phytoestrogens can form a large part of dietary intake in certain ethnic groups and these patients can be advised to continue what is considered to be their normal levels of dietary intake. Most studies evaluating effectiveness of phytoestrogens are of poor quality and in the very many studies undertaken (181 by 2007) very few natural health products were shown to reduce hot flush frequency.\(^10,19\) Data on phytoestrogen safety and survival benefits in breast cancer patients are inconsistent and as they are known to have estrogenic activities, isoflavones including Red Clover are not recommended for women who have had breast cancer.\(^4,26,45\)

6. Herbal treatments
Some studies show effectiveness of Black Cohosh in hot flush reduction, although less so in breast cancer patients.\(^4,26\) Black Cohosh can be associated with major adverse effects such as constipation, arrhythmia, weight gain and abdominal cramps.\(^10,20\) Black Cohosh interferes with tamoxifen activity and should be avoided by patients taking tamoxifen.\(^4\) NICE 2015 recommended that women with a history of, or at higher risk
of, breast cancer should be advised that there is some evidence that St John’s Wort may have benefit for vasomotor symptoms but that because of uncertainty about appropriate doses, persistence of effect and potential for serious drug interactions that it should not be recommended. In particular, it may affect the metabolism of other medications and, most importantly for breast cancer patients, that of tamoxifen. There are no studies of more than poor quality evaluating St John’s Wort in non-breast cancer patients, and its effect on vasomotor symptoms may be due to its low dose anti-depressant activity. A recent literature review suggests that some of the herbal medicines may have an effect in the relief of anxiety and depression. If a herbal treatment is chosen, patients should look for the Traditional Herbal Remedy (THR) stamp validating strength and quality.

7. Behavioural therapies
The North American Menopause Society (NAMS) Statement in 2015 recommended a cognitive behavioural therapy (CBT) approach that combines relaxation techniques, sleep hygiene and learning to take positive healthy attitude to a menopause challenge. One study found hypnotherapy as effective as Gabapentin in hot flush reduction. Supporting clinical studies demonstrated the effect in reducing women’s ratings of their hot flush problems. Additionally, clinical hypnosis was found to have better results than a structured attention approach in post-menopausal breast cancer survivors. CBT is also recommended as a treatment option for anxiety experienced during the menopause transition and post-menopause. A CBT approach which is theory based can have an impact on both vasomotor symptom perception and control and reduction in stress and wellbeing, sleep problems and vasomotor symptomatology. There are two-way interactions between mood and vasomotor symptoms with 10% of women more likely to have depressed mood during menopause.

The Women’s Health Concern fact sheet, prepared by Professor Myra Hunter, provides guidance on cognitive behavioural therapy in a self-help format for women to access directly. The appreciation of the benefit of behavioural therapies on vasomotor symptoms perhaps suggests that the mechanism by which SSRIs work for hot flushes could be as a result of their direct class effect on mood.

8. Other treatments
Stellate ganglion block in symptomatic women with a diagnosis of breast cancer is theoretically a treatment option but, to date, there are only six small clinical articles. Electro acupuncture, EA, as compared with Gabapentin found highest effectiveness in the electro acupuncture group and lowest adverse effects. Acupuncture reduces hot flushes and improves sleep patterns in postmenopausal women, although clinical trials demonstrate benefit generally similar to that of sham acupuncture.

Treatments for women who have had breast cancer
Most women diagnosed and treated for breast cancer will live with their cancer, rather than die from it. A common consensus is to avoid estrogen replacement therapy for women who have had breast cancer. More research is needed into the safety of possibly using estrogen based therapies particularly in receptor negative patients but for the moment most clinical guidelines will consider estrogen treatment contraindicated. Even BRCA gene carriers who become menopausal following risk reducing surgery will be guided to take estrogen replacement only up to the age of 50.
There are a variety of position statements, guidelines and consensus statements for the management of vasomotor symptoms and the value and safety of alternative treatments for women who have had breast cancer, from international and national societies. A meta-analysis of adverse effects in non-hormonal drugs in breast cancer survivors shows a much higher level of adverse effects with 81% of SAEs in one treatment group compared with those on placebo, low dose therapies and acupuncture. The North American Menopause Society (NAMS) Consensus Statement September 2015 looks for solid evidence of a few therapies that work, so that patients don’t waste time experimenting with things that really don’t work. NAMS recommends SSRIs, SNRIs, Gabapentin, Pregablin, Clonidine, CBT and clinical hypnosis. The UK guidelines, i.e. NICE CG 23 and NICE CG 80, indicate that SSRIs, SNRIs and Gabapentin are no better than placebo and that Paroxetine and Fluoxetine may reduce the efficacy of tamoxifen. For women who have had breast cancer, NICE CG 80 recommends Clonidine, Venlafaxine and Gabapentin, although NICE 2015 indicates that only St John’s Wort may improve symptoms, but it is not recommended because of serious drug interactions.

Isoflavones, Red Clover and Black Cohosh are not recommended for women who have had breast cancer by any of the international bodies.

**New developments**

Studies with neurokinin receptor 3 antagonists on women with hot flushes demonstrate a rapid effect on vasomotor symptoms.

Fezolinetant is a Neurokinin 3 receptor antagonist, licensed to manage vasomotor symptoms, which are the commonest symptoms of menopause that women experience. Neurokinin antagonist medication influences changes in brain neurotransmitters which regulate the underlying process of vasomotor symptoms via the Hypothalamo-Pituitary-Ovarian axis. Symptomatic women are more sensitive to changes in brain neurotransmitters.

Fezolinetant was licensed by the MHRA on 14 December 2023 and it is currently available on private prescription. A NICE Technology Appraisal (publication date to be confirmed) is underway to review the clinical and cost effectiveness of fezolinetant; if recommended, it will be available to prescribe on the NHS.

**Summary practice points**

- As clinicians we must be familiar with alternative therapies, to help inform and guide women as to which options are most likely to be beneficial to them.
- Few complementary and alternative treatment options have proven evidence of effectiveness, but although many options do not stand up to scrutiny from a robust and evidence-based perspective, there will be individual women who will benefit from some of these treatments.
- Placebo effect is not inconsiderable and, in menopausal studies, will play a part in individual experience and reported benefits.
References


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