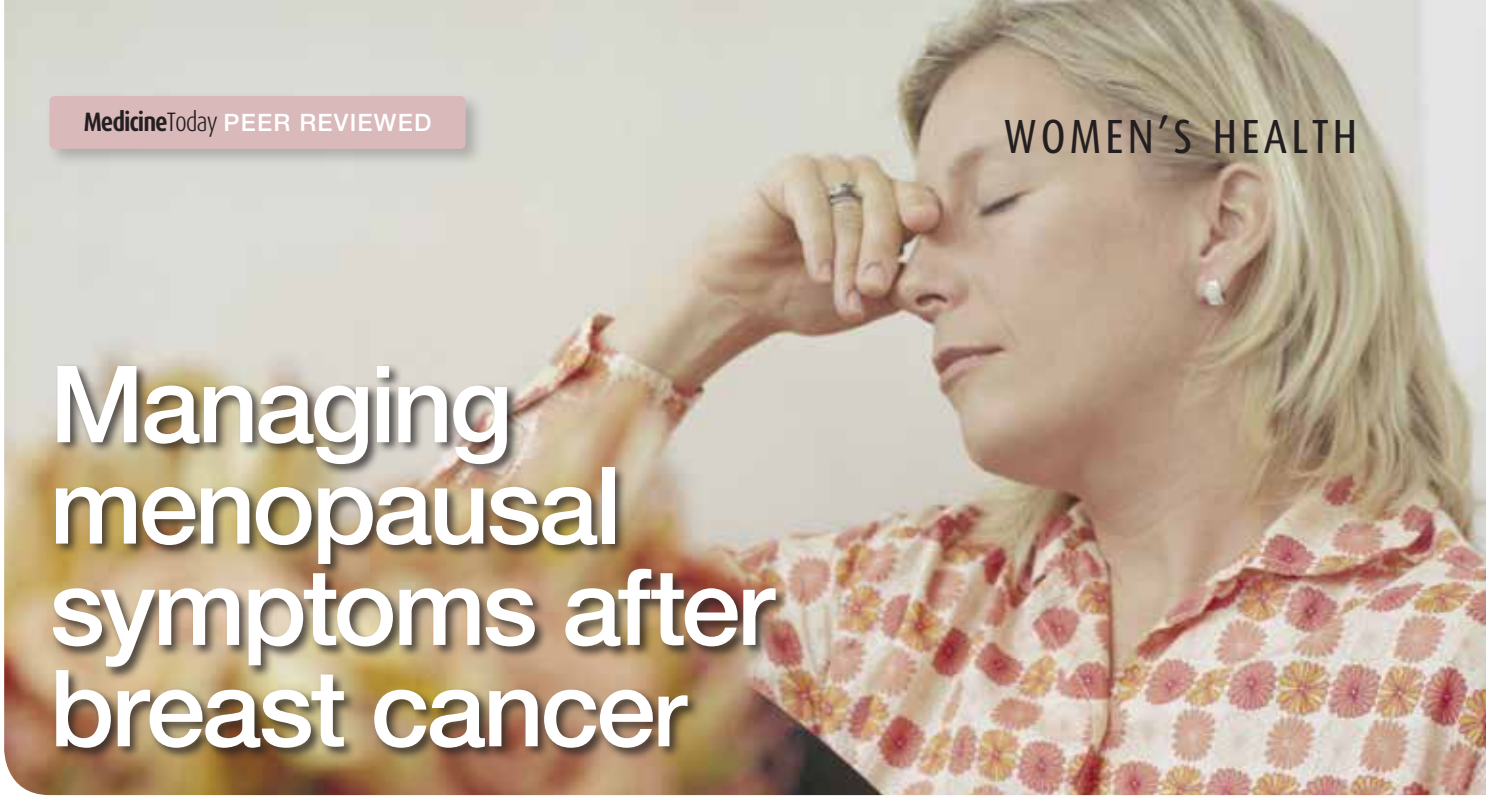

# Managing menopausal symptoms after breast cancer

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**Menopausal symptoms are common in breast cancer survivors and several treatment options are available.**

Breast cancer is the most common cancer in women, with 35% of breast cancers being diagnosed in premenopausal women.[1] It carries a lifetime risk of affecting one in eight women in developing countries. With improvements in early detection and management, more women are surviving breast cancer. As a result, the management of short- and long-term consequences of treatment, such as menopausal symptoms, has become an increasingly important component of postcancer care. GPs will see these patients regularly and much can be done to support affected women.

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## MENOPAUSAL SYMPTOMS AFTER BREAST CANCER

Most women develop menopausal symptoms following breast cancer treatment, with 40 to 65% experiencing moderate to severe symptoms.[2,3] Common symptoms include vasomotor symptoms, vaginal dryness, mood changes and reduced libido.[2,3] There are several reasons why women develop menopausal symptoms after breast cancer treatment including cessation of hormone replacement therapy (HRT) at breast cancer diagnosis, ovarian failure secondary to chemotherapy, bilateral oophorectomy as a treatment for breast cancer and the antioestrogen effects of endocrine therapy. Compared with natural menopause, chemotherapy induced or surgically induced menopause is associated with more severe vasomotor symptoms.[4] Also, younger age at menopause increases the risk of osteoporosis.[5,6] The side effects of antioestrogen endocrine therapy for breast cancer may reduce patient compliance and may therefore increase the risk of cancer recurrence.[7]

Sexual dysfunction after breast cancer is the result of a range of factors including vaginal dryness secondary to menopausal status and endocrine therapy causing discomfort during sex. Changes in libido and in body image after breast cancer surgery, as well as fatigue and sleep and mood disturbances, may all impact negatively on sexual function.

## MANAGEMENT OF MENOPAUSAL SYMPTOMS AFTER BREAST CANCER

### Hormone replacement therapy

The use of HRT in women who have had breast cancer has been associated with an increased risk of recurrent disease and is generally contraindicated. The Hormonal Replacement Therapy After Breast Cancer – Is It Safe? (HABITS) study, a randomised controlled trial (RCT) of HRT use after early breast cancer, was ceased prematurely after an increased risk of cancer recurrence was identified in the HRT group.[8] The Stockholm trial, also an

RCT on HRT use after breast cancer, was also ceased prematurely after the results of the HABITS trial were revealed. However, when data collected up until this point were analysed, no significant difference in the rate of cancer recurrence between women treated with HRT or no HRT was identified.[9] Although suggestions that the HRT protocols, study populations and length of follow up may explain the different results of these studies, safety concerns have prevented further RCTs in this area and HRT use in this clinical setting. 'Bioidentical hormones' should also be avoided in women who have had breast cancer because they may have a similar effect on the breast as HRT.

Tibolone, a synthetic corticosteroid with oestrogenic, progestogenic and androgenic properties, is an effective treatment for women with menopausal symptoms. However, it has been associated with a relative risk increase of 1.48 of breast cancer recurrence in women with a personal history of breast cancer, and is therefore contraindicated in this setting.[10]

The safety of vaginal oestrogens for the management of women with vaginal dryness after breast cancer has not been established in an RCT.[11] Observational studies and studies of breast cancer treatment that have allowed the use of vaginal oestrogens have not demonstrated an increased risk of cancer recurrence with their use.[12,13] However, no large-scale RCTs of vaginal oestrogen use in women who have had breast cancer have been performed, and it is unlikely they will be, given the low recurrence rates and need for long-term follow up. However, elevated serum oestrogen levels have been demonstrated in women using vaginal oestrogen while taking aromatase inhibitors, raising safety concerns.[11]

For women with resistant atrophic symptoms, vaginal oestrogens may be used after considering individual clinical circumstances. Oestriol is preferred in this setting, because it is a less potent oestrogen than oestradiol.[14] An alternative approach, given the contribution of endocrine therapy to menopausal symptoms, is to review the risks and benefits of changing to tamoxifen or ceasing endocrine therapy. This should always be performed in a multidisciplinary context.

## Complementary therapies and psychological interventions

Data on the effects of complementary therapies such as soy isoflavones (e.g. red clover) and black cohosh on menopausal symptoms after breast cancer are limited and have revealed mixed results.[15] Their pro-oestrogenic properties have an unknown effect on the breast and are of particular concern in women who have a personal history of breast cancer. The safety of these complementary medications in women who have had breast cancer has not been established and they should therefore be avoided.

Interventions such as cognitive behavioural therapy, meditation and controlled breathing may reduce the impact of vasomotor symptoms and can be used safely after breast cancer.[16,17] Acupuncture has not been shown to reduce vasomotor symptoms.[18]

## Nonhormonal pharmacotherapy

In response to the safety concerns regarding the use of HRT in women who have had breast cancer, several nonhormonal medications have been found to reduce the severity and frequency of vasomotor symptoms. Although the exact mechanism of action is unknown, serotonin–noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine and desvenlafaxine, and selective serotonin reuptake inhibitors (SSRIs), such as escitalopram, citalopram, fluoxetine and paroxetine, significantly reduce vasomotor symptoms compared with placebo. However, this use is off label.[19] Venlafaxine to a maximum dose of 75 mg/day is associated with a reduction in the severity and frequency of vasomotor symptoms of up to 66%.[20,21]

Side effects of SNRIs and SSRIs, including mouth dryness, constipation, nausea, headaches, dizziness, sleep disturbance and sexual dysfunction, may limit their use in some individuals. GPs prescribing these same medications for depression and anxiety will be familiar with these issues. Paroxetine and fluoxetine use should be avoided in patients taking tamoxifen, because they can reduce its efficacy through inhibition of the cytochrome P450 enzyme CYP2D6.[22,23] Gabapentin (up to 900 mg/day; off-label use) has also been found to reduce the severity and frequency of vasomotor symptoms by up to 66%.[20,24] In a head-to-head comparison there was no difference in efficacy between gabapentin and venlafaxine; however, gabapentin was associated with more side effects,[20] including dizziness, unsteadiness and fatigue. Clonidine, an antihypertensive medication, is associated with about a 40% reduction in vasomotor symptoms.[19]

The above medications work through different mechanisms, so if one is ineffective or associated with troublesome side effects, clinical benefit might be achieved by using an alternative medication. One medication at a time should be trialled so that the efficacy of each one is known and to avoid worsening side effects that can occur with the use of multiple medications. Occasionally, the use of gabapentin and an SNRI or SSRI concurrently may be more effective that one medication alone; however, as suggested above, this should be trialled with caution and in the context of a specialist service. In addition to their direct impact on vasomotor symptoms, the sedative effect of some of these medications may reduce the impact of sleep disturbances associated with menopause. Stellate ganglion block, which requires sedation and is associated with a one in 1000 risk of significant complications, has been shown to reduce moderate to severe vasomotor symptoms and objective measures of vasomotor symptoms.[25,26]

Nonhormonal management of sexual dysfunction includes water- or silicone-based lubricants for women with vaginal dryness, assessment and management of pelvic floor dysfunction, and psychological interventions for women with a low libido. The first-line treatment of depression associated with menopause is antidepressant medications.[27] If vasomotor symptoms are also troublesome, an antidepressant with efficacy against vasomotor symptoms should be chosen. Psychological interventions can also

be used in the context of depression and vasomotor symptoms in women who have had breast cancer.[16,28]

If premature menopause has resulted from breast cancer treatment, consideration of osteoporosis prevention, screening and management is part of holistic general practice.

## CONCLUSION

The menopausal consequences of breast cancer treatment can be severe and impact negatively on a woman's quality of life and her compliance with endocrine therapy used to reduce cancer recurrence. It is important that women feel supported and are well informed about the options they have to improve their quality of life having survived the initial impact of a breast cancer diagnosis. We have seen a recent increase in the number of effective nonhormonal treatments for women with vasomotor symptoms, which are a safe alternative to HRT for those who have had breast cancer. Women whose symptoms, particularly vaginal dryness, are refractory to these methods may warrant consideration of hormonal treatments. In this setting the risks and benefits to the individual should be discussed in the context of a multidisciplinary specialist service.[29] MT

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