BMS | Consensus Statement for the Association of Breast Surgeons (ABS)

The diagnosis of the menopause and management of oestrogen deficiency symptoms and arthralgia in women treated for breast cancer

This consensus statement by the British Menopause Society, revised for the ABS, provides an overview of the management of women experiencing estrogen deficiency symptoms and arthralgia following a breast cancer diagnosis. It is now recommended breast cancer patients are referred to health care professionals with an expertise in menopause for management of such symptoms.[1] As women may present to primary care and/or members of their breast cancer multi-disciplinary team for advice about symptom management, it is essential both have an understanding of symptom aetiology and likely current management strategies to ensure appropriate gynae-endocrinology referral and guidance.

Key points

1. An early menopause, estrogen deficiency symptoms and arthralgia are common side effects of systemic breast cancer therapies.
2. Symptoms may persist for the duration of treatment and in some cases continue after treatment completion.
3. The NICE Menopause Guidance [NG23] recommends referral of women to a healthcare professional with expertise in gynaecological endocrinology for counselling about the risk of developing an early menopause and the management of symptoms associated with breast cancer treatment.
4. Lifestyle measures and non-hormonal interventions should be first-line management for estrogen deficiency symptoms but if these are ineffective systemic hormone replacement therapy or low-dose topical estrogen may be considered but only after taking specialist advice.
5. Lifestyle measures such as weight loss and increased exercise may also improve arthralgias associated with aromatase inhibitors and tamoxifen.
6. Switches to endocrine breast cancer treatment may alleviate symptoms of estrogen deficiency and arthralgia but these should only be instigated in secondary care, ideally after breast multi-disciplinary team review, to ensure consistency of advice across all involved specialties.

Introduction

The development, introduction and now widespread use of systemic breast cancer therapies in the management of early stage disease is the most significant contributor to improvements in breast cancer survival.[2,3] Unfortunately, estrogen deficiency symptoms and arthralgia may be induced, or pre-existing symptoms exacerbated by these therapies and result in their discontinuation.[4] Treatment of vasomotor symptoms and vulvo-vaginal atrophy may be problematic as hormone replacement therapy (HRT) is contra-indicated in women with estrogen responsive breast cancer, the efficacy of some HRT alternatives to treat vasomotor symptoms is not widely appreciated, and there is lack of consensus about the optimal management of arthralgia.[5,6] Whilst there is awareness amongst breast multi-disciplinary teams such symptoms may occur, they are not best placed to manage and provide the most suitable follow-up for these problems, which can be complex to resolve and are best dealt with by health professionals with an interest in the menopause. Breast cancer teams, however, have an important role in identifying symptoms and ensuring appropriate referral.

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Symptoms associated with adjuvant systemic therapy

1. *Vasomotor symptoms*

   Iatrogenic symptoms induced by endocrine therapy or ovarian suppression have been reported to be more problematic and longer-lasting than those associated with a natural menopause. There is often a mismatch of perception between patients and health care professionals, with many women considering stopping treatment because of side effects for which management has never been discussed.[5,7] In premenopausal women the symptoms following a chemotherapy or gonadotrophin-releasing hormone agonist (GnRHa)-induced ovarian suppression are usually more severe than those associated with tamoxifen.[8,9] The reported persistence of symptoms after completion of tamoxifen in younger patients is probably due to prior chemotherapy exposure inducing an early menopause.[9] In postmenopausal women both tamoxifen and aromatase inhibitors are associated with induction of vasomotor symptoms.[10] Symptoms usually persist for the duration of exposure but their severity may decrease over time.[11,12]

2. *Gynaecological symptoms and sexual dysfunction*

   Iatrogenic ovarian suppression, tamoxifen and aromatase inhibitors are all associated with symptoms attributable to vulvovaginal atrophy, which in turn can lead to dyspareunia and contribute to loss of sexual desire and reduced libido.[13] In contrast, in some women tamoxifen does not cause vaginal dryness but induces a mild non-purulent, non-itch producing white or clear vaginal discharge. This side-effect is likely to be due to the estrogenic effects of tamoxifen on the vagina and cervix. In postmenopausal women, aromatase inhibitors may induce more severe vulvovaginal symptoms than tamoxifen, vaginal dryness may worsen with increasing duration of therapy, and loss of libido can persist after completion of treatment.[11,13] Tamoxifen is associated with a small elevation in the risk of endometrial cancer in postmenopausal but not premenopausal patients by courtesy of its oestrogen-agonist effect on the postmenopausal endometrium (in premenopausal women, it does not appear to stimulate endometrial proliferation).[14] Overall endometrial cancers diagnosed in postmenopausal women are no different regarding stage, grade, histology and phenotype from those diagnosed in the general population.[14] In contrast, aromatase inhibitors are associated with no or a reduced risk.[15] It is hypothesised aromatase inhibitors may increase the risk of women developing symptoms of urogenital prolapse due to anti-oestrogenic effects on collagen but whilst preliminary clinical study suggests an adverse effect of faecal incontinence, no negative effect on urinary incontinence or pelvic organ prolapse has yet been reported.[16] Chemotherapy may also impact adversely on sexual function as a result of its other adverse effects such as hair loss, fatigue, weight gain and body image.[13]

3. *Joint and musculoskeletal symptoms*

   Musculoskeletal symptoms associated with the use of aromatase inhibitors is estimated to affect just under one half of treated women.[17,18] They usually develop within a few months of commencing treatment and they may persist for the duration of use.[6,19,20] Common symptoms include morning stiffness and pain affecting the hands, knees, hips, lower back, and shoulders.[6] These most likely result from estrogen deprivation but inflammatory pathways and a tenosynovitis type effect with fluid retention in joints may also have a role in their aetiology.[19] Previous treatment with taxane-based chemotherapy, increases the risk of the development of aromatase inhibitor-induced arthralgia, but other predictors of these side effects are unclear.[6,19]

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Practice Points

I. Estrogen deficiency symptoms and aromatase inhibitor-induced arthralgia usually become apparent within a few months of starting therapies and may persist after treatment is completed.

II. Familiarity of members of the breast multi-disciplinary team with the type and duration of iatrogenic symptoms will aid consultation with patients and ensure appropriate referral to a specialist with an interest in the menopause.

III. It is important to ask patients about symptoms associated with sexual dysfunction as often they will not volunteer this information spontaneously.

Risk of early menopause associated with adjuvant systemic therapy

Chemotherapy-induced ovarian suppression results in cessation of menstruation and for some women, this may be permanent, resulting in an early menopause and implications for future fertility.[20] The associated risk of an early menopause is related to age as it is more likely in those over the age of 40 consequent to natural ovarian follicle depletion and the regimen used, for example, alkylating agents such as cyclophosphamide are more gonadotoxic than taxanes.[21,22]

Tamoxifen has been reported to be associated with a small increased risk of developing an early menopause, when used alone or following chemotherapy.[21] With the former this descriptive association was restricted to women over 45 and probably reflects older age at exposure rather than a treatment effect. With respect to the latter, the menstrual irregularity or absence described is almost certainly due to the impact of prior chemotherapy and supported by a recent study suggesting no added impact of tamoxifen on ovarian reserve.[21-27]

Temporary ovarian suppression induced by short-term use of a GnRHa during neoadjuvant or adjuvant chemotherapy appears to reduce the risk of chemotherapy-induced premature ovarian insufficiency and may therefore maintain fertility.[28] When used as a therapeutic intervention in women with breast cancer, GnRHa are prescribed for a longer duration, that is between two to five years.[2] Irrespective of whether a GnRHa is commenced at the time of chemotherapy or after its completion, the proportion of women reporting an early menopause appears similar at approximately 20%, which again implies risk is attributable to chemotherapy exposure only.[26]

The impact of breast cancer and its treatment on fertility should be discussed as soon as possible after diagnosis, between women and their breast specialist team, especially in those recommended chemotherapy.[29,30] If fertility referral is appropriate and egg harvesting and cryopreservation recommended, this must be initiated prior to commencing treatment, however, this should not delay the start of therapy.[29] Women must be fit for ovarian stimulation and oocyte collection and estimated to have a good prospect for long-term survival.[30]

Most women, if they resume menstrual bleeding following completion of chemotherapy, do so within two years, however in about 10% of women menstruation, albeit irregular, may resume between three and five years after the last cycle of chemotherapy.[25] The risk of chemotherapy-induced amenorrhoea lasting more than two years is lower in women under the age of 39.[25] Whilst a return of menstruation may not indicate ovulatory cycles, amenorrhoea following chemotherapy may not signify infertility. As it is not possible to reliably predict which women may have been rendered infertile by treatment,

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it is reasonable to recommend non-hormonal contraception following chemotherapy for a minimum of two years to avoid unplanned pregnancy. If there has been amenorrhoea for two years, menopause can be confirmed by appropriate biochemical testing (see below).[25] If the results do not indicate menopause, contraception should be continued for a further year and testing repeated. Non-hormonal contraception is recommended if there is a history of breast cancer to reduce the risk of promoting an estrogen-sensitive recurrence or a new contralateral primary and to avoid increasing the risk of a venous thrombotic event. Barrier methods or the Cu-IUD are the preferred contraceptive choices. Emergency contraception may be used if indicated as it is extremely unlikely to cause any harm.[31]

In general, women who have undergone menopause before the age of 50 should use contraception until 2 years after their menopause. Women who have undergone menopause after the age of 50 should use contraception until one year after their last period.

Diagnosis of the menopause in women treated for breast cancer

There is no agreed published consensus for the diagnosis of menopause in younger women treated for breast cancer. In the absence of such, the following is recommended:

1. If adjuvant systemic therapy in premenopausal women consists of tamoxifen alone, the diagnosis of menopause can be made if there has been amenorrhoea for at least twelve months combined with elevated FSH levels (i.e. FSH >30 IU/l) on two blood samples taken four to six weeks apart.[1] As serum FSH assays can be unreliable in the presence of tamoxifen, the latter should be stopped six to eight weeks in advance of performing this investigation.[32] This is of particular relevance for women eligible for extended adjuvant therapy, beyond 5 years' treatment with tamoxifen, where an aromatase inhibitor may be recommended if post-menopausal status is confirmed.[2]
2. Following chemotherapy exposure, the diagnosis of premature menopause may be based on a combination of the presence of menopausal symptoms, absence of menstruation and elevated FSH levels on two blood samples taken 4-6 weeks apart. In chemotherapy-treated women, amenorrhoea for two years is a reasonable time frame for suspecting the possibility of an early onset of menopause.[25] If tamoxifen is being used, it should be stopped for 6 to 8 weeks prior to checking serial FSH serum assays.
3. If a younger patient has completed treatment with a combination of a GnRHa and aromatase inhibitor (irrespective of prior chemotherapy use), a washout period of 12 weeks should be allowed in order to reverse the former's suppressive effect on the hypothalamic-pituitary axis before performing serial FSH assays.[33]
4. Preliminary clinical trial data suggests undetectable serum levels of anti-Müllerian hormone (using a highly sensitive assay) in women over 40 at completion of chemotherapy may be a reliable predictor of permanent ovarian failure and that the sensitivity and specificity of such assays may in addition be unaffected by concurrent tamoxifen exposure. However, larger, confirmatory trials are required before this is recommended for clinical practice.[34,35]

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Practice points:

I. It is the responsibility of a patient's specialist breast team to arrange fertility review if there is risk of fertility loss.

II. Women should be advised to use non-hormonal contraception if they have become amenorrhoeic.

III. If there is doubt about the diagnosis of menopause, referral to a specialist with expertise in menopause or reproductive medicine should be made.

Management of vasomotor symptoms, vulvo-vaginal atrophy and arthralgia

A number of recent evidence-based consensus position statements and guidelines have concluded lifestyle changes and non-hormonal alternatives to HRT should be first-line management for symptomatic women with a history of breast cancer. The maximum treatment for many studies, however, is 3 months, so the efficacy in the longer term is uncertain.[36,37]

In the UK, clinical practice is directed by the 2015 NICE Menopause Guidance (NG23) and the NICE guidance (NG101) on early and locally advanced breast cancer.[1,2] The conclusions of the 2015 menopause NICE guidance on interventions for vasomotor symptoms are limited for application in women with breast cancer as the statistical methodology relied on an analysis of evidence mainly from women without a diagnosis of breast cancer. Comparison of treatments was undertaken separately for women with and without breast cancer but data was very limited for the latter.[38,39] However, these are summarised with explanation and expansion as appropriate, below and where relevant, comparison with other publications.

1. General recommendations for the management of women with breast cancer1

I. Offer information and counselling to breast cancer patients about:

- a. The risk of possibility of developing an early menopause and menopausal symptoms associated with breast cancer treatment.
- b. All management options, including lifestyle changes and interventions that could help general health and well-being.
- c. The quality, purity and constituents of complementary therapies may be unknown (based on the lack of information on quality control, efficacy and safety about over-the-counter herbal preparations and complementary therapies).

II. Refer breast cancer patients to a healthcare professional with expertise in the menopause.

2. Vasomotor symptoms

A recent Cochrane systematic review of placebo-controlled randomised trials in women with breast cancer have showed mild to moderate effect of clonidine, selective serotonin release inhibitors (SSRIs) and selective noradrenaline release inhibitors (SNRIs), gabapentin and relaxation therapy on reducing hot flushes in women with a history of breast cancer.[40]

The conclusion of the UK 2015 menopause guideline that SSRIs, SNRIs and gabapentin should not be routinely offered as first-line therapy was based on the finding that although these are effective, compliance was very poor in trials reviewed because of side effects.[1] SSRIs and SNRIs may inhibit the activity of one of the main enzymes (i.e. CY2D6) responsible for converting tamoxifen to its active metabolite and hence potentially reduce its anti-neoplastic action. This occurs to varying degrees and current recommendations are that paroxetene and fluoxetine, whose inhibitory action is strong, should be avoided in women treated with tamoxifen.[1]

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I. St John's wort may be effective in the treatment of hot flushes, but risk of interaction with tamoxifen, docetaxel and anti-coagulants raises safety issues for its use in this patient group. There is also uncertainty about the appropriate dose, persistence of efficiency and variation of potency of over-the-counter preparations.[1]
II. Soy and red clover (isoflavones) have estrogenic activity and should be avoided in women with breast cancer.[2]
III. Black cohosh, vitamin E and magnetic devices are not advised.[2]
IV. Clonidine, SSRIs, SNRIs and gabapentin may alleviate symptoms as mild to moderate symptom benefit has been reported, but their effects can be outweighed by adverse effects.[36,38,40,41]
V. The absence of government regulation (e.g. quality, purity of constituents) and clinical data supporting efficacy and safety for non-commercial bioidentical formulations, which in addition may contain active ingredients, has been highlighted in guidelines. Bioidenticals should be contra-indicated in women with breast cancer.[1,42]
VI. Consider cognitive behavioural therapy (CBT) to alleviate low mood or anxiety that arises as a result of the menopause.[1,36,43] A recent systematic review concluded that mindfulness, cognitive behavioural and behaviour-based therapy may be useful for the treatment of natural and treatment-induced menopausal symptoms since it alters perception of the symptoms rather than frequency.[43]
VII. Do not offer HRT routinely to women with menopausal symptoms and a history of breast cancer but it may, in exceptional cases, be offered to women with severe menopausal symptoms for whom other treatments have failed.[2] Any decision to prescribe HRT should involve the patient's specialist breast team and documented informed consent must be obtained, after associated risks and uncertainty have been explained. It should be appreciated that previous breast cancer is a contra-indication in all summaries of product characteristics for all types of HRT. It should not be prescribed in women treated with aromatase inhibitors as the therapeutic benefit of aromatase inhibitors is mediated via a reduction in endogenous estrogen synthesis.[2,5] It may be safe to prescribe HRT in women who are symptomatic on tamoxifen and although direct clinical evidence is lacking, the efficacy of tamoxifen in premenopausal patients despite high endogenous serum estrogen levels and lack of an increased risk of breast cancer diagnosis in tamoxifen chemoprevention trials that permitted the use of HRT imply this may be safe practice.[44,45]

The NICE Menopause Clinical Guidance Group (CGG) did not review lifestyle changes (e.g. use of portable fans, dressing in easily shed layers, avoiding triggers such as alcohol, weight loss) but advice about this should always be provided in the general advice for symptomatic women.[5,36]

The use of progestogens for symptom management in women with breast cancer is controversial due to their potential proliferative effect on occult breast cancer micro-metastases, as evidenced by the increased risk of diagnosis in women exposure to combined rather than unopposed HRT and absence of long-term efficacy and safety data.[5] No studies evaluating progestogens were reviewed by the NICE Menopause CGG as none met the selection criteria for inclusion and the NICE guidance on early and advanced breast cancer does not recommend their use in this patient group.[1,2]

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Overall, lifestyle changes, SSRI, SNRIs, gabapentin, pregabalin, clonidine and CBT are recommended for the management of vasomotor symptoms. Research is ongoing to evaluate fully the efficacy and safety of other interventions including acupuncture, stellate ganglion block and newer pharmacological treatments such as neurokinin 3 receptor antagonists.[6] For individual women whose symptoms persist despite these measures, the NICE UK breast cancer guidance (NG101) is that systemic HRT can be considered, but not all international guidelines and position statements have adopted such a pragmatic approach.[2,23,36,41,46]

Practice points:

I. Refer symptomatic patients to a specialist with an interest in the menopause.

II. If a patient develops vasomotor symptoms an indication of how troublesome they are likely to be can be estimated after about 3 to 6 months from the start of treatment as if vasomotor symptoms will reduce with time, they usually do so at around 3 months.[10]

III. A variety of non-hormonal methods of treatment of vasomotor symptom are available to treat vasomotor symptoms and should be used first, in addition to lifestyle changes but if these are ineffective, systemic HRT may be considered.

IV. Use of bioidentical preparations is contra-indicated

V. In postmenopausal patients, switching from an aromatase inhibitor to tamoxifen may alleviate vasomotor symptoms.

VI. Systemic HRT should not be prescribed in women taking aromatase inhibitors.[5]

VII. It is not known if it is safe to prescribe HRT in women taking tamoxifen.

VIII. Ideally changes to breast cancer treatment or use of HRT should be discussed following breast multi-disciplinary and gynae-endocrine review, as changes to treatment could potentially affect disease-free survival, particularly in higher-risk women.

IX. Women may develop symptoms after they have been discharged from specialist follow-up and contact their breast unit or clinical nurse specialist. There should be a pathway in place to triage concerns so patients can be directed to the most appropriate source of advice (i.e. primary care or gynae-endocrine).

3. Vulvo-vaginal atrophy

I. Commercially available vaginal moisturisers and vaginal lubricants are recommended as first-line treatment.[1,47] It has been suggested due to the weak oestrogenic activity of parabens, that lubricants containing these are avoided (e.g. K-Y jelly, Replens, Astroglide), however, clinical data to support or refute an adverse effect on women treated for breast cancer is completely lacking.[48]

II. If symptoms persist, low-dose vaginal estrogen can be considered in women who have estrogen negative tumours or who are taking tamoxifen, but due to absence of clinical trial evidence confirming lack of an adverse effect, advice about prescribing should follow that as for systemic HRT, above, and should be discussed with the relevant oncology team.

III. Low-dose vaginal estrogens should not be used in women taking aromatase inhibitors.

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IV. The oral SERM, ospemifene, is not recommended for the treatment of refractory vaginal symptoms as there is a lack of any evidence about safety in women with breast cancer, although preclinical studies suggest a neutral effect on breast tissue.[1,5] Available studies only have short-term follow-up using unreliable surrogates for predicting future risk (i.e. clinical breast examination, change in mammographic breast density, breast tenderness).[49] The Food and Drug Administration and Endocrine Society support this recommendation against its use although The European Medicines Agency state it may be used after completion of breast cancer treatment.[41,50,51]

All guidelines and consensus statements concur with the recommendations of the NG23 for use of vaginal moisturizers and lubricants as initial treatment and consideration of low-dose topical estrogen if symptoms are refractory.[5,36,41,44,46]

Alternative interventions, which may be possible options for future management of symptoms in breast cancer patients include vaginal laser treatment (i.e. the fractional CO2 and erbium lasers) and intravaginal dehydroepiandrosterone (DHEA) but both require further evaluation. Preliminary study of both laser treatments and DHEA for their short-term efficacy in breast cancer patients is encouraging.[52-55] For laser treatments, evidence of long-term efficacy and direct head-to-head comparison with topical oestrogen is necessary before informed recommendations can be made. DHEA has the theoretical advantage of local delivery of active estrogen and androgen metabolites via the activity of aromatase in vaginal epithelial cells, with minimal, probably clinically insignificant increases in serum estradiol, estriol or free testosterone and appears efficacious in women treated with tamoxifen and aromatase inhibitors, the latter suggesting these may not impair intracellular, vaginal aromatase action. However, its safety in this group of women requires confirmation in clinical trials.[47]

Practice points:

I. If symptoms of vulvo-vaginal atrophy are not relieved by vaginal moisturizers and lubricants:
- ***a. Topical estrogen should not be used if a woman is using an aromatase inhibitor due to concern systemic absorption (albeit very low) may negate the latter's efficacy.***[5]
- ***b. If a woman is using an aromatase inhibitor, switching to tamoxifen may ameliorate symptoms. This beneficial effect can take up to three months to become evident.***
- ***c. If switching to tamoxifen fails to improve symptoms, additional prescription of low-dose topical estrogen can be considered.***
- ***d. No changes to breast cancer medication should be initiated in primary care. Discussion with the breast specialist team is obligatory, as changes to therapy could potentially affect disease-free survival, particularly in higher-risk women.***

II. Ospemifene should not be prescribed to women with a history of breast cancer

III. In addition to management of vulvo-vaginal atrophy, women with symptoms of sexual dysfunction may require referral for psycho-sexual counselling, education about use of vaginal dilators, pelvic floor relaxation techniques and support for management of body image concerns arising from previous breast surgery, treatment-induced hair loss or thinning or other reasons.[23]

IV. Women may develop symptoms after they have been discharged from specialist follow-up and contact their breast unit or clinical nurse specialist. There should be a pathway in place to triage concerns so patients can be directed to the most appropriate source of advice (i.e. primary care or gynae-endocrine).

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4. Musculoskeletal symptoms

As yet, the optimal management of aromatase inhibitor-induced arthralgia is to be determined. A qualitative analysis of 19 studies (with meta-analysis of 15 of these) concluded pharmacological approaches, acupuncture, and relaxation techniques showed moderate to large effects on associated pain, but there was no significant impact with nutritional supplementation (i.e. glucosamine, omega-3 fatty acid, high dose vitamin D2).[56] None of the pharmacological studies, which evaluated switching of aromatase inhibitors, the SNRI duloxetine, prednisolone or immunological therapies were randomised or placebo-controlled and overall most of the studies reviewed were uncontrolled single patient group pre-test / post-test assessments, which raises concern about bias and reliability of outcomes. A recent randomised placebo-controlled trial has reported a significant reduction in average joint pain in women treated with aromatase inhibitors over a treatment period of three months with duloxetine, but discontinuation rates were high due to low grade toxicities experienced by significantly more of women allocated to receive duloxetine (e.g. fatigue, nausea, dry mouth, headache).[57] Evidence and advice about benefit of physical exercise is conflicting.[6,56]

No recommendations were made in the NICE menopause guidance, nor the recently up-dated NICE clinical guidance on early and locally advanced breast cancer for the management of musculoskeletal symptoms induced by aromatase inhibitors.[1,2] One randomised study reviewed by the NICE menopause Clinical Guidance Group showed improvements in physical functioning and bodily pain up to nine months following group CBT versus usual care (i.e. patient access to clinical specialists and breast cancer support services).[58] However, musculoskeletal symptoms were not specifically assessed and the proportion of women taking aromatase inhibitors is unknown.

Practice points

I. In the absence of consensus and randomised controlled trials concerning the management of aromatase inhibitor-induced arthralgia it is reasonable to recommend hypermobilisation of the joints after periods of rest to reduce tenosynovitis type symptoms exercise, yoga, weight loss,

a trial of regular paracetamol or systemic or locally delivered NSAIDs as first-line measures.[59-64]

II. If symptoms persist:

- ***a. Switching between non-steroidal aromatase inhibitors (letrozole, anastrozole) or between non-steroidal and steroidal (i.e. exemestane) aromatase inhibitors may be of some benefit.***[65-67]
- ***b. Switching patients to tamoxifen from an aromatase inhibitor may be of benefit as the former is much less likely to induce arthralgia.***[10]
- ***c. Ideally changes to breast cancer treatment or use of HRT should be discussed following breast multi-disciplinary and gynae-endocrine review, as changes to treatment could potentially affect disease-free survival, particularly in higher-risk women.***

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What evidence is available regarding the use of HRT for menopausal symptom relief in breast cancer survivors?

Definitive evidence from clinical trials in women with previous breast cancer exposed to systemic HRT or topical estrogen is lacking. Three randomised trials of systemic HRT (with or without additional topical estrogen) were all stopped following an initial interim analysis from one trial group that showed an increased risk of recurrence. However, similar analyses from the other trial groups did not.[67-69] As all trials were stopped at an early stage, no firm conclusions can be made. Evidence from studies on the use of topical estrogen is also inconclusive as although none reported an increased risk of recurrence, their reliability is hampered by small event numbers and uncontrolled, observational methodology.[70-75] A large randomised trial of tibolone closed prematurely when interim analysis showed an increased risk of recurrence and also appeared to reduce the efficacy of concomitantly prescribed aromatise inhibitors, although this was not an a priori hypothesis.[76] It can be hypothesised HRT will not reduce the therapeutic impact of tamoxifen due to the latter's strong binding affinity for the estrogen receptor but it could negate the efficacy of aromatase inhibitors, which reduce oestrogen synthesis.

Breast cancer treatment and chemoprevention trials confirm estrogen deprivation or antagonism reduces the risk of the diagnosis and recurrence of hormone sensitive but not hormone insensitive breast cancer.[2,77] Concern exists therefore, HRT use will increase the risk of recurrence in estrogen receptor positive cancer and it is also important to be aware of the risk of late recurrence in this patient cohort, which may occur many years after treatment completion.[78] Furthermore, it may incorrect to assume HRT is risk free in women with estrogen receptor negative disease as there is a very small risk of diagnosis of an estrogen receptor positive recurrence or a contralateral breast primary in this patient group.[79,80] Additional factors, which could influence risk, include time from breast cancer diagnosis, extent of breast surgery and concurrent use of tamoxifen. However, these, along with cancer estrogen receptor status have not been confirmed or refuted in published clinical evidence to date. A final consideration is whether It HRT is efficacious in symptomatic women taking tamoxifen. One breast cancer chemoprevention trial found that systemic HRT was not but randomised trials of HRT in breast cancer patients suggests otherwise.[69, 81, 82]

Some patients, after trying alternatives to HRT for symptom relief unsuccessfully, may request to have systemic or topical HRT. Counselling such women should account for these prevailing uncertainties. Whilst NICE and the UK National Cancer Research Institute Symptom Management Breast Group recommend research investigating non-hormonal alternatives for symptom management, NICE has identified a need for clinical trials evaluating the safety of systemic and topical HRT in specific patient cohorts (e.g. women with estrogen receptor negative cancer or those with estrogen receptor positive disease taking tamoxifen).[1,7]

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Miss Jo Marsden, Consultant Breast Surgeon, King's College Hospital, London, Mr Mike Marsh, Consultant Gynae-endocrinologist, King's College Hospital, London, Dr Anne Rigg, Consultant Medical Oncologist, Guy's and St Thomas' Hospital, London on behalf of The British Menopause Society.

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