The specialist authority for menopause & post reproductive health

The management of estrogen deficiency symptoms, arthralgia and menopause diagnosis in women treated for early breast cancer

The British Menopause Society (BMS) is the specialist authority for menopause and post reproductive health in the UK. The BMS educates, informs and guides healthcare professionals, working in both primary and secondary care, on menopause and all aspects of post reproductive health.

BMS consensus statements, prepared by specialists from the BMS medical advisory council, address key disorders and controversial topics relating to menopause and post reproductive health. They reflect new studies together with recent medical and scientific information from articles in professional journals, plus informal consensus.

The consensus statements are evidence-based, comprehensively referenced and peer reviewed and they are regularly updated.

This guidance document by the British Menopause Society 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 healthcare professionals with an expertise in menopause for management of such symptoms, which in turn often involves liaison with patients' breast cancer teams.[1] However, as many women initially present to primary healthcare professionals for advice, this statement is aimed to support the latter in such consultations by providing information about symptom aetiology, current management strategies and controversies and identifying useful practice points.

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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 Guideline [NG23] recommends referral of women to a healthcare professional with expertise in menopause for counselling about the risk of developing an early menopause and the management of estrogen deficiency 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 with agreement from the breast specialist team.

Introduction

Breast cancer is the most commonly diagnosed female malignancy in the UK. Despite the risk of diagnosis increasing rapidly in the third and fourth decades, it is predominantly a condition of the post-menopause as approximately 80% of cases occur in women over the age of 50.[2] The development, introduction and now widespread use of breast cancer systemic therapies in the management of early stage disease, the aim of which is to eradicate dormant occult micro-metastases, is the most significant contributor to the improvements in breast cancer survival.[3,4] Unfortunately, estrogen deficiency symptoms and arthralgia may be induced, or pre-existing symptoms exacerbated by these therapies and result in their discontinuation.[5] 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.[6,7] Effective patient care, however, requires more than simply advising about potential interventions. For many women, the opportunity to have informed discussion with a healthcare professional about the reasons for symptom development and their duration can be of therapeutic benefit in itself. However, these discussions may be difficult if the clinician has little knowledge concerning the management of breast cancer.[8]

Principles of early breast cancer management

The majority of women presenting with breast cancer in the UK have early stage disease, that is they do not have detectable systemic metastases. Management, therefore, consists of (1) local control for the prevention of local complications and recurrence in the breast and ipsilateral axilla using surgery and radiotherapy and (2) adjuvant systemic therapy to prevent the development of distant metastases by eradicating occult, micro-metastases.[3] It is systemic and not local control therapy, which confers survival benefit. The range of systemic adjuvant treatments that can be prescribed for early breast cancer include chemotherapy, anti-estrogenic endocrine therapy, gonadotrophin-releasing hormone agonists [GnRHa], targeted biological therapy such as Herceptin (trastuzumab) and bisphosphonates.[3]

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Selection of adjuvant therapy

This is individualised for every patient and based on the predictive and prognostic features of the diagnosed cancer.[3] To aid treatment discussion, oncologists may use:

— PREDICT, an online tool, which estimates the average survival rate (for up to fifteen years) with different therapy combinations for cancers with similar features by age-group.[9]

— Tumour profiling (genomic) tests to guide adjuvant chemotherapy decisions.[10]

Most women are recommended a combination of therapies.

Predictive factors – breast cancer receptor status

1. *Estrogen receptor (ER) expression*. This determines whether anti-estrogenic endocrine therapy is indicated. Most breast cancers are estrogen receptor positive (ER+ve), and hence, anti-estrogenic endocrine therapy is recommended. The Selective Estrogen Receptor Modulator (SERM) tamoxifen is effective in both pre- and postmenopausal patients due to its estrogen receptor antagonist activity in the breast. It is offered as initial therapy to all premenopausal women, irrespective of risk of recurrence. Postmenopausal women estimated to be at high or medium risk of recurrence are recommended initial treatment with aromatase inhibitors such as letrozole (Femara®), anastrozole (Arimidex®) and exemestane (Aromasin®), which reduce estrogen synthesis in peripheral fat as trials suggest superiority to tamoxifen in this patient cohort. Tamoxifen is recommended as initial treatment in postmenopausal women at low risk of recurrence or those at higher risk unable to tolerate an aromatase inhibitor or where an aromatase inhibitor is contra-indicated.[3] The minimum duration of anti-estrogenic endocrine therapy is 5 years. Extended duration of therapy up to a maximum of 10 years can be offered or considered to further reduce risk of recurrence but determined on an individual patient basis.[3]
   In younger women at high risk of recurrence gonadotrophin-releasing hormone agonists (e.g. goserelin [Zoladex®]) may be used in combination with aromatase inhibitors, as such regimens are associated with less recurrence than with tamoxifen. The optimal treatment duration for such regimens is uncertain but currently is 5 years.[3]
2. *Human epidermal growth factor 2 receptor (HER2)* expression. Trastuzumab, a monoclonal antibody that blocks the HER2 receptor is indicated for cancers over-expressing this receptor (HER2 positive cancer).[2] Most breast cancers, however, do not and trastuzumab is not indicated. The treatment duration is for one year and it is used alongside chemotherapy and radiotherapy.[3]

Prognostic factors

1. These include breast cancer axillary nodal status, tumour size, tumour grade, presence of lympho-vascular invasion and HER2 receptor over-expression. Oncologists use these tumour characteristics to estimate the risk of systemic recurrence (i.e. whether this is low, intermediate or high) and inform decisions about other systemic therapies such as chemotherapy and bisphosphonates.
2. Unless there is a contra-indication, chemotherapy is recommended in women deemed to be at high risk of recurrence but for those estimated to be at intermediate risk based on the prognostic features listed above, where the added benefit of chemotherapy is uncertain, tumour profiling tests, which analyse the activity of groups of genes in an individual breast cancer, are used to guide decisions about its use. Genomic tests currently recommended by NICE include Oncotype DX, Prosigna and EndoPredict.[10] In addition to a cytotoxic effect on malignant cells, chemotherapy has a cytotoxic effect on ovarian follicles, which may confer added therapeutic benefit in premenopausal women with hormone sensitive cancer.[11] In early stage

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disease, the chemotherapy regime and hence duration of treatment, is tailored to the individual patient but will usually contain both a taxane and anthracycline.[3]

3. Bisphosphonates may reduce bone recurrence and breast cancer mortality in postmenopausal women with early-stage disease and is offered to postmenopausal women with lymph node involvement and considered in those without nodal involvement whose cancers have other prognostic features, placing them at high risk of recurrence.[3]

Follow-up for early breast cancer

The UK breast cancer follow-up pathway, prior to the Covid-19 pandemic, was in the process of change, with a move away from routine, out-patient-based appointments with clinical breast examination to supported, patient-led follow-up. This was based on a lack of evidence that the former reduced breast cancer mortality, or adequately met patients' supportive needs.[3,12] The onset of the pandemic has accelerated this transition. It is now recommended women treated for breast cancer are issued a written care plan at the end of their 'active' treatment (i.e. any or all of the following; surgery, chemotherapy, trastuzumab and radiotherapy). This care plan should be agreed with named healthcare professional(s) at the treating breast unit, shared with their GP and include dates for review of adjuvant endocrine therapy for women with ER+ve cancer, details of surveillance mammography and information about signs and symptoms of recurrence, or treatment side effects, with contact details for immediate referral to specialist care or support services. The latter should encompass a pathway for women experiencing estrogen deficiency symptoms arising from a natural or chemotherapy-induced menopause, or to tamoxifen or aromatase inhibitor exposure. Whilst telephone consultation is encouraged, clinical review may be required, as appropriate.[3,13]

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 healthcare professionals, with many women considering stopping treatment because of side effects for which management has never been discussed.[6,14] In premenopausal women the symptoms following a chemotherapy or GnRHa-induced ovarian suppression are usually more severe than those associated with tamoxifen.[15,16] The reported persistence of symptoms after completion of tamoxifen in younger patients is probably due to prior chemotherapy exposure inducing an early menopause.[16] In postmenopausal women both tamoxifen and aromatase inhibitors are associated with induction of vasomotor symptoms.[17] Symptoms usually persist for the duration of exposure but their severity may decrease over time.[18,19]

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.[20] 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.[18,20]

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Tamoxifen is associated with a small elevation in the risk of endometrial cancer in postmenopausal but not premenopausal patients by courtesy of its estrogen-agonist effect on the postmenopausal endometrium (in premenopausal women, tamoxifen does not appear to stimulate endometrial proliferation).[21] Overall endometrial cancers diagnosed in postmenopausal women are no different regarding stage, grade, histology and phenotype from those diagnosed in the general population.[21] In contrast, aromatase inhibitors are associated with no, or a reduced, risk.[22] It is hypothesised aromatase inhibitors may increase the risk of women developing symptoms of urogenital prolapse due to anti-estrogenic 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.[23] 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.[20]

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.[24,25] They usually develop within a few months of commencing treatment and they may persist for the duration of use.[7,26,27] Common symptoms include morning stiffness and pain affecting the hands, knees, hips, lower back, and shoulders.[7] 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.[26,28] Previous treatment with taxane-based chemotherapy, increased body weight and recency of menopause onset (ie < 5 years) have all been reported to increase the risk of aromatase inhibitor-induced arthralgia but further study is required to conform or refute these findings. Currently it is not possible to predict which women will develop symptoms with any reliability. However, research is taking place to identify genetic determinants, which may predispose to aromatase inhibitor-induced musculoskeletal symptoms. [7,28]

Practice Points

I. Most women will receive a combination of adjuvant systemic treatments.

II. 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.

III. Familiarity of the primary healthcare professionals with the type and duration of iatrogenic symptoms will aid consultation in primary care with breast cancer patients and appropriate referral for management.

IV. 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.[29] 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.[29,30]

Tamoxifen has been reported to be associated with a small increased risk of developing an early menopause, when used alone or following chemotherapy.[29] With the former this descriptive association was restricted to women over 45 and probably reflects

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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 research findings suggesting no added impact of tamoxifen on ovarian reserve.[29-35]

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.[36] 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.[3] 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.[34]

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.[37,38] 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.[37] Women must be fit for ovarian stimulation and oocyte collection and estimated to have a good prospect for long-term survival.[38]

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.[31] The risk of chemotherapy-induced amenorrhoea lasting more than two years is lower in women under the age of 39.[33] 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, 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).[33] 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.[39]

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:

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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.[40] 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.[3]
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.[33] 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 to reverse the former's suppressive effect on the hypothalamic-pituitary axis before performing serial FSH assays.[41]
4. Clinical evidence suggests undetectable serum levels of anti-Müllerian hormone in women over 40 at completion of chemotherapy may be a reliable predictor of premature or early menopause (serum assays are unaffected by concurrent tamoxifen use). In BRCA1 mutation carriers treated for breast cancer, however, larger, confirmatory trials are required before this is recommended in clinical practice.[42,43]

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.

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

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.[1,44,45]

In the UK, clinical practice is directed by the 2015 NICE Menopause Guideline (NG23) and the NICE guidance (NG101) on early and locally advanced breast cancer.[1,3] The conclusions of the NG23 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.[46,47] However, these are summarised with explanation and expansion as appropriate below and, where relevant, comparison with other publications.

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1. General recommendations for the management of women with breast cancer[1]

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

I. Non hormonal options should be first-line management in women with breast cancer. A Cochrane systematic review of placebo-controlled randomised trials in women with breast cancer showed a mild to moderate effect of clonidine, selective serotonin release inhibitors (SSRIs), selective noradrenaline release inhibitors (SNRIs), gabapentin and relaxation therapy on reducing hot flushes in women with a history of breast cancer.[48] However, with the exception of relaxation therapy, their symptomatic benefit can be outweighed by adverse effects.[1,44,46,48,49] The NG23 reported efficacy similar to that of placebo with SSRIs, SNRIs, gabapentin, isoflavones and St John's Wort.[1]

II. SSRIs and SNRIs may inhibit the activity of one of the main enzymes (i.e. CYP2D6) responsible for converting tamoxifen to its active metabolite and hence potentially reduce its anti-neoplastic action. This occurs to varying degrees and current recommendation is that paroxetene and fluoxetine, whose inhibitory action is strong, should be avoided in women treated with tamoxifen.[1] The SNRI venlafaxine is unlikely to adversely inhibit the activity of CYP2D6, which makes it a suitable option.

III. Although the NG23 reported St John's Wort may be effective in the treatment of hot flushes, there is a risk of interaction with tamoxifen, docetaxel and anti-coagulants, which raises significant 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]

IV. Soy and red clover (isoflavones) have estrogenic activity and should be avoided in women with breast cancer.[3]

V. Black cohosh, vitamin E and magnetic devices are not advised.[3]

VI. 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.[1,50]

VII. Consider cognitive behavioural therapy (CBT) to alleviate low mood or anxiety that arises because of the menopause.[1,44,51] 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.[51]

VIII. 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.[3] 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 product summary characteristics for all types of HRT. It should not be

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prescribed in women treated with aromatase inhibitors as the therapeutic benefit of aromatase inhibitors is mediated via a reduction in endogenous estrogen synthesis.[3,6] 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.[52,53]

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.[6,44]

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 exposed to combined rather than unopposed HRT and absence of long-term efficacy and safety data.[6] 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.[1,3]

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 and oxybutynin.[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.[3,31,44,49,54]

Practice points:

I. If a patient develops vasomotor symptoms an indication of how likely they may remain troublesome can be estimated if they persist beyond 3 to 6 months from the start of treatment. Temporary symptoms usually abate after about 3 months.[17]

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

III. Use of compounded bioidentical preparations is contra-indicated.

IV. In postmenopausal patients, switching from an aromatase inhibitor to tamoxifen may reduce vasomotor symptoms.

V. Systemic HRT should not be prescribed in women taking aromatase inhibitors.[6]

VI. 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 estrogen synthesis.

VII. No change to breast cancer treatment or use of HRT should be initiated without discussion between the patient, their menopause specialist (whether this is primary or secondary care based) and their surgery/oncology team. Communication with the latter is recommended, even if the patient has been

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discharged, as changes to treatment, or hormone re-exposure following treatment completion could potentially affect disease-free survival, particularly in higher-risk women. The local breast unit clinical nurse specialist is a useful source for up-to-date contact information.

VIII. In a symptomatic woman who has completed breast cancer therapy and been discharged from specialist follow-up, health care professionals in primary care should contact the patient's breast care nurse (or breast clinical nurse specialist at the local breast unit) for advice as they are best placed to triage concerns and advise where to direct the patient.

3. Vulvo-vaginal atrophy

I. Commercially available vaginal moisturisers and vaginal lubricants are recommended as first-line treatment.[1,55] It has been suggested due to the weak estrogenic 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.[56]

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, or if the patient has been discharged, by enquiry to the local breast oncology specialist (their information can be accessed by the useful unit's breast clinical nurse specialist).

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

IV. The oral SERM, ospemifene is licensed in the UK for use in women who have completed their breast cancer therapy. Whilst preclinical studies suggest a neutral effect on breast tissue there is a lack of long-term safety data from clinical trials.[1,6] Available evidence consists of short-term follow-up using unreliable surrogates for predicting future risk (i.e. clinical breast examination, change in mammographic breast density, breast tenderness).[57] If it is considered in a woman previously treated for breast cancer, it would be prudent to inform her breast specialist team in advance. In women who are currently being treated for breast cancer with anti-estrogenic therapy there is no data about the combined impact of ospemifene with tamoxifen or aromatase inhibitors and it is not recommended.

All guidelines and consensus statements concur with the recommendations of the NG23 for use of vaginal moisturisers and lubricants as initial treatment and consideration of low-dose topical estrogen if symptoms are refractory.[6,44,49,52,54]

Alternative interventions, which may provide future options for symptom management in breast cancer patients include vaginal laser treatment (i.e. the fractional CO_2 and Erbium Yag lasers) and intravaginal dehydroepiandrosterone (DHEA).

I. In a small series of breast cancer patients treated with fractional CO_2 laser therapy, although significant improvements in sexual quality of life and urinary function were reported, there were no changes in vaginal pH level and epithelial maturation pattern on pap smear.[58] Placebo, or active-controlled trials are required to fully evaluate

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long-term efficacy and safety. This has been given further emphasis given the lack of efficacy of fractional CO_2 laser therapy in a randomised comparison with sham treatment, which failed to show any benefit after a follow-up of one year (women with hormone-dependent malignancy were excluded).[59] Due to a lack of appropriate long-term safety and efficacy data, NICE recommends laser therapy should only be used in the context of a clinical trial and this should apply to women with a diagnosis of breast cancer.[60]

II. Intravaginal DHEA has the theoretical advantage of local delivery of active estrogen and androgen metabolites via the activity of aromatase in vaginal epithelial cells. Preliminary, uncontrolled studies show it to be efficacious in the presence of tamoxifen and aromatase inhibitors.[61,62] Although systemic absorption is purported to be minimal, statistically significant plasma estradiol and testosterone serum levels in the lower half of the postmenopausal range have been reported following administration.[63] Further clinical trial evidence about the safety and efficacy of DHEA is required in women treated for breast cancer.

Practice points:

I. If symptoms of vulvo-vaginal atrophy are not relieved by vaginal moisturisers 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.***[6]
- ***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 currently being treated with anti-estrogenic therapy.

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.[31]

IV. In a symptomatic woman who has completed breast cancer therapy and been discharged from specialist follow-up, healthcare professionals in primary care should contact the breast clinical nurse specialist at the local breast unit for advice as they are best placed to triage concerns and advise where to direct the patient.

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4. Musculoskeletal symptoms

Currently there is no UK consensus about the management of musculoskeletal symptoms induced by aromatase inhibitors. No recommendations were made in the 2015 NICE menopause guidance, nor the recently up-dated NICE clinical guidance on early and locally advanced breast cancer.[1.3]

The optimal management of aromatase inhibitor-induced arthralgia is yet to be determined, however, several pharmacological and complementary therapies have been evaluated, which show promise. Preliminary randomised data suggests potential benefit with a wide variety of pharmacological agents likely mediated via anti-inflammatory or analgesic pathways. These include the SNRI duloxetine, oral testosterone, diuretics and omega-3 fatty acid.[28] Most of these studies are of a short-duration (less than 6 months) and further longer-term, controlled evaluation is required to determine efficacy and side-effect profiles. Interestingly, the use of oral testosterone (i.e. 40mg or 80 mg of testosterone undecanoate) was not associated with any increase in serum estradiol when compared to women allocated placebo).[64] Uncontrolled data suggests that bisphosphonates may reduce aromatase-induced arthralgia, in addition to preventing bone loss.[65] Switching between aromatase inhibitors (i.e. letrozole and anastrozole) and intermittent letrozole dosing are further areas of current investigation.

Of complementary interventions, aerobic exercise and resistance training have been shown to improve pain symptoms and muscle strength and yoga to improve myalgia and arthralgia.[28] Acupuncture has also been reported to be of benefit in reducing pain scores and large-scale randomised trials are ongoing.[28] A randomised study of group CBT versus usual care (i.e. patient access to clinical specialists and breast cancer support services) showed improvements in physical functioning and bodily pain up to nine months post intervention. However, musculoskeletal symptoms were not specifically assessed and the proportion of women taking aromatase inhibitors is unknown.[66]

Practice points.

I. In the absence of consensus 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. [67-69]

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 benefit*** [70-71]
- ***b. Switching patients to tamoxifen from an aromatase inhibitor may be of benefit as the former is much less likely to induce arthralgia***[17]
- ***c. 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.***

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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.[72-74] 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.[75-80] 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.[81] 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 estrogen 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.[3,82] 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.[83] Furthermore, it may be 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.[84.86] 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 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.[74, 86,87]

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]

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WRITTEN: MARCH 2022
NEXT REVIEW DATE: MARCH 2025

Q4P2223

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