Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer

Maria Alice Franzoi, Elisa Agostinetto, Marta Perachino, Lucia Del Mastro, Evandro de Azambuja, Ines Vaz-Luis, Ann H Partridge, Matteo Lambertini

The growing availability of more effective therapies has contributed to an increased survival of patients with breast cancer. In hormone receptor-positive early disease, increased survival is strongly correlated with the use of adjuvant endocrine therapy, but this therapy can cause side-effects that have major consequences in terms of treatment adherence and patients' quality of life. In premenopausal breast cancer survivors, these side-effects might be even more prominent due to the abrupt suppression of oestrogen associated with the most intense endocrine therapies. An important ambition of cancer care in the 21st century is to recover pre-cancer quality of life and emotional and social functions, which is only possible through the mitigation of the side-effects of anticancer treatments. This Review presents a comprehensive summary of the efficacy and safety data of the available interventions (hormonal and non-hormonal pharmacological strategies, non-pharmacological approaches, and complementary and alternative medicine) to control selected side-effects associated with adjuvant endocrine therapy (hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, and fatigue), providing updated, evidence-based approaches for their management.

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Academic Trials Promoting Team, Jules Bordet Institute and Université Libre de Bruxelles, Brussels, Belgium (M A Franzoi MD, E Agostinetto MD, E de Azambuja MD)**; Medical Oncology and Hematology Unit, IRCCS Istituto Clinico Humanitas—Humanitas Cancer Center, Humanitas Research Hospital, Milan, Italy** (E Agostinetto)**; Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Policlinico San Martino Hospital** (M Perachino MD, M Lambertini MD)**, and Department of Internal Medicine and Medical Specialties, School of Medicine, University of Genoa, Genoa, Italy** (M Perachino, L Del Mastro MD, M Lambertini)**; Breast Unit, IRCCS Policlinico San Martino Hospital, Genoa, Italy** (L Del Mastro)**; Unit 981—Molecular Predictors and New Targets In Oncology, Department of Medical Oncology, INSERM and Institut Gustave Roussy, Paris, France** (I Vaz-Luis MD)**; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA** (Prof A H Partridge MD)

Correspondence to:
Dr Matteo Lambertini, Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Policlinico San Martino Hospital, University of Genoa, Genoa 16132, Italy
matteo.lambertini@unige.it

Introduction

Breast cancer mortality rates have been decreasing over the past 20 years, and patients with breast cancer now represent the largest group of cancer survivors.[1] About 70% of breast cancers are hormone receptor-positive, for which the mainstay of treatment is oestrogen deprivation (endocrine therapy).[2] Adjuvant therapy with either tamoxifen or aromatase inhibitors reduces breast cancer recurrence and improves overall survival in patients with hormone receptor-positive breast cancer.[3,4] However, the benefits achieved with adjuvant endocrine therapy come at a cost. Distressing side-effects associated with adjuvant endocrine therapy include hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, bone density loss, depression, cognitive dysfunction, and fatigue.[5,6] There is solid evidence showing that these long-lasting side-effects substantially impair patients' quality of life and treatment adherence.[7]

In premenopausal patients with breast cancer, adjuvant endocrine therapy can be escalated with the addition of ovarian function suppression to tamoxifen or to an aromatase inhibitor.[8,9] Because of the abrupt decrease in oestrogen concentrations induced by ovarian function suppression, the side-effects of endocrine therapy can be even more prominent in premenopausal patients.[10] A recent study on premenopausal women with breast cancer found a rate of 16% non-adherence assessed through biochemical testing 1 year after prescription of tamoxifen, which was hypothesised to partly correlate with the presence of side-effects (fatigue and musculoskeletal symptoms). Importantly, non-adherence to tamoxifen resulted in impaired cancer-specific outcomes.[11] Ovarian function suppression increases the occurrence of side-effects of adjuvant endocrine therapy in premenopausal women; however, similar quality-of-life indicators have been reported for tamoxifen or aromatase inhibitors combined with ovarian function suppression. Patients treated with tamoxifen plus ovarian function suppression are more affected by hot flushes and night sweats, whereas patients treated with aromatase inhibitors plus ovarian function suppression report higher rates of sexual dysfunction and musculoskeletal symptoms.[12] Collectively, these side-effects can be severely bothersome and affect treatment adherence, as reflected in observed rates of early discontinuation: about 20% for both oral endocrine therapy (all types) and ovarian function suppression (regardless of the prescribed oral endocrine therapy).[8]

Although the rates of non-adherence are reported to be lower for postmenopausal patients, decreased quality of life[6] and treatment discontinuation[13] due to side-effects are also important issues for these patients.[14] In addition, treatment adherence appears to be different in clinical trials and in clinical practice, where discontinuation rates from oral adjuvant endocrine therapy are higher, varying from 31% to 73% after 5 years of treatment.[13,15,16]

Despite the high frequency of adverse events related to endocrine therapy, this topic is often underestimated and underaddressed during follow-up consultations, when the focus is usually on the risk of disease recurrence.[10,17] Chemotherapy-induced toxicities tend to be accepted by patients and physicians because the adjuvant or neoadjuvant treatment period is short and these toxicities are mostly reversible. By contrast, patients are asked to take adjuvant endocrine therapy for 5 years or 10 years, throughout which there is a continual potential to develop toxicities, even if such adverse events are of lower grade.[6] Proactive symptom management is an important element of survivorship care to ensure patients have the best possible treatment outcomes alongside the complex balance of tolerability, treatment adherence, and quality of life.

	Intervention	Control group	Study outcome	Results
HABITS[19] (2004), n=434	Oestrogen–progesterone combination	No hormone therapy	Risk of breast cancer recurrence	HR 3·50 (95% CI 1·50–8·10); p value not provided; trial stopped early due to increased risk of recurrence
Stockholm[20] (2005), n=378	Oestrogen–progesterone combination	No hormone therapy	Risk of breast cancer recurrence	HR 1·80 (95% CI 1·03–3·10); p value not provided; trial stopped after combined analysis with the HABITS trial
LIBERATE[21] (2009), n=3148	Tibolone	Placebo	Risk of breast cancer recurrence	HR 1·40 (95% CI 1·14–1·70); p=0·0009 for all patients; 1·25 (0·98–1·59); p=0·076 for patients taking tamoxifen; 2·40 (1·01- 5·00); p=0·047 for patients taking aromatase inhibitors; trial stopped early due to increased risk of recurrence

HR=hazard ratio.

Table: **Randomised controlled trials evaluating hormone-replacement therapy in patients with early breast cancer**

This work is a comprehensive overview that aimed to summarise the efficacy and safety data of the available interventions (hormonal and non-hormonal pharmacological strategies, non-pharmacological approaches, and complementary and alternative medicine) to control selected side-effects associated with adjuvant endocrine therapy (hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, and fatigue) to provide updated evidence-based approaches for their management. These side-effects were chosen for their high prevalence and inconvenience to patients. Other important side-effects related to endocrine therapy (eg, cognitive dysfunction, depression, anxiety, distress about body image, insomnia, cardiovascular toxicity, and bone density loss) are not discussed in the present manuscript because of length constraints, but they warrant separate ad-hoc investigations.

See Online for appendix

Management of endocrine therapy-related side-effects

Previous data suggest that a comprehensive menopausal assessment intervention (including symptom assessment, education, counselling, and specific pharmacological and behavioural interventions according to the symptoms present) is associated with a substantial improvement in symptom control.[18]

Although the most effective therapy to treat symptoms related to oestrogen deficiency is hormonal replacement, this approach is contraindicated in breast cancer survivors because it increases the risk of recurrence (table).[19–21] Although safe and effective non-hormonal treatments are still needed, several therapeutic options have already shown benefits in randomised controlled trials for the management of side-effects of adjuvant endocrine therapy in breast cancer survivors (figure 1).

Hot flashes

Pharmacological strategies

For non-hormonal strategies, several studies have investigated the use of antidepressants (including selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors) for the control of hot flashes in breast cancer survivors. The most studied agent is venlafaxine, which has been shown, in several randomised controlled trials, to reduce hot flashes by up to 60% (appendix p 3).[22–25] Different daily doses from 37·5 mg to 150 mg have been tested. Higher doses have shown a major reduction in hot flashes, but are also associated with important adverse events, such as mouth dryness, decreased appetite, nausea, and constipation.[26,27] Other serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, including duloxetine, escitalopram, paroxetine, and sertraline, have also shown positive results for the control of hot flashes in breast cancer survivors (appendix pp 3–4). Although controversial, selective serotonin reuptake inhibitors are potent inhibitors of CYP2D6 and could potentially reduce the bioavailability of tamoxifen.[28,29]

The anticonvulsants gabapentin and pregabalin are efficacious alternatives to treat hot flashes in breast cancer survivors. A crossover trial showed that gabapentin and venlafaxine have similar efficacy and cause similar reductions of hot flashes (66%), with patients preferring venlafaxine.[23] The α-adrenergic agonistic antihypertensive clonidine induces a 40% reduction in hot flashes (compared with placebo) in breast cancer survivors.[30] Because of the important side-effects related to the use of clonidine and of the results of a randomised trial showing the superiority of venlafaxine,[25] clonidine is generally not used as a first option for the treatment of hot flashes in breast cancer survivors.

A placebo-controlled trial showed positive results with lower doses of the anticholinergic oxybutynin (2·5 mg or 5 mg twice a day) for the treatment of hot flashes in patients with and without breast cancer.[31] A greater improvement in hot flashes and overall quality of life was observed when compared with placebo.[31] Treatment-related side-effects were mainly grade 1 or 2 and included dry mouth, difficulty urinating, and abdominal pain.[31] Importantly, although cognitive impairment was not evaluated in this trial, anticholinergic drugs can induce this potential adverse effect, of which physicians should be aware of.[31]

The choice of non-hormonal pharmacological therapy should be a shared decision between physician and patient. This discussion should also consider concomitant medications, comorbidities, and the safety profile of the proposed pharmacological strategies, including potential drug interactions. Considering that the efficacy of most of these therapies has also been shown with lower doses, starting with a low dose to evaluate response and tolerability is preferable.

For hormonal strategies, the progesterone analogues megestrol[32] and medroxyprogesterone[33,34] are highly efficacious for the treatment of hot flashes in women with breast cancer (appendix p 5). Although isolated progestogens have been used for the treatment of metastatic breast cancer in the past, their safety is not yet established in patients with early breast cancer. There are concerns associated with their use because the combination of oestrogen and progesterone has been shown to increase the risk of breast cancer recurrence.[19,21]

Non-pharmacological strategies

Weight control and dietary intervention might be an important strategy to reduce hot flashes in breast cancer survivors. As suggested by two cohort studies, weight gain was independently associated with the risk of developing hot flashes in women taking aromatase inhibitors or tamoxifen.[35,36] Although weight control can be achieved with a dietary intervention, a subgroup analysis of the WHEL study,[37] which investigated the effect of a high-vegetable, high-fibre, low-fat diet in breast cancer survivors, showed no decrease in vasomotor symptoms for patients receiving tamoxifen assigned to the intervention group.

A stellate ganglion block procedure is effective in the control of hot flashes in breast cancer survivors taking endocrine therapy, as initially shown in small single-arm studies with an improvement in the hot flash score of up to 60% (appendix p 6). Although one study showed a greater improvement in hot flash score with stellate ganglion block versus pregabalin,[38] a more recent study comparing this strategy to paroxetine showed similar results in both groups.[39] Therefore, considering the invasiveness of stellate ganglion block, the pharmacological approach might be preferred as a first strategy.

Cognitive behavioural therapy is another intervention that can help breast cancer survivors to manage vasomotor symptoms by affecting their perception and cognitive appraisal of hot flashes (appendix p 6). The randomised MENOS 1 trial[40] compared usual care versus usual care plus 6 weeks of group cognitive behavioural therapy (including psychoeducation, pace breathing, and relaxation). The intervention group reported a significant reduction of the perceived burden of hot flashes and night sweats, with a sustained effect after 26 weeks. However, there was no significant difference in the frequency of hot flashes between the two groups at either 9 weeks or 26 weeks. The dropout rates in this trial were low, suggesting that this intervention was highly acceptable.[40] The absence of adverse events and the additional benefits on mood and sleep[40] observed with this strategy call for additional studies comparing or adding this approach to non-hormonal active treatments.

Figure 1: **Interventions that showed positive results in randomised controlled trials for the management of adjuvant endocrine therapy side-effects in breast cancer survivors**
Compelling evidence refers to data from several randomised controlled clinical trials. Preliminary evidence refers to fewer or smaller randomised controlled clinical trials. SNRIs=serotonin–norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors. TCM=Traditional Chinese Medicine.

Complementary and alternative medicine

Data from randomised trials suggest that acupuncture might be an efficacious option for the treatment of hot flashes in breast cancer survivors receiving adjuvant endocrine therapy (appendix p 7). The efficacy of this intervention was initially reported as inconsistent, and data showed that sham acupuncture has also a positive effect on hot flash scores (placebo effect). Nevertheless, a more recent randomised trial suggested that patients treated with true acupuncture have a higher benefit in reduction of hot flashes composite score when compared with sham acupuncture, gabapentin, or placebo.[41,42] The durability of the therapeutic effects after treatment is an

interesting potential advantage of this therapy because the positive effect on hot flashes scores persisted in the acupuncture group for 4 months after treatment completion, which did not happen in the gabapentin group.[41] Whenever available, this intervention could be considered for breast cancer survivors because it has very few side-effects and is associated with additional benefits in other potential target symptoms, such as cancer-related fatigue[43] and joint pain.[44]

Two randomised trials showed that hypnosis can improve hot flashes in breast cancer survivors (appendix p 9). Elkins and colleagues[45] showed a significant benefit of hypnosis in hot flash score (68% reduction after five sessions), anxiety, depression, and sleep compared with a control group. A subsequent smaller study randomly assigned breast cancer survivors with hot flashes to hypnotherapy versus gabapentin and showed an improvement on the hot flash score in both groups, without significant differences.[46] Hypnosis might therefore be a useful intervention, and has fewer safety concerns than pharmacological approaches. However, the restricted availability of this intervention might be a challenge to a routine and widespread inclusion in patients' survivorship care.

Yoga and relaxation training (appendix pp 9–10) sessions can help to reduce hot flashes in breast cancer survivors, according to the encouraging results of small randomised trials.[47,48] Additionally, the simple measure of using a cool pad pillow topper can bring comfort to patients having sleep disturbances due to hot flashes.[49]

Supplements (ie, black cohosh, soy phytoestrogens, magnesium, and vitamin E) and magnet therapy have been tested and found to have no effect on hot flashes compared with placebo. Although the results of some prospective single-arm studies and case-control studies suggested that homoeopathy could improve hot flashes, randomised, placebo-controlled trials of this approach yielded negative results (appendix p 8).

Sexual dysfunction

Sexual dysfunction in breast cancer survivors can have several manifestations, such as physical and vulvovaginal changes (eg, vaginal dryness and dyspareunia), and psychosocial effects (eg, decreased libido, changes in body image and self-esteem, and barriers to intimacy and partner communication). A comprehensive assessment and a multidisciplinary approach to this issue are needed.

Pharmacological strategies

Local hormone-based therapies include oestradiol-releasing intravaginal tablets, low-dose vaginal inserts, oestrogen-based vaginal creams, oestradiol-releasing vaginal rings, vaginal testosterone, and vaginal dehydroepiandrosterone. Each is systemically absorbed at different rates, and all of them have been shown to be effective in treating vaginal symptoms related to oestrogen deprivation. Oestrogen-based vaginal treatments, particularly, also result in improvements in the vaginal mucosa (appendix p 17). Currently, there is no formal evidence of increased risk of breast cancer recurrence with local vaginal oestrogen therapy, but several studies have shown that these agents can cause an elevation of serum oestradiol concentrations. This elevation in serum oestradiol could be of concern in premenopausal patients with breast cancer who are receiving ovarian suppression plus an aromatase inhibitor because achieving complete suppression of ovarian function is necessary for aromatase inhibitors to have an anticancer effect.[50] Short-term follow-up and small sample sizes are important limitations of the studies investigating these strategies.

Ospemifene is an oral selective oestrogen receptor modulator used for the treatment of moderate to severe dyspareunia associated with vaginal dryness related to menopause.[51] Although preclinical studies suggest that ospemifene might block oestrogen activity in breast cells,[52] there are no data yet supporting the safety of ospemifene in patients with breast cancer.

Until there is a clearer understanding of the potential effect of local hormone-based therapies on breast cancer recurrence, non-hormonal approaches should be the first-line choices for the management of genitourinary symptoms in breast cancer survivors. In case of severe refractory symptoms, temporary low-dose vaginal oestrogen therapy can be considered as a treatment option, after discussion of its potential risks and uncertainties with the patient.

The results of a small, randomised, placebo-controlled trial suggest that 4% aqueous lidocaine compresses applied to the vulvar vestibule before vaginal penetration can effectively improve dyspareunia and sexual distress in patients with breast cancer taking endocrine therapy. Lidocaine might, therefore, be a useful temporary strategy for patients reporting insertional pain.[53]

Randomised trials support the use of vaginal lubricants (water-based formulations, polycarbophil, and hyaluronic acid moisturisers) to treat genitourinary symptoms in breast cancer survivors receiving adjuvant endocrine therapy (appendix p 16). Placebo-controlled studies have shown that lubricants can moderately decrease dyspareunia, vaginal dryness,[54–56] and sexual distress.[56] Given their wide availability, low cost, and negligible side-effects, vaginal lubricants should be offered as a first approach to all breast cancer survivors reporting sexual dysfunction and vaginal symptoms. One study has also reported positive results with vitamin D or E vaginal suppositories, which resulted in a significant improvement in vaginal maturation index and vaginal symptoms compared with a placebo.[57]

Non-pharmacological strategies

Several studies have shown a benefit of cognitive behavioural therapy for breast cancer survivors facing sexual dysfunction (appendix p 15). In a Dutch trial, breast cancer survivors receiving adjuvant endocrine therapy

were randomly assigned to 24 weeks of internet-based cognitive behavioural therapy (done by a psychologist or sexologist specialised in the field) versus waitlist control.[58] Patients in the experimental group reported improvements in overall sexual function, sexual desire, arousal, and vaginal lubrication, as well as improvement in sexual pleasure, discomfort during sex, and sexual distress.[58] A telephone counselling intervention has also shown a positive effect on sexual dysfunction.[59] An in-person 6 week sexual life reframing programme (including interventions on psychological but also physical aspects of sexual health) delivered to breast cancer survivors has also shown a significant improvement in sexual satisfaction.[60] A small single-arm study tested a brief psychosexual intervention targeted to manage sexual dysfunction and psychological distress in young breast cancer survivors treated with ovarian function suppression.[61] In this study, participants received a 4 h group intervention that included sexual health rehabilitation, body awareness exercises, and mindfulness-based cognitive therapy skills followed by a telephone call 1 month later. Female sexual health and anxiety improved significantly from baseline to 2 months.[61] Based on the available evidence, cognitive behavioural therapy should be highly encouraged for breast cancer survivors facing sexual dysfunction. Dedicated and experienced counselling in this regard should be made available to all patients facing these side-effects.

Several retrospective and single-arm prospective studies have shown a positive effect of vaginal (CO_2 or erbium) laser for genitourinary symptoms related to sexual dysfunction, such as vaginal dryness, dyspareunia, vaginal itching, and burning in breast cancer survivors (appendix pp 15–16). A significant improvement of vaginal atrophy (vaginal health index) was reported with this intervention.[62,63] However, despite promising initial results, the absence of well designed randomised trials and of long-term safety follow-up and the high costs of this treatment option limit a broader recommendation.

In a small single-arm study, local intramucosal injections of autologous platelet-rich plasma combined with hyaluronic acid was been reported to improve vaginal atrophy and sexual distress in breast cancer survivors (appendix p 17). However, additional evidence is needed before this approach can be considered in clinical practice.

Weight gain

Weight management has an important role in breast cancer survivorship care because obesity or weight gain might lead to poorer breast cancer prognosis, as well as serious comorbidities, fatigue, functional decline, and poorer health and overall quality of life.[64] Furthermore, fat tissue is an additional source of serum oestrogen precursors that are metabolised to oestrogen by the enzyme aromatase.[64] Therefore, weight gain could affect the efficacy of adjuvant endocrine therapy. In premenopausal patients with breast cancer receiving ovarian function suppression plus aromatase inhibitors, higher body-mass index was shown to be a risk factor for incomplete ovarian function suppression.[50,65]

Randomised trials have shown that weight loss is feasible in patients receiving adjuvant endocrine therapy,[66–70] and it should be recommended for breast cancer survivors with overweight or obesity. The most efficient interventions include a multidisciplinary approach with regular physical exercise, diet, and cognitive behavioural therapy. Ongoing studies are addressing how to support breast cancer survivors in losing weight and the potential effect of diet and weight loss on breast cancer outcomes (NCT02750826 and NCT04304924).

Both in-person or remote interventions have proven efficacy and are superior to standard medical care (where oncologists encourage patients to keep a healthy diet and achieve or maintain an ideal body-mass index). Several studies have investigated interventions targeting weight loss in breast cancer survivors taking adjuvant endocrine therapy (appendix pp 21–24). There is a growing number of smaller pilot studies investigating the use of eHealth tools, such as mobile apps and self-monitoring devices, with promising results. These interventions, if proven to be efficacious in subsequent properly powered and designed studies, might help physicians to assist breast cancer survivors at a low cost and with relatively easy implementation.

Musculoskeletal symptoms

Pharmacological strategies

Some patients with aromatase inhibitor-induced musculoskeletal symptoms might benefit from the strategy of switching to a different aromatase inhibitor, allowing them to continue therapy (appendix p 27). A multicentre study showed that, after switching to a different aromatase inhibitor, 39% of the patients were able to continue the second aromatase inhibitors for a median of 13·7 months.[14] The ATOLL study,[71] evaluating the switch from anastrozole to letrozole, both non-steroidal aromatase inhibitors, reported that 72% of patients continued therapy after 6 months. However, a considerable proportion of patients continued to have musculoskeletal symptoms, including 74% of patients complaining of arthralgia, 21% of myalgia, 16% of arthritis, 14% of tendinitis, and 13% of polyalgic syndrome, after taking letrozole for 6 months.[71] A crossover trial of a switch from exemestane (a steroidal aromatase inhibitor) to letrozole or vice versa showed less worsening of the functional status after 3 months with the second aromatase inhibitor when compared with the first one.[72]

The use of duloxetine for 13 weeks can reduce aromatase inhibitor-induced joint pain in breast cancer survivors. In a randomised trial,[73] after 12 weeks of treatment, the average joint pain score was 0·82 points lower for patients who received duloxetine than for patients who received placebo (95% CI –1·24 to –0·40; p=0·0002). Grade 3 adverse events were rare, but low-grade toxicities,

including fatigue, nausea, dry mouth, and headache, were significantly more frequent in the duloxetine group.[73] Of note, patients taking duloxetine reported additional substantial improvements in quality of life that could be multifactorial, rather than exclusively the result of improved pain control. Duloxetine is also an effective hot flashes treatment, and this potential positive effect in multiple symptoms (including depression) should be considered together with its safety profile when prescribing this therapy.

Although one randomised trial suggested a benefit of high-dose vitamin D in reducing musculoskeletal symptoms in breast cancer survivors taking endocrine therapy, all other trials reported negative results (appendix p 27). Therefore, vitamin D is not generally recommended for this purpose, but should be used for the prevention of bone density loss during therapy with aromatase inhibitors. Other medications investigated for the control of aromatase inhibitor-induced joint pain include furosemide, glucosamine plus chondroitin, calcitonin, and a short course of low-dose oral prednisolone with positive results. However, the evidence for the use of these therapies derives from small single-arm studies and, therefore, is insufficient to support a formal recommendation (appendix p 27).

Non-pharmacological strategies

Control of musculoskeletal symptoms is one of the potential benefits of physical exercise in breast cancer survivors (appendix p 28). In the phase 3 HOPE trial,[74] patients with breast cancer with joint pain during therapy with aromatase inhibitors were randomly assigned to 150 min per week of aerobic exercise and supervised strength training twice per week, or usual care. At 12 months, worst joint pain scores decreased by 29% in the exercise group and increased by 3% in the usual care group ($p<0·001$). Additionally, pain severity, pain interference, and other pain scores decreased significantly for women assigned to the exercise group and increased in the usual care group.[74] Other exercise options (eg, Nordic walking, home-based walking, and aquatic exercises) were also evaluated in smaller trials with shorter follow-up periods and reported a positive effect on joint pain (appendix p 28).

Complementary and alternative medicine

Acupuncture can be a complementary therapy for the control of musculoskeletal symptoms (appendix pp 28–29). Similarly to its effect on hot flashes control, sham acupuncture also produces a placebo effect when used for joint pain. In a multicentre randomised trial, true acupuncture compared with sham acupuncture or with waitlist control in patients with breast cancer receiving an aromatase inhibitor resulted in a significant reduction in joint pain at 6 weeks.[44] In this study, the maintenance of true acupuncture once a week for an additional 6 weeks, compared with sham acupuncture, was associated with significant improvements in average pain, but no significant improvement in worst pain, pain interference, pain severity, or worst stiffness at 12 weeks.[44]

Several reports from single-arm trials and qualitative research showed the benefit of yoga in improving musculoskeletal symptoms (appendix p 29). In a post-hoc analysis of a randomised trial, a 4 week standardised yoga intervention (YOCAS) in breast cancer survivors taking endocrine therapy showed greater reductions in musculoskeletal symptoms such as general pain, muscle aches, and total physical discomfort from pre-intervention to post-intervention than the control group.[75] However, the primary endpoint of this trial was sleep quality, and questionnaires designed to specifically measure musculoskeletal symptoms were not used. Additional studies to better elucidate the true effect of yoga on musculoskeletal symptoms are needed.

The use of omega-3 supplementation was compared with placebo in a randomised phase 3 trial, and no difference in joint pain was found across groups.[76] Therefore, omega-3 supplementation should not be recommended for the treatment of musculoskeletal symptoms, although it can be considered for patients with obesity, for whom it has been shown to have benefits in a subsequent post-hoc analysis. Neuromuscular tapping and the traditional Chinese medicine Yi Shen Jian Gu granules have shown positive preliminary results in reducing joint pain induced by aromatase inhibitors, warranting further investigation in properly designed clinical trials (appendix p 29).

Fatigue

Non-pharmacological strategies

Physical exercise is the most studied intervention targeting fatigue in breast cancer survivors taking endocrine therapy and should be recommended for the management of this side-effect. Several randomised trials have shown a positive effect of physical exercise in reducing fatigue scores and improving quality of life, anxiety, and depression. Various types of exercise seem effective, with more evidence available for regular aerobic and muscle strength training.[77,78] Home-based and outdoor walking have also shown benefit and should be encouraged (appendix pp 35–37).

Cognitive behavioural therapy is another non-pharmacological intervention that effectively helps women to face fatigue related to adjuvant endocrine therapy and potentially reduces its intensity and interference with daily life. Cognitive behavioural therapy can also help patients to engage in healthy habits that additionally reduce fatigue. Several randomised trials have tested the efficacy of this intervention with positive results (appendix pp 37–38). Because cognitive behavioural therapy can be costly and time-consuming, the CHANGE study[79] evaluated the effect of an internet-based cognitive behavioural therapy compared with usual care, and showed that significantly less fatigue and clinically significant, self-rated improvement

can be achieved with the intervention. Additional benefits included significant less functional impairment and psychological distress, and better quality of life compared with usual care. This internet-based intervention was based on a previous face-to-face cognitive behavioural therapy protocol that was shown to be effective for severe fatigue in cancer survivors. An ongoing non-inferiority trial (NTR5179) is comparing internet-based cognitive behavioural therapy versus a face-to-face approach. Results of this study and future cost-effectiveness analyses will be important for a broader dissemination of this strategy.

Complementary and alternative medicine

Several small studies have investigated the effect of acupuncture for fatigue control in patients with breast cancer taking adjuvant endocrine therapy (appendix p 33). A randomised trial of an 8 week course of acupuncture compared with waitlist control and sham acupuncture showed a significant improvement in fatigue, anxiety, and depression during the 12 week intervention and follow-up period for the acupuncture group.[43] By contrast, sham acupuncture did not produce a significant reduction in fatigue and anxiety symptoms.[43] This study is consistent with the growing body of literature suggesting that acupuncture might be effective for fatigue, anxiety, and depression in breast cancer survivors.

Two forms of self-administered acupressure (relaxing or stimulating acupressure) were compared with usual care in a randomised trial for breast cancer survivors with fatigue.[80] At 6 weeks, the percentages of patients achieving normal fatigue levels (Brief Fatigue Inventory score <4) were higher for patients assigned to relaxing acupressure (66%) or stimulating acupressure (60%) interventions compared with control (31%; p=0·01), with sustained results at 10 weeks.[80] Although the results appear interesting, the placebo effect was not examined in this study.

A number of pilot studies investigating yoga and mindfulness interventions compared with waitlist control or usual care have shown positive effects in lowering fatigue scores and improving overall quality of life and mood distress in the intervention group (appendix pp 33–34). Compared with usual care, a 12 week intervention of yoga and meditation was shown to improve menopausal symptoms, quality of life, and fatigue scores immediately after the end of the intervention and at a 3 month follow-up.[81] A 6 week programme of mindfulness-based stress reduction compared with usual care was also shown to be effective on immediately improving psychological symptoms and fatigue, with a sustained effect up to 12 weeks.[82] Yoga and mindfulness interventions can, therefore, be an important treatment option for breast cancer survivors taking endocrine therapy, and efforts should be made to increase their availability.

Other interventions such as martial arts (eg, qigong or Tai Chi Easy) and ginseng supplements might help to decrease fatigue scores, as suggested by randomised trials (appendix pp 34–35). Studies to further increase the knowledge on these interventions are needed. Melatonin might help to control insomnia, but appears to have no effect on improving fatigue (appendix p 35).

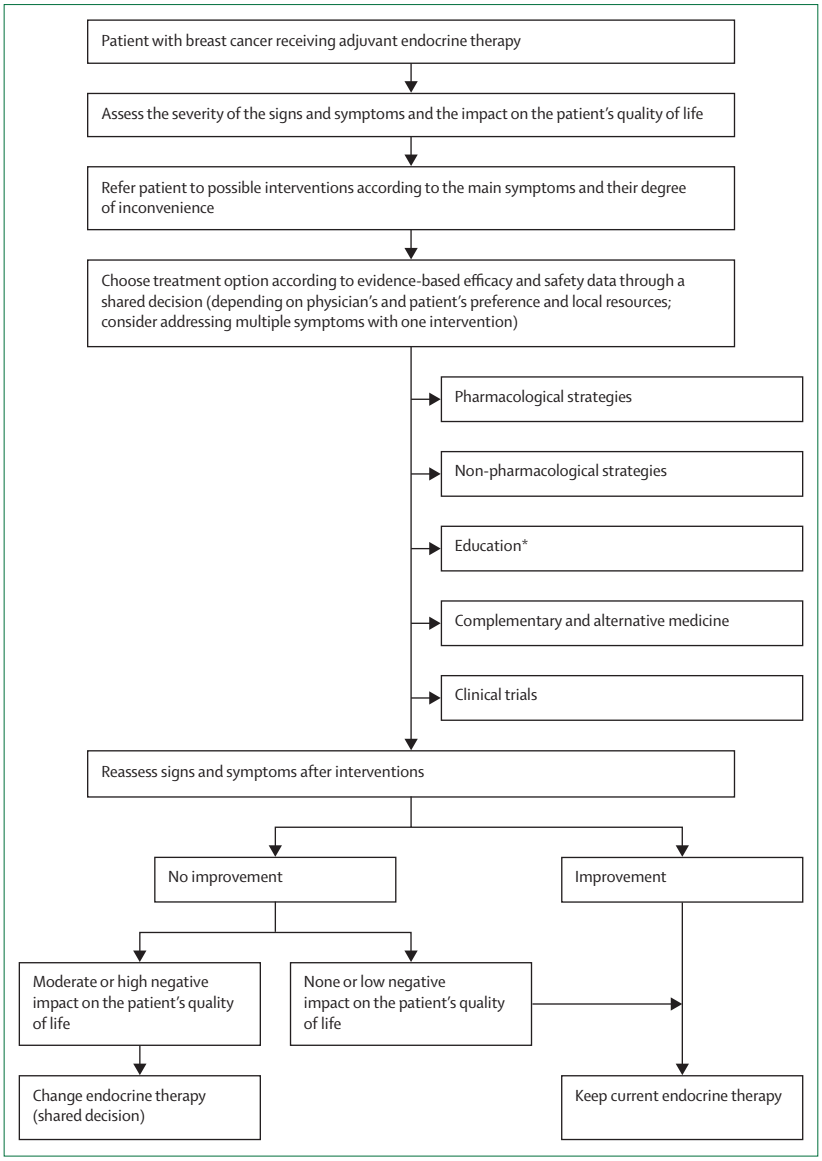

Figure 2: **Workflow to assess side-effects of endocrine therapy in breast cancer survivors**
*Internet-based and technology devices can be a good vehicle for this approach.

Conclusion

Hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, and fatigue are prevalent side-effects in patients with breast cancer undergoing adjuvant endocrine therapy. The burden of these unaddressed symptoms (often for several years) on patients should not be underestimated.

Endocrine therapy side-effects must be routinely assessed during consultations because several

√√√ Probably efficacious (data from RCTs) √√ Might be efficacious (data from RCTs with smaller samples)
√ Could be effective (single-arm studies) .. No sufficient data for breast cancer survivors

	Hot flashes	Sexual dysfunction	Weight gain	Musculo-skeletal symptoms	Fatigue
SSRIs and SNRIs	√√√	..	..	√√√	..
Anticonvulsants	√√√	..	..	..	..
Oxybutynin	√√√	..	..	..	..
Aromatase inhibitor switch	..	..	..	√√	..
Vaginal lubricants or moisturisers	..	√√√	..	..	..
Vaginal CO_2 laser	..	√	..	..	..
Stellate ganglion block	√√	..	..	..	..
Cognitive behavioural therapy	√√√	√√√	√√√	√√√	√√√
Physical exercise	..	..	√√√	√√√	√√√
Acupuncture	√√	..	..	√√√	√√
Hypnosis	√√	..	..	..	..
Yoga and mindfulness	√√	..	√	√√	√√

Figure 3: **Efficacy of selected non-hormonal interventions to control endocrine therapy side-effects in breast cancer survivors**
RCTs=randomised controlled trials. SNRIs=serotonin–norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors.

Search strategy and selection criteria

We searched PubMed for publications from inception to Aug 10, 2020, using the search terms "breast cancer" OR "breast neoplasm" OR "breast tumor" OR "breast tumors" OR "breast tumour" OR "breast tumours" OR "breast neoplasms" [Medical Subject Headings]) AND "endocrine therapy side-effects" OR ''endocrine therapy toxicity" OR "early menopause" OR "sexual dysfunction" OR "genitourinary syndrome" OR "vaginal dryness" OR "dyspareunia" OR "vaginal atrophy" OR "Hot flashes" OR "vasomotor symptoms" OR "weight gain" OR ''weight loss" "asthenia" OR "arthralgia" OR ''fatigue" OR ''quality of life" OR ''QoL" NOT (animals [Medical Subject Headings] NOT humans [Medical Subject Headings]) with no time restriction. We reviewed only papers in English investigating an intervention in breast cancer survivors treated with adjuvant endocrine therapy. The full list of assessed articles and their main findings are available in the appendix. The final references included in this manuscript were selected on the basis of their relevance to the scope of this Review.

interventions are available to control or reverse them. This is crucial to increase treatment adherence and quality of life during adjuvant endocrine therapy. An individualised approach when choosing an intervention to control these symptoms is likely to have better chances of achieving a positive effect. The presence and degree of severity of the specific side-effects and their impact on everyday life should be assessed during consultations, and balanced with the expectations of the patient with the intervention. Notably, the instruments for outcome measures frequently differ among the studies, making it difficult to aggregate and pool the data to give clear treatment recommendations. Additionally, the duration of the supportive intervention is an important knowledge gap, considering the indication of endocrine therapy for up to 5–10 years after diagnosis.

After careful consideration of the efficacy, safety, and adverse event profile of the treatment options, a decision should be made taking into account the resources available, reimbursement by private and or public health care systems, consequences on patients' financial resources, and patients' preference (figure 2). Some interventions might be effective for different symptoms (figure 3), which should be taken into consideration during the decision process, as the ability to address multiple symptoms with one intervention could, ultimately, be the key to improving the patient's quality of life. We acknowledge that complementary and alternative medicine strategies are not completely unified procedures and that, consequently, the results of the intervention might vary according to the protocol used, training of the health-care professional, and the patient's characteristics. In addition, few studies compared complementary and alternative medicine strategies with traditional interventions.

A multidisciplinary, certified, and dedicated team facilitating patient access to effective interventions should be pursued. Remote interventions (internet, telephone, and home-based) could also be effective and might be a good vehicle for disseminating these important interventions at a lower cost and time with a greater reach, including breast cancer survivors living in remote areas. Considering the potential upcoming availability of escalated adjuvant strategies,[83] including combinations with targeted agents characterised by a peculiar safety profile,[84] the burden of endocrine therapy-related side-effects is expected to become even more relevant in the near future and a growing attention to their proper management is likely to become essential.

Contributors
MAF and ML conceptualised the manuscript and wrote the original draft. MAF did the search, data collection, data analysis, figures, and revision of the manuscript. EA did the data collection, data analysis, and revision of the manuscript. MP did the data collection and revision of the manuscript. LDM, EdA, IL-V, AHP, and ML did the data analysis and revision of the manuscript. ML supervised the project.

Declaration of interests
LDM reports an advisory role for Roche, Novartis, Merck Sharp and Dohme, Pfizer, Ipsen, AstraZeneca, Genomic Health, Lilly, Seattle Genetics, Eisai, Pierre Fabre, and Daiichi Sankyo; honoraria from Roche, Novartis, Lilly, and Merck Sharp and Dohme; and travel grants from Roche, Pfizer, and Celgene. IV-L reports honoraria paid to institution from AstraZeneca, Amgen, and Pfizer. EdA reports honoraria from and an advisory board for Roche; and travel grants from Roche, and Novartis; research grants from Roche, Radius, AstraZeneca, Lilly, Merck Sharp and Dohme, Novartis, Synthon, Servier, and Pfizer paid to Institut Jules Bordet. AHP reports royalty payments for coauthoring the breast cancer survivorship section of UpToDate. ML reports an advisory role for

Roche, Lilly, AstraZeneca, and Novartis; and honoraria from Pfizer, Lilly, Takeda, Novartis, Roche, and Sandoz. All other authors declare no competing interests.

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