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Estrogen deprivation effects of endocrine therapy in breast cancer patients: Incidence, management and outcome

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ABSTRACT

Endocrine therapy is one of the standard adjuvant treatments to reduce the risk of recurrence and mortality in patients with hormone receptor positive early breast cancer. Despite its proven efficacy, ET side effects, which persist over time even if low grade, may deteriorate quality of life. During follow-up visits, emphasis is generally placed on the risk of disease recurrence, while the topic of ET side effects is commonly neglected and discussed only briefly. This could lead to poor adherence to therapy and early treatment discontinuation, resulting in worse survival outcomes.

The aim of this review is to provide an overview of the available evidence on the incidence and reporting of ET-related side effects (including vasomotor symptoms, musculoskeletal disorders and genitourinary syndrome of menopause, as well as fatigue, psychological and ocular disorders, dysmetabolic effects and loss of bone density) and of the pharmacological and non-pharmacological strategies available to mitigate symptom burden.

Introduction

With more than 2 million new diagnoses per year, breast cancer (BC) is the most common malignancy and the leading cause of cancer-related death worldwide [1]. Most BC cases are diagnosed at an early stage, with the disease limited to the mammary gland and the loco-regional lymph nodes. Luminal-like BC is the most frequent molecular subtype, accounting for about 70% of the diagnoses [2].

Endocrine therapy (ET) represents the cornerstone for the adjuvant treatment of luminal-like early BC (eBC) and it encompasses different agents: tamoxifen [(Tam), a selective estrogen receptor modulator (SERM)], aromatase inhibitors [(AIs), both nonsteroidal such as letrozole and anastrozole and steroidal such as exemestane, which block estrogen production from the adipose tissue] and, for premenopausal patients, ovarian function suppression (OFS), achieved by oophorectomy, ovarian irradiation or, most commonly, using luteinizing hormone-releasing hormone agonists (LHRHa) [3–5].

Despite its proven efficacy, the side effects of ET have the potential to deteriorate quality of life (QoL) and adversely affect treatment adherence [6]. Given the short duration of (neo)adjuvant chemotherapy (CT)

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with mostly reversible toxicities, CT-induced side effects are generally accepted. In contrast, patients undergoing adjuvant ET will receive it for five to seven/ten years, with toxicities that, despite being low-grade, tend to persist over time and eventually worsen QoL. Also, these potential long-term and late complications are often underreported; as a result, many BC patients are unaware, inadequately prepared, and unable to effectively manage their symptoms [7,8]. This could result in suboptimal adherence to therapy, early discontinuation of treatment, and ultimately, negatively impact upon survival outcomes [9].

In the past two decades, several randomized clinical trials (RCTs) have investigated and proposed pharmacological and non-pharmacological strategies for managing ET toxicities, demonstrating that addressing these side effects may improve symptom burden [10].

This review aims to assess the incidence and reporting of ET-related side effects and examine both hormonal and non-hormonal pharmacological interventions, along with non-pharmacological strategies, for managing these adverse events. By presenting a contemporary, evidence-based approach, we aim to provide guidance on how to effectively address and control ET-related adverse events Fig. 1 and Table 1.

Vasomotor symptoms

Up to 95% of all premenopausal patients and 30% of all postmenopausal patients receiving adjuvant ET for eBC experience vasomotor symptoms (VMS), which manifest as hot flushes and/or night sweats [11]. Although frequently overlooked, they are a cause of distress for the patients and represent the most common cause of early ET interruption [12,13].

The combined analysis of the SOFT and TEXT trials reported how for premenopausal patients with Hormone receptor-positive (HR-positive) eBC, a significant improvement in disease-free survival (DFS) and freedom from distant recurrence can be obtained by combining of OFS to exemestane/Tam with respect to Tam alone [14]. Hot flushes and sweating were reported by 91.7% and 54.5% of patients receiving OFS + exemestane respectively, and by 93.3% and 59% of patients receiving OFS + Tam [15]. At predefined time points, these patients were administered a questionnaire to evaluate changes in QoL from the beginning of ET and patients treated with OFS + Tam experienced a greater worsening of VMS compared to patients treated with OFS + exemestane, although these symptoms improved over time [16].

A lower percentage of patients receiving an AI or Tam alone complain about VMS. In the ATAC trial, postmenopausal patients with eBC were randomized to receive 5 years of adjuvant ET with anastrozole or Tam and a significant improvement in DFS was observed in favor of anastrozole. In terms of QoL, a significantly lower incidence of hot flushes was registered in the group of patients receiving anastrozole (35.7%) compared to Tam (40.9%) [17].

VMS are due to the altered function of the thermoregulatory center localized in the hypothalamus, caused by the hypoestrogenism induced by ET [18]. Hot flushes are generally preceded by an increase in body temperature, which induces a series of compensatory mechanisms aiming to dissipate the heat, such as cutaneous vasodilation, with subsequent occurrence of sweating and skin reddening [18]. These events are regulated by several neurotransmitters, mostly serotonine and noradrenaline [19].

Selective serotonin reuptake inhibitors (SSRIs) and serotonine-noradrenaline reuptake inhibitors (SNRIs) can improve consistently the occurrence of VMS in menopause [9,19]. In particular, venlafaxine (SNRI) has demonstrated to lower the incidence of hot flushes in up to

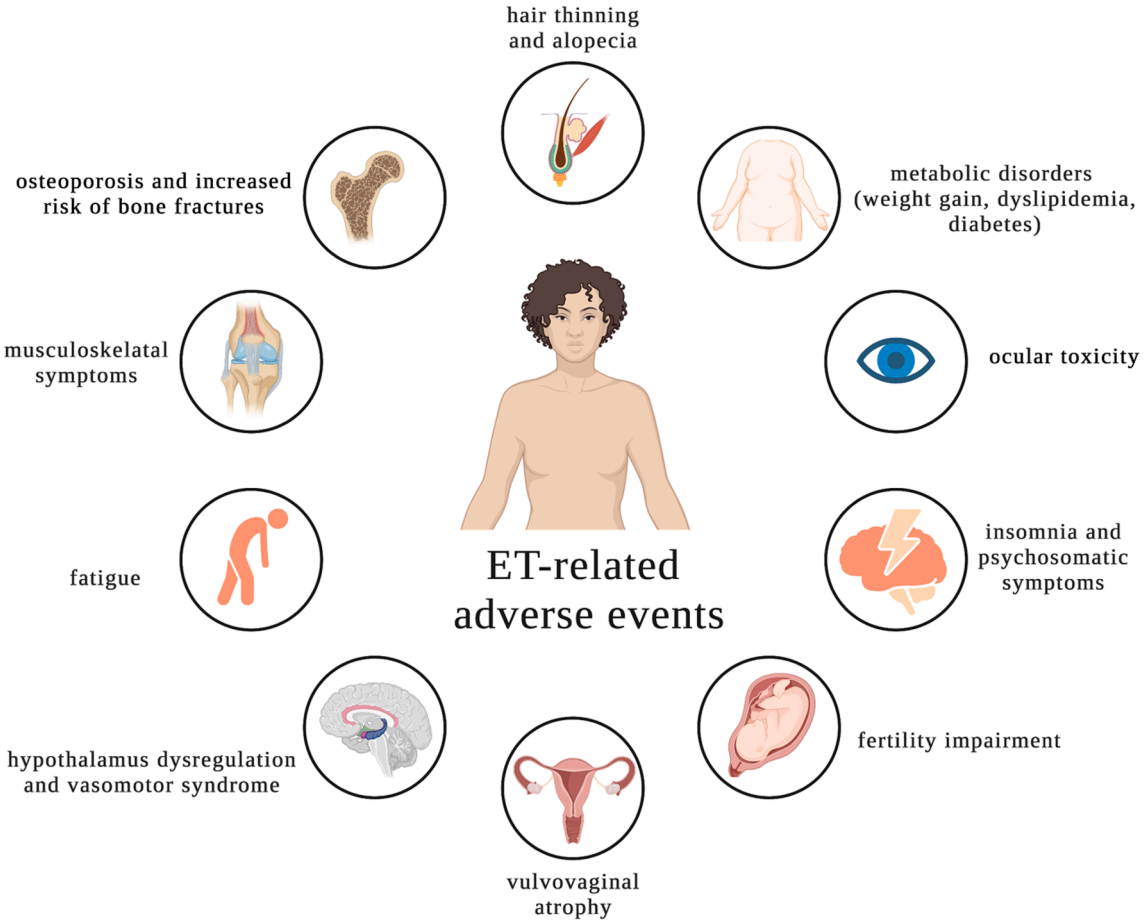

Fig. 1. Graphical representation of endocrine therapy-related toxicities. Abbreviations: ET = endocrine therapy.

Table 1
Therapeutic strategies for the management of major endocrine therapy-related side effects in breast cancer patients.

ET-related side effects	Incidence	Therapeutic Strategies			References
Vasomotor symptoms	>95%	*Pharmacological*	*Hormonal*	NA	
			Non-hormonal	SSRIs and SNRIs*	Shams, 2014; Loprinzi 2000; Stubbs 2017
				gabapentin and pregabalin	Bordeleau, 2010
				clonidine	Loibdl, 2017
		Non-pharmacological		cognitive behavioral therapy	Mann, 2011
				acupuncture	Ee, 2017
				herbal and pollen extracts	Winther, 2005
Musculoskeletal symptoms	>46%	*Pharmacological*	*Hormonal*	AIs switch	Briot, 2010
			Non-hormonal	duloxetine*	Henry, 2021
				omega-3 fatty acids	Shen, 2018
				glucosamine and chondroitin sulfate	Greenlee, 2013
				vitamin D	Khan, 2017; Niravath, 2019
				vitamin B12	Campbell, 2018
				diuretics (furosemide and spironolactone)	Alhanafy, 2018
				bisphosphonates	Santa-Maria, 2018
		Non-pharmacological		physical exercise	Campbell, 2018; Lu, 2020
				acupuncture	Hershman, 2022
				auriculotherapy	Hyder, 2021
				physiotherapy	Hyder, 2021
				curcumin	Hyder, 2021
				cannabidiol	Hyder, 2021
Metabolic disorders	~20%	*Pharmacological*	*Hormonal*	NA	
			Non-hormonal	NA	
		Non-pharmacological		physical exercise	Artene, 2017; Pakiz, 2011; Zhong, 2014
				dietary measures	Artene, 2017; Pakiz, 2011
Genitourinary syndrome of menopause	25–55%	*Pharmacological*	*Hormonal*	vaginal hormones	Moegele, 2013
			Non-hormonal	vaginal lidocaine	Goetsch MF, 2015
				vaginal lubricants	Advani, 2017; Lee, 2011
				vaginal suppositories with vitamin D-E	Parnan, 2016; Keshavarzi, 2019
				vaginal CO2 or erbium laser*	Jugulytė, 2023
				vaginal oxygen with hyaluronic acid	Massarotti, 2023
		Non-pharmacological		cognitive behavioral therapy	Hummel, 2018
Fertility impairment	NA	*Pharmacological*	*Hormonal*	transient suspension of ET	Partridge, 2023
			Non-hormonal	fertility-preserving procedures	Paluch-Shimon, 2020; Lee, 2006; Lambertini, 2020
		Non-pharmacological		NA	
Osteopenia/osteoporosis	NA	*Pharmacological*	*Hormonal*	NA	
			Non-hormonal	calcium and vitamin D supplementation*	de Groot, 2018; D'Oronzo, 2019; ESMO guidelines, 2020
				bisphosphonates*	
				denosumab*	
		Non-pharmacological		physical exercise	ESMO guidelines 2020; Malagrinò, 2023
				calcium-enriched diet	
				quit smoking	
				limit alcohol consumption	
Alopecia	2.5–9%	*Pharmacological*	*Hormonal*	NA	
			Non-hormonal	topical/oral minoxidil*	Freites-Martinez, 2018; Badri, 2022
		Non-pharmacological		wigs, tattoos	Ferreira, 2019
Fatigue	60%	*Pharmacological*	*Hormonal*	NA	
			Non-hormonal	NA	
		Non-pharmacological		physical exercise	Huang, 2010
				dietary measures	Huang, 2010
				cognitive behavioral therapy	Eichler, 2015
				yoga	Berger AM, 2015
				acupuncture	Berger AM, 2015
Insomnia	50%	*Pharmacological*	*Hormonal*	NA	
			Non-hormonal	benzodiazepines	Vaidya, 2011
		Non-pharmacological		sleep hygiene measures	Berger AM, 2015
				cognitive behavioral therapy	Aricò, 2016
				physical exercise	Berger AM, 2015
				yoga	Mustian, 2013; Berger AM, 2015
				mindfulness-based stress reduction programs	Andersen, 2011
				acupuncture	Huang, 2006
Psychosomatic disorders	~30%	*Pharmacological*	*Hormonal*	NA	
			Non-hormonal	SSRIs	Strazzanti, 2020
				benzodiazepines	Vaidya, 2011

(*continued on next page*)

Table 1 (*continued*)

ET-related side effects	Incidence	Therapeutic Strategies			References
		Non-pharmacological		cognitive behavioral therapy	Berger AM, 2015
				physical exercise*	Wang, 2020
				acupuncture*	Wang, 2020
Ocular toxicity	~30%	*Pharmacological*	*Hormonal*	topical androgens (eye drops, patches)*	Peck, 2017; Wang, 2020 [110]
				oral androgens	Peck, 2017
			Non-hormonal	lubricating eye drops	Peck, 2017
		Non-pharmacological		NA	

Abbreviations: AIs = aromatase inhibitors; ET = endocrine therapy; SNRIs = serotonin–noradrenaline reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; NA: not available;

* Level of Evidence 1.

37–61% of patients when administered at the daily doses ranging from 37.5 mg to 150 mg. However, higher dosages increase the risk of adverse events such as xerostomia, lack of appetite, nausea and constipation [20]. Thereby, the use of venlafaxine at a daily dose of 37.5 mg appears to be a suitable therapeutic option, due to its favorable balance of benefit and tolerability. While other SSRIs/SNRIs have been evaluated in this setting, it should be noted that certain SSRIs, such as paroxetine and fluoxetine, strongly inhibit the enzyme CYP2D6, which is involved in the metabolism of Tam [21,22].

Other classes of agents have been employed for the management of VMS. Anticonvulsants, such as gabapentin and pregabalin, for example, have exhibited similar efficacy to venlafaxine in reducing the occurrence of VMS in eBC patients. However, in a RCT comparing venlafaxine versus gabapentin, venlafaxine was generally preferred due to its better tolerability profile [23]. Another potential alternative is clonidine, an antihypertensive agent capable of reducing by up to 37% the occurrence of VMS. Nevertheless, it is less effective than venlafaxine in managing these symptoms and has a worse toxicity profile [24].

Additionally, complementary and alternative medicine approaches should be considered. For example, pollen-based remedies have demonstrated to reduce the frequency of VMS in up to 65% of patients receiving ET when compared to placebo [25].

Finally, non-pharmacological interventions including acupuncture, cognitive behavioral therapy (CBT) and physical activity can ameliorate the frequency and severity of VMS [26–28].

Recently, the phase 3 SKYLIGHT 1 trial has investigated the role of fezolinetant (neurokinin-3 receptor antagonists) for the management of VMS in postmenopausal patients [29]. In comparison to placebo, fezolinetant has shown significant improvement in both frequency and severity of VMS, and this effect was sustained over time [29]. Currently, there is a lack of data regarding the efficacy and safety of fezolinetant specifically in BC patients.

Musculoskeletal ***symptoms***

Arthralgias, or joint pain, are experienced by as many as 46% of BC patients receiving AIs and lead to early treatment discontinuation in one-third of patients [30,31]. In the SOFT trial, an analysis of QoL questionnaires revealed that younger patients (under 35-year-old) experienced less prominent bone and joint pain compared to older patients. Among patients treated with OFS + exemestane, most developed bone and joint pain after 6 months from the beginning of ET, and the symptom gradually stabilized over time. Conversely, patients treated with Tam alone or in combination with OFS had a slower onset of joint pain, but eventually reached a similar level as those in the OFS + exemestane group within 24 months [32].

In the ALIQUOT trial, which involved 181 HR-positive eBC patients, participants were randomized to receive either 12 weeks of letrozole followed by 12 weeks of anastrozole, or vice versa: up to 52% of the patients reported joint pain, with around 20% experiencing grade ≥ 2 severity. There was no significant difference in the frequency and severity of arthralgias between the two different AIs. It is worth noting that joint pain typically started after switching to the second AI, indicating a time-dependent occurrence of this symptom [33].

The adjuvant treatment landscape for HR-positive eBC has recently expanded to include abemaciclib, (CDK4/6 inhibitor), which has been approved for use in this setting on the basis of the significant improvement in invasive DFS (IDFS) observed in the monarchE trial, when it was added to conventional ET [34]. Notably, when assessing the toxicity profile of this combination, the occurrence of ET-related side effects, particularly arthralgias, was less frequent in patients receiving the experimental treatment (26.6% versus 37.9%) [35].

Switching to a different AI can be a viable therapeutic option for patients who experience arthralgias. In the ATOLL trial, 72% of the patients who discontinued anastrozole due to musculoskeletal symptoms were switched to letrozole, resulting in a 19% reduction in joint pain and a significant improvement in QoL [36].

Amongst potential pharmacological interventions, the use of the SNRI duloxetine can be considered. In a RCT involving postmenopausal eBC patients with AI-related arthralgias, duloxetine treatment led to a 50% improvement in mean pain compared to the control group. Furthermore, pain scores returned to similar levels between the two arms after discontinuing the drug, confirming the analgesic effect of duloxetine [31].

The use of testosterone, due to its anti-inflammatory properties, has been explored as a means to alleviate joint pain [37–39]. In a phase II study involving eBC patients receiving adjuvant anastrozole, the administration of testosterone at a daily dose of 80 mg resulted in a 70% reduction in pain over a 3-month period, compared to a 43% reduction in the group receiving a daily dose of 40 mg [38]. In another RCT, postmenopausal patients with HR-positive eBC who were treated with anastrozole or letrozole and experienced moderate-to-severe arthralgias were randomly assigned to receive surgically implanted pellets containing a combination of testosterone (120 mg) and anastrozole (8 mg), or placebo, with 64% of the patients in the experimental group reporting improved joint pain at 3 months [37]. However, although in this trial testosterone may have led to improvements in certain AI-related symptoms, particularly in areas such as strength, lack of energy, urinary frequency, and stress incontinence, it did not demonstrate significant benefits in addressing the primary musculoskeletal symptoms of joint pain and stiffness [37]. Therefore, clinicians should have caution when considering testosterone for AI-related arthralgias, as it may not have provided comprehensive relief for musculoskeletal symptoms.

Additionally, the use of omega-3 fatty acids (O3-FA) has been investigated in BC patients receiving AIs, based on the positive results observed in a *meta*-analysis involving patients with rheumatoid arthritis. In the subgroup of BC patients with a body mass index (BMI) $\geq$ 30 kg/m^2, the use of O3-FA was associated with significant improvement in pain scores compared to placebo [40].

Regarding other pharmacological interventions, a recently published trial showed no significant impact of high-dose vitamin D supplementation upon AI-related joint pain [41,42]. Glucosamine and chondroitin

sulfate have been also evaluated in this context, revealing a significant improvement in the incidence and severity of joint pain in over half of the patients [43,44]. Another phase II study evaluated the effect of vitamin B12 supplementation on musculoskeletal symptoms and reported a mean pain score improvement of 34% at 23 months compared to baseline [45].

In a prospective phase II study, the combination of furosemide 20 mg and spironolactone 50 mg every other day for four weeks was evaluated and 84% of patients treated with AIs experienced a significant reduction in pain, stiffness and functional limitations, with improvements noticeable as early as the first week of treatment [46].

Considering the role of bisphosphonates in this context, the ZAP study enrolled 59 postmenopausal patients who received zoledronic acid one-to-two weeks before letrozole, followed by a subsequent administration at six months. At the end of the first year of ET, a significantly lower incidence of arthralgias was observed in these patients compared to the control cohort from the ELPh study, where patients received letrozole alone [47].

Finally, the American College of Sports Medicine recommends that cancer patients engage in moderate physical activity for approximately 30 min, 3 times a week [48]. A *meta*-analysis involving nine studies demonstrated that aerobic exercise can improve musculoskeletal symptoms and QoL, regardless of the specific exercise program undertaken [49].

Additionally, acupuncture has shown a long-term beneficial effect in managing AI-related arthralgias [50].

*Metabolic **disorders***

Estrogen deprivation is a key factor contributing to the development of dysmetabolic events, including weight gain, diabetes, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD). Weight gain poses a significant risk for the occurrence of metabolic syndrome, related comorbidities, and the risk of BC recurrence, particularly in postmenopausal patients, as adipose tissue becomes the primary source of estrogen synthesis.

Approximately 20% of patients receiving Tam and 21% of patients receiving AIs report weight gain with a negative impact upon body perception and overall QoL [51,52]. Furthermore, weight gain is among the predominant toxicities that persist in long-term follow up, causing ongoing discomfort throughout the duration of ET [53]. In a case-cohort study involving over 2,000 patients who received adjuvant ET for HR-positive eBC, nearly 20% of the population developed diabetes mellitus, with a higher risk observed in patients treated with AIs compared to those receiving Tam [54]. In fact, hypoestrogenism induced by ET can lead to insulin resistance and alteration of glucose homeostasis, thereby increasing the risk of type II diabetes mellitus [55].

The association between AIs and dyslipidemia is currently a topic of debate. In the BIG 1–98 trial, 43% of patients treated with letrozole developed mild-to-moderate hypercholesterolemia compared to 19% of patients receiving Tam [56]. Conversely, in the MA.17 trial, letrozole treatment in patients previously treated with Tam did not result in increased serum levels of total and LDL cholesterol, or triglycerides [57]. Similarly, conflicting data have been reported regarding the use of anastrozole. The ITA trial reported a higher incidence of dyslipidemia in patients who switched to anastrozole after at least 2 years of adjuvant Tam [58]. However, other trials have shown that treatment with anastrozole has no impact/favorable impact on the lipid profile [59]. Finally, exemestane treatment has not been found to significant impact on the lipid profile [59]. Overall, these findings suggest that treatment with AIs may be associated with an increased risk of dyslipidemia and cardiovascular diseases. On the contrary, the evidence is more robust for the treatment with Tam, which has consistently shown a significant reduction in total and LDL cholesterol levels, indicating a cardioprotective effect [60]. Actually, several trials have indeed reported a higher risk of cardiovascular events in patients receiving AIs, particularly those with pre-existing cardiac conditions, whereas a lower risk is reported for patients receiving Tam [61–63].

NAFLD has been observed in over one third of BC patients receiving ET, particularly those treated with AIs, potentially due to the increased risk of dyslipidemia associated with AIs [64,65].

Several trials have investigated the efficacy of lifestyle-based interventions, such as physical exercise and healthy diet, in managing body weight and reducing the risk of the other ET-related metabolic complications. The Dieta trial examined the efficacy of a diet rich in proteins, probiotics and calcium alone or in combination with isometric exercises in patients receiving adjuvant ET for eBC. Both study groups demonstrated significant weight loss, but it was more pronounced in the group that also engaged in physical activity, which also presented significant reductions in body fat [66].

Weight loss and physical activity have been shown to reduce circulating levels of cytokines and pro-inflammatory markers, which are associated with BC recurrence and metabolic comorbidities [67]. Furthermore, evidence suggests that moderate-to-high intensity exercise programs can lower circulating levels of total cholesterol and triglycerides, thereby reducing the risk of NAFLD [68]. Physical activity can also reduce insulin resistance, generalized body inflammation, and lower endogenous estrogens levels [69]. To date, no pharmacological intervention has proven to be effective in the treatment and/or prevention of metabolic disorders in BC patients. For example, a recent RCT conducted on overweight/obese BC patients showed that the combination of a Mediterranean diet with naltrexone/bupropion did not lead to significative changes in body weight and metabolic indexes compared to the Mediterranean diet alone [70].

*Genitourinary **syndrome of menopause***

The hypoestrogenism occurring in menopause can lead to thinning of the vaginal and urinary epithelium, causing symptoms such as vaginal dryness, dyspareunia, and dysuria. These symptoms are collectively referred to as genitourinary syndrome of menopause (GSM) [71].

All endocrine agents used in the treatment of HR-positive BC can contribute to some form of sexual dysfunction, affecting both pre- and postmenopausal patients and significantly impacting their QoL. In fact, it is estimated that up to 20% of patients receiving adjuvant ET discontinue treatment prematurely due to gynecological adverse events [72].

In SOFT and TEXT trials, vaginal dryness and dyspareunia were reported in varying percentages ranging from 42 to 54% and 24–32%, respectively, across all three therapy groups. The highest incidence was observed in patients receiving OFS + exemestane [73]. Furthermore, when comparing the incidence of gynecological symptoms over a period of 5 years of therapy, a significant worsening of vaginal dryness was observed in the OFS + exemestane group, while no significant change was observed in terms of vaginal discharge [16].

In postmenopausal patients, data on the occurrence of gynecological adverse events are available from major trials that compared Tam with AIs. In the IES trial, switching to exemestane after 2–3 years of adjuvant Tam therapy resulted in a significant improvement in DFS [74]. In this trial, a higher occurrence of gynecological symptoms and vaginal bleeding was observed in patients who continued treatment with Tam compared to those who switched to exemestane (9.0% versus 5.8% and 5.5% versus 4.0%, respectively) [74]. Similarly, in the ATAC trial, gynecological symptoms were more frequently reported by patients receiving Tam, particularly vaginal bleeding (10.2% versus 5.4%) and vaginal discharge (13.2% versus 3.5%).

While hormone replacement therapy would be the most appropriate therapeutic strategy for these symptoms, given their dependence on an abrupt decrease in circulating estrogen levels, the safety of estrogen-based agents in BC patients is not definitively established. Therefore, non-hormonal agents should be preferred for the management of GSM [72].

Vitamin D-E vaginal suppositories have shown activity in improving vaginal atrophy in eBC patients receiving ET [75,76]. Alternatively, vaginal lidocaine, as well as vaginal lubricants and moisturizers, can be used in this context [77,78]. Another potential option is the use of intravaginal CO2 or erbium lasertherapy, which can stimulate collagen synthesis and blood vessels formation, promoting vaginal remodeling and rejuvenation [79]. An emerging approach involves the combination of intravaginal oxygen with hyaluronic acid, which has shown promise in ameliorating vaginal atrophy and other GSM symptoms in BC patients receiving ET [80].

In addition to physical symptoms, patients with a new cancer diagnosis may experience psychological conditions related to the gynecological sphere, such as body image dysperception and loss of libido. A recent RCT has reported the effectiveness of CBT in managing psychosocial sexual dysfunctions, including improvements in libido, body image perception, vaginal lubrication, and discomfort during sexual intercourse [81].

*Fertility **impairment***

Up to 7% of all new BC diagnoses occur in women under the age of 40, and young age is considered a negative prognostic factor [82]. Both CT and ET can cause significant adverse effects in young patients, and fertility preservation is a major concern. International guidelines recommend offering fertility counselling to all patients diagnosed with BC at a childbearing age [83,84]. However, a study evaluating fertility-related concerns reported that over one-third of these patients do not receive adequate onco-fertility counseling and, although 51% of patients expressed concerns about fertility problems after CT and/or ET, only 10% agreed to undergo fertility-preserving procedures [85].

Although no clear consensus has been reached, it is generally recommended to wait at least one year after completing CT before attempting pregnancy [86]. After completing the CT program, for patients with HR-positive eBC, pregnancy concerns remain due to the potential teratogenicity of endocrine agents such as Tam.

In this context, the results of the POSITIVE trial, recently presented at the 2022 San Antonio Breast Cancer Symposium, are significant. This trial enrolled eBC patients younger than 42 years of age who had completed 18–30 months of adjuvant ET and that expressed their desire to interrupt the treatment to attempt pregnancy [87]. With a median follow-up of more than 3 years, 8.9% of the patients experienced a breast cancer free interval (BCFI) event, compared to 9.2% reported in the comparative cohort of the SOFT and TEXT trials considered by the investigators [87].

Additionally, 72% of the patients had at least one pregnancy during follow-up, and 76.3% resumed ET after a median interruption of 26 months [87]. This trial demonstrated that a temporary suspension of ET is a safe option for patients desiring pregnancy (with a majority achieving a live birth) and does not compromise the efficacy of the therapy. Therefore, this possibility should be considered in the process of onco-fertility counselling and discussed carefully with patients, taking into account the need for longer follow-up to draw definitive conclusions regarding the efficacy and safety of this approach.

*Bone **health***

After reaching peak bone mass, bone health is primarily influenced by the process of remodeling, which involves the continuous formation and resorption of bone tissue by osteoclasts and osteoblasts [88,89]. ET negatively impacts bone health by accelerating this turnover process due to its effects on bone metabolism and its prolonged use [90,91]. AIs decrease the levels of circulating residual estrogens by inhibiting androgen conversion, thereby increasing bone turnover [92]. On the other hand, Tam exhibits variable pharmacological effects depending on the target tissue, acting as an ER antagonist in breast tissue and an agonist on bone resorption [93]. The impact of Tam on bone mineral density (BMD) is influenced by endogenous estrogen levels, leading to reduced bone resorption in postmenopausal women but loss of bone mass in premenopausal patients [94,95]. Notably, in premenopausal patients, the association of OFS and Tam results in greater bone loss compared with OFS alone. Furthermore, the combination of OFS and AIs accelerates bone loss to a greater extent than the combination with Tam [96,97]. In a *meta*-analysis of seven RCTs involving postmenopausal patients, the use of AIs for five years was associated with an increased risk of bone fractures (7.5%) compared to Tam for five years (5.2%) [95]. Furthermore, a recent RCT reported a clinical fracture rate of 9.6% with AIs [98]. Among premenopausal patients undergoing OFS, instead, the 5-year incidence of bone fractures is higher with AIs compared to Tam (6.8% vs 5.2%, respectively) [15].

International guidelines recommend a careful assessment of fracture risk in premenopausal patients receiving OFS and in postmenopausal patients treated with AIs [99–101]. Baseline evaluation of BMD using dual-energy X-ray absorptiometry (DXA) scan and consideration of additional risk factors can help identify patients at increased risk for fractures [100]. Additionally, patients receiving adjuvant ET should be advised to adopt a bone-healthy lifestyle, which includes quitting smoking, limiting alcohol consumption, engaging in physical activity, consuming a calcium-enriched diet, and considering vitamin D supplementation (1000–2000 IU daily) [89,102]. Although there may be slight variations among international guidelines, in eBC patients receiving adjuvant ET with AIs and/or OFS, the initiation of antiresorptive therapy should be considered under certain conditions. These include a BMD T-score below −2, an annual BMD reduction exceeding 5%, or the presence of at least two risk factors such as age over 65 years, T- score below −1.5, a history of smoking, a BMI below 24, a family history of hip fracture, a personal history of fragility fracture before age 50, or the use of glucocorticoids for more than six months [100,102,103]. Antiresorptive therapies currently available for the management of bone health in BC patients include bisphosphonates (analogues of pyrophosphates that accumulate at sites of bone remodeling) and denosumab (monoclonal antibody that binds to the RANK receptor involved in osteoclasts activation) [102,104,105]. Notably, apart from their osteoprotective effects, antiresorptive agents may also have an impact on the metastatic process by modifying the bone microenvironment and exert a benefit upon bone recurrence and BC-related mortality [102,105–110].

Alopecia

The occurrence of alopecia is reported in up to 9% of BC patients receiving Tam and 2.5% of patients receiving AIs. Specifically, hair thinning in the upper part of the scalp, known as “androgenetic” alopecia, is observed [111–113]. Typically, this type of alopecia is of low grade and tends to occur within the first year of treatment [113]. Despite being frequently underreported, alopecia can deeply impact patients’ body perception and QoL and it is estimated that up to 8% of patients receiving an endocrine agent, discontinue treatment early due to the occurrence of alopecia [111]. Additionally, nearly 20% of patients receiving ET describes alopecia as the adverse event with the greatest psychological impact [111].

Minoxidil, primarily used as an anti-hypertensive agent in cases resistant to three lines of therapy, has been associated with the adverse effect of hypertrichosis [114,115].

Application of topical minoxidil 5% on a daily basis has demonstrated activity in improving the severity of alopecia in approximately 80% of patients receiving ET [113]. Currently, only the topical formulation of the drug is approved by both FDA and EMA for the treatment of androgenetic alopecia. However, a recent case report has shown the effectiveness of oral minoxidil in managing AI-related alopecia that did not respond to the topical formulation [116].

In cases where the pharmacological approach fails or is not preferred by the patient, the use of wigs or tattoos can be considered as alternative option [117].

Fatigue

Fatigue is a common complaint among patients receiving AIs, with more than 80% referring it as moderate-to-severe and with a significant impact on QoL [118]. Despite its high prevalence, there is limited data available on effective pharmacological and non-pharmacological interventions for its management.

Methylphenidate, a psychostimulant typically used for of attention deficit hyperactive disorder, has been studied for its potential in managing fatigue in cancer patients, but a RCT in BC patients receiving adjuvant CT found no improvement in fatigue or overall QoL with methylphenidate. Also, to date, there is no evidence regarding its use in BC patients receiving ET [119,120].

Fatigue is known to be associated with a sedentary lifestyle and higher BMI. Therefore, incorporating physical activity and making dietary changes can reduce the intensity of fatigue associated with ET and improve other related symptoms such as insomnia or anxiety [121].

Non-pharmacological interventions, such as CBT, are recommended for fatigue management, especially when combined with complementary or alternative medicine approaches like yoga or acupuncture that can provide additional support and contribute to improving the overall well-being of patients [119,122].

Insomnia

More than half of BC patients receiving ET experience sleep disturbances, which can have a detrimental impact on their daily activities and lead to mood disturbances, impaired concentration, and attention difficulties [123,124]. Insomnia can be attributed to various factors, including the psychological distress associated with the diagnosis and the side effects encountered during treatment [125]. Additionally, menopausal symptoms, particularly VMS, often contribute to sleep disturbances in patients receiving ET [126]. Pharmacological interventions, such as benzodiazepines (BZD), are commonly prescribed for patients who report anxiety and sleep disturbances, with lorazepam being the most frequently used [127]. However, the primary approach to managing insomnia is typically non-pharmacological. Practicing good sleep hygiene habits (sleeping in a dark environment and engaging in stress-reducing activities like reading or listening to soothing sounds) has proven to be effective against sleep disturbances [119]. A recent review assessing sleep outcomes in BC patients found that CBT, employing both psychological techniques focused on relaxation and practical strategies of sleep hygiene, effectively improved sleep duration and quality, with long-lasting effects [124]. Mindfulness-based stress reduction programs combining meditations session with yoga, offer another valuable strategy to enhance sleep quality [128].

Engaging in physical activity has also a positive effect on sleep deprivation. In a small trial involving BC patients on ET, regular physical exercise significantly improved the frequency and severity of sleep disturbances [129]. Furthermore, a larger study involving cancer patients with sleep disturbances, a significant proportion (75%) of whom had BC, reported that yoga substantially improved sleep quality and daytime functioning [130].

Acupuncture is an additional option that has demonstrated efficacy in reducing nocturnal VMS and associated sleep disturbances [131].

*Psychosomatic **symptoms***

Psychosomatic symptoms, such as generalized pain, cognitive dysfunctions, and mood disorders, are reported by more than one third of BC patients undergoing ET [132].

Depression and anxiety, which are common psychosomatic manifestations, can be managed pharmacologically using BZD or SSRIs. However, it is important to note that the use of SSRIs may be limited due potential interactions with Tam [133].

A systematic review and *meta*-analysis involving over 800 BCE patients examined the effects of acupuncture physical activity, and other interventions on psychosomatic symptoms. The findings revealed that acupuncture showed improvement in generalized pain, while no significant beneficial effects were observed for acupuncture or physical activity in relation to other symptoms [134].

*Ocular **toxicity***

Approximately 30% of BC patients undergoing ET experience ocular toxicity. The use of AIs can lead to dry eye syndrome due to the absence of estrogens' protective effect on the ocular surface [135]. Tam has also been associated with various forms of ocular toxicity, primarily affecting the retina [135].

Androgens have been investigated in different formulations (eye drops, transdermal patches, or oral tablets) for managing dry eye syndrome. Androgen-based eye drops have demonstrated the ability to improve dry eye symptoms in up to 30% of patients after six months of therapy, while transdermal patches applied to the eyelids have shown even greater efficacy, improving symptoms in approximately 50% of affected individuals [136]. A systematic review has confirmed the effectiveness of androgen-based eye drops in alleviating ocular symptoms, with mild adverse events (such as mild acne) and therefore it should be considered the preferred mode of administration [136].

Conversely, the use of exogenous estrogens is not recommended as they have been shown to reduce lipid production from the meibomian glands [136].

Conclusions

Endocrine therapy, individualized based on menopausal status and risk of disease recurrence, is the cornerstone of adjuvant treatment for hormone receptor positive early breast cancer.

Despite its proven efficacy, endocrine therapy is associated with adverse events, resulting from the estrogen deprivation caused by these agents.

Commonly reported endocrine-related adverse events in breast cancer patients include vasomotor symptoms, musculoskeletal disorders and genitourinary syndrome of menopause, fatigue, psychological disorders, ocular toxicity, dysmetabolic effects, and loss of bone density. It is important to note that the adjuvant treatment landscape is rapidly expanding, with the introduction of biological agents such as CDK4/6 inhibitors and PARP inhibitors in combination with conventional endocrine therapy, bringing a new set of potential adverse events that need to be considered.

Although being often underreported and underestimated, these toxicities have a significant impact on patients' physical, psychosocial and emotional well-being and can affect treatment adherence and survival outcomes.

Therefore, proactive management of symptoms plays a central role in this context, and a multidisciplinary approach that combines various pharmacological (hormonal and non-hormonal) and non-pharmacological strategies (such as cognitive-behavioral therapy and lifestyle modifications) is crucial for effectively managing endocrine-related adverse events.

CRediT authorship contribution statement

Linda Cucciniello: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Giovanna Garufi:** Conceptualization, Formal analysis, Writing – original draft. **Rossana Di Rienzo:** Conceptualization, Formal analysis, Writing – original draft. **Claudia Martinelli:** Conceptualization, Formal analysis, Writing – original draft. **Giuliana Pavone:** Conceptualization, Formal analysis, Writing – original draft. **Mario Giuliano:** Conceptualization, Formal analysis, Writing – review & editing. **Grazia Arpino:** Conceptualization, Formal analysis, Writing – review & editing. **Filippo Montemurro:**

Conceptualization, Formal analysis, Writing – review & editing. **Lucia Del Mastro:** Conceptualization, Formal analysis, Writing – review & editing. **Michelino De Laurentiis:** Conceptualization, Formal analysis, Writing – review & editing. **Fabio Puglisi:** Conceptualization, Formal analysis, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.G. has served on the advisory boards for AstraZeneca, Daichii Sankyo, Exact Sciences, Lilly, MSD, Novartis, Pfizer, Roche, Seagen; has received travel grants from Roche, Celgene, Pfizer and research funding (to the institution) from Novartis and AstraZeneca. G.A. has received honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Roche, Pfizer, Lilly, AstraZeneca, Novartis and Gilead; has received travel grants from Roche, Lilly, AstraZeneca and Gilead; has served on the advisory boards for Roche, Novartis, Lilly, Pfizer, MSD, Dompè, Pierre Fabre, Eisai, Sophos, Epionpharma, Gilead, Seagen, Astra Zeneca and Exact Science.

F.M. has received fees for consultant/advisory role for Roche, AstraZeneca, Seagen, Novartis, Daichii Sankyo, MSD and Pierre Fabre; has received fees as speaker from AstraZeneca, Daichii Sankyo, MSD, Novartis, Pfizer and Eli Lilly; from May 15th 2023, he's employed at F Hoffmann La Roche, Basel SW. L.D.M. has received personal fees from Eli Lilly, Novartis, Roche, MSD, Pfizer, Exact Sciences, Pierre Fabre, Daiichi Sankyo, AstraZeneca, Seagen, Eisai, Ipsen and Gilead. M.D.L. reports personal fees from Pfizer, Novartis, Roche, AstraZeneca, Eli Lilly, MSD, Daiichi-Sankyo, GSK, Sanofi, Celtrion, Organon and Seagen. F.P. has received honoraria for speakers' bureaus, consultancy, advisory board from Amgen, Exact Sciences, Pierre-Fabre, Gilead, Pfizer, Celgene, GSK, Daiichi Sankyo, Ipsen, Seagen, Takeda, Eli Lilly, MSD, Novartis, AstraZeneca, Roche, Eisai, Viatris; research funding from AstraZeneca, Roche, Eisai. The remaining authors declare no competing interests.

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