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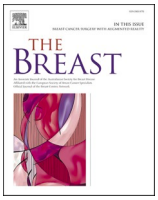

Managing sexual health challenges in breast cancer survivors: A comprehensive review

Linda Cucciniello [a,b], Federica Miglietta [c,d], Valentina Guarneri [c,d], Fabio Puglisi [a,b,*]

[a] Department of Medicine, University of Udine, Udine, Italy
[b] Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy
[c] Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy
[d] Istituto Oncologico Veneto - IOV IRCCS, Padova, Italy

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ABSTRACT

The significant advancements in breast cancer management have led to an increase in the prevalence of breast cancer survivors. Despite their efficacy, these treatments can cause a variable range of side effects, significantly deteriorating the patients' quality of life.

Sexual dysfunction, and in particular the genitourinary syndrome of menopause, represent one of the major causes of quality-of-life impairment among breast cancer patients, potentially affecting treatment adherence and compliance. If in the general population, hypoestrogenism-related symptoms are typically managed through systemic or topical estrogen administration, this approach is contraindicated in breast cancer patients for the potential increased risk of disease recurrence, urging the investigation of alternative measures.

The aim of this review is to summarize the most up-to-date pharmacological and non-pharmacological interventions, as well as supportive measures, available for the management of sexual dysfunctions in breast cancer patients and survivors.

1. Introduction

Breast cancer (BC) stands as the most frequently diagnosed solid tumor and the leading cause of cancer-related death among women worldwide. In the last years, we have witnessed significant improvements in BC management, mostly driven by improved early detection capabilities and the expansion and effectiveness of treatments. As a direct consequence, the prevalence of BC survivors has dramatically increased over the past years, with nearly 8 million women globally living at least 5 years after BC diagnosis, accounting for approximately 40 % of all cancer survivors. This number is anticipated to rise further [1].

Within this framework, although in the last years the preservation of quality of life in BC survivors has gained deeper interest, it still represents a substantially neglected and under-emphasized issue. Indeed, BC patients and survivors face multifaceted challenges, and a prominent factor contributing to undermining their long-term well-being is represented by sexual health dysfunctions. These disorders encompass a wide range of physical symptoms, psychological consequences and social implications strictly related to both BC diagnosis and the treatments associated with it, including surgery, radiotherapy, and systemic treatments.

The complexity of this matter is further exacerbated by a substantial risk of under-reporting and limited discussion, stemming from mutual reluctance on the part of both patients and doctors, thus unavoidably and unacceptably leading to undertreatment.

As visually depicted in Fig. 1, besides from patient-specific characteristics affecting to varying degree the subsequent probability of facing sexual health problems, the main mechanisms contributing to sexual dysfunction associated with BC treatments and diagnosis encompass emotional distress (such as anxiety and depression, potentially leading to restriction of sexual desire and self-esteem), body image concerns and alterations (breast and axilla surgery/radiotherapy, alopecia or partial hair loss, loss of nipple/breast sensation, treatment-related weight gain) and early/premature menopause with subsequent onset of genitourinary syndrome of menopause (GSM).

Sexual health symptoms are observed in a not negligible proportion (up to 55 %) of both pre-menopausal and post-menopausal BC patients

* Corresponding author.
E-mail addresses: linda.cucciniello@cro.it (L. Cucciniello), federica.miglietta@iov.veneto.it (F. Miglietta), valentina.guarneri@ioveneto.it (V. Guarneri), fabio.puglisi@cro.it (F. Puglisi).

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treated with endocrine agents [2]. All endocrine agents employed in the management of hormone receptor (HR)-positive BC can induce sexual health dysfunctions, with variable magnitude of severity.

With respect to the pre-menopausal setting, in the SOFT and TEXT trials, sexual health dysfunctions (mostly vaginal dryness and dyspareunia) were reported by variable percentages of patients (42–54 % and 24–32 % respectively) across the three treatment groups [tamoxifen (Tam) only versus Tam plus ovarian function suppression (OFS) versus exemestane + OFS], with the highest incidence observed among patients receiving exemestane + OFS [3].

Post-menopausal patients treated with Tam, experienced a higher frequency of gynecological adverse events with respect to those receiving anastrozole in the ATAC trial, especially vaginal bleeding and vaginal discharge (reported by 10.2 % versus 5.4 % and 13.2 % versus 3.5 % of patients, respectively) [4]. Likewise, in the IES trial (that randomized patients with early HR-positive BC to receive 5 years of adjuvant ET with Tam or switch from Tam to exemestane after the initial 2–3 years of treatment), a higher incidence of sexual health dysfunction and vaginal bleeding was reported among patients who continued treatment with Tam, with respect to those that switched to exemestane (9.0 % versus 5.8 % and 5.5 % versus 4.0 % of patients, respectively) [5].

"Sexual health dysfunction" is an expression that encompasses a broad range of hypoestrogenism-related symptoms globally resulting from the atrophy affecting the vulvovaginal and bladder-urethral areas, and it can exert a substantial impact on quality of life and possibly affect treatment adherence and early discontinuation [2]. It is currently estimated that, in up to 20 % of cases, adjuvant endocrine treatment (ET) is discontinued prematurely due to the insurgence of gynecological adverse events [6]. Thereby, international guidelines recommend that BC patients engage in regular gynecological follow up visits, aiming to an early identification and multimodal treatment of sexual health symptoms [7].

In the present narrative review, we comprehensively discuss the most up-to-date interventions (summarized in Fig. 2 and Table 1) and supportive measures that can be offered to patients and survivors suffering from sexual health impairments related to BC diagnosis and treatments, with a specific focus on the management of GSM.

Search strategy and selection criteria

References for this Review were mostly identified through searches of PubMed employing several search terms, including: "breast cancer", "vaginal atrophy", "genitourinary syndrome of menopause", "hypoestrogenism", "systemic estrogens", "topical estrogens", "vaginal laser", "androgens", "tibolone", "vitamin D and vitamin E vaginal suppositories", "vaginal moisturizers", "vaginal lubricants", "vaginal lidocaine", "vaginal oxygen and hyaluronic acid", "pelvic floor muscle therapy", "lifestyle", "psychological interventions" from inception until December 2023. All but one of the reviewed articles and reviews were published in English. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Local non-hormonal treatment options

Non-hormonal agents should be preferred for the management of GSM in BC patients, including vitamin D and vitamin E vaginal suppositories, vaginal moisturizers and lubricants, vaginal lidocaine, and intravaginal laser therapy.

Among these options, due to their accessibility and cost-effectiveness, vaginal lubricants and moisturizers represent the preferred initial therapeutic choice for addressing GSM in BC patients, whether they have completed adjuvant treatments or not.

Vaginal moisturizers are effective in controlling vaginal symptoms only if employed on a regular basis, independently from the frequency of sexual activity, with the aim to sustain vaginal integrity and elasticity. Specifically in early BC patients with GSM, a phase III randomized clinical trial demonstrated that treatment with a polycarbophil-based vaginal moisturizer is effective in treating vaginal dryness and dyspareunia. However, it should be noted that the observed benefit was not significantly superior to that reported when using a placebo product [8].

Instead, vaginal lubricants should be employed in case of regular sexual activity, being particularly effective in reducing discomfort during intercourse [9]. Different forms are available, with water-based and silicone-based vaginal lubricants being the most commonly employed. A post hoc analysis of a clinical trial involving 39 post-menopausal BC patients referring discomfort during sexual intercourse revealed a slight benefit (*p-value* 0.02) in favor of the use of silicone-based lubricants over water-based products. However, despite the treatment, most patients in

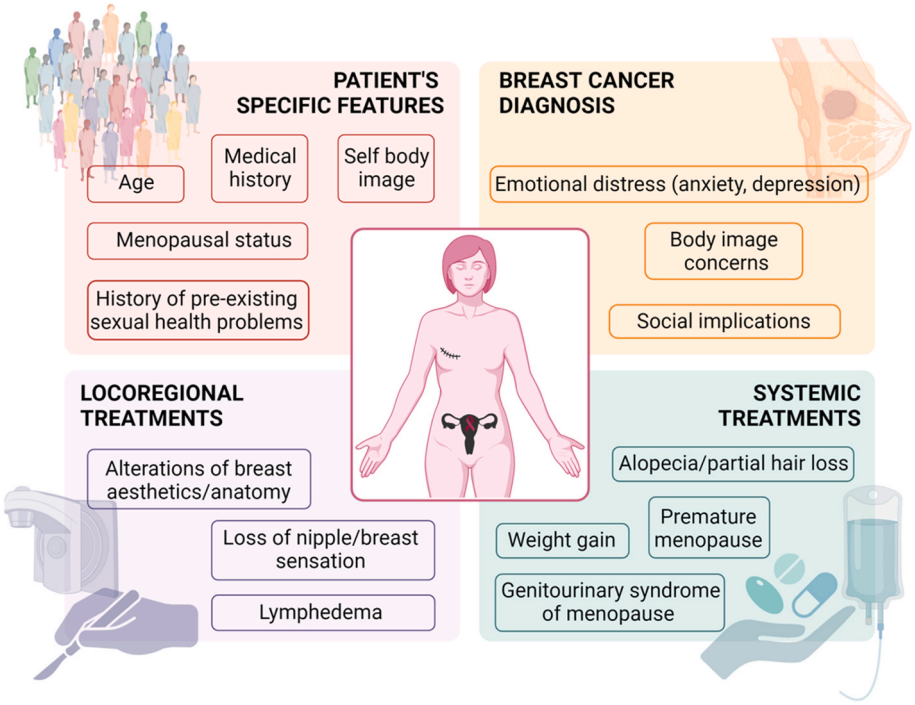

Fig. 1. Key factors influencing sexual health dysfunction in breast cancer patients.

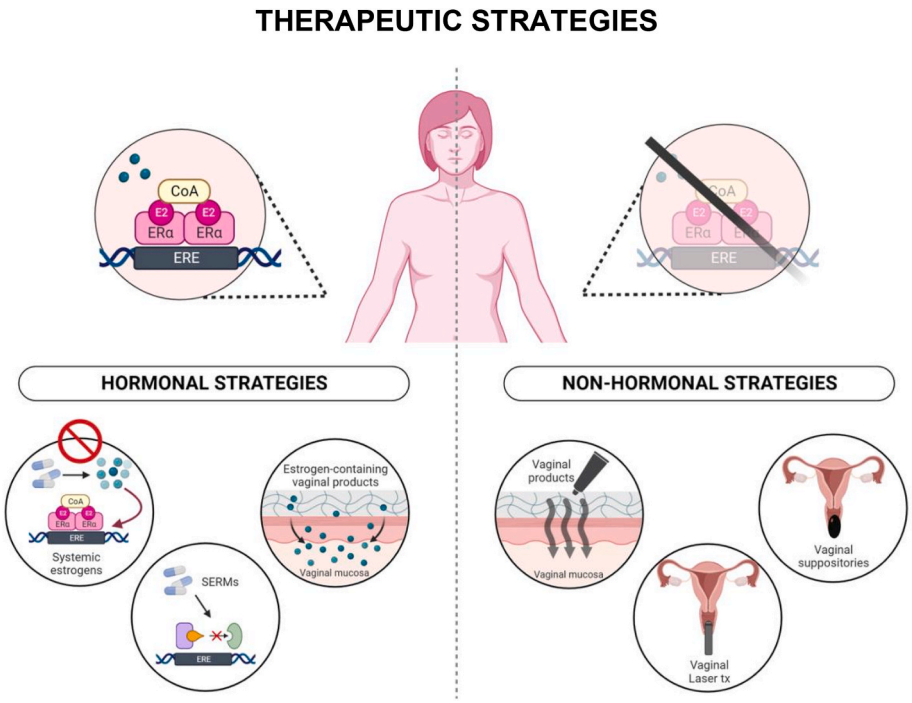

Fig. 2. Available treatment options for the management of genitourinary syndrome of menopause.

both treatment arms continued to experience distress [10]. In addition to moisturizers and lubricants, the use of vaginal dilators is also recommended as they have shown efficacy in enhancing vaginal wall elasticity and reducing discomfort during sexual intercourse in a clinical trial involving patients with gynecological cancers [11].

Vaginal pH-balanced gels may represent an alternative to lubricants and moisturizers. In a randomized clinical trial, 86 post-menopausal early BC patients experiencing vaginal symptoms, were randomized to receive either a pH-balanced gel or placebo. The treatment with the vaginal gel demonstrated significant benefits in terms of reducing vaginal pH (*p-value* <0.001), improving the vaginal maturation index (VMI, *p-value* <0.001), and enhancing the vaginal health index (VHI, *p-value* 0.002) [12]. Both VMI and VHI can be employed as indicators of the severity of atrophic vaginitis. VMI, calculated through a cytological examination of vaginal smears, depends upon the percentage of superficial, intermediate and parabasal cells. In detail, a higher percentage of parabasal cells, which represent the most immature vaginal epithelial cells, as well as a lower count of the more mature superficial cells, is indicative of lower concentrations of circulating estrogens and of a lower VMI, suggesting more severe GSM symptoms [13]. VHI, on the other hand, is determined according to the evaluation of vaginal wall elasticity, vaginal pH, integrity of the vaginal epithelial wall, fluid volume and moisture [12].

In a phase III randomized clinical trial involving 96 pre-menopausal patients with early BC undergoing adjuvant therapy with Tam and presenting GSM symptoms, participants were randomized to receive either vitamin D or vitamin E vaginal suppositories or a placebo. Patients receiving vitamin D or vitamin E vaginal suppositories showed significant improvements compared to those receiving a placebo, particularly in terms of the VMI (*p-value* <0.001) and in reduction of vaginal pH (*p-value* <0.001) [14].

For patients primarily experiencing dyspareunia among all GSM symptoms, a short-term treatment with vaginal lidocaine 4 % could serve as a potential option. In a randomized clinical trial, 46 BC patients presenting dyspareunia and discomfort during sexual activity were randomly assigned to apply either saline or 4 % lidocaine solution to the vulvar vestibule before vaginal penetration for 2 months. The application of 4 % lidocaine led to a significant improvement in dyspareunia (*p-value* 0.007) and alleviated sexual distress [15].

Vaginal laser therapy, utilizing both CO2 or erbium lasers, has shown the ability to restore the vaginal epithelium and stimulate the regeneration of connective tissue, thereby enhancing vaginal elasticity [16]. CO2 laser and photothermal Erbium:Yag laser are most commonly employed in the general, non-oncological population. Their efficacy and safety have been investigated in numerous clinical trials, which generally considered 3 session of laser treatment every 30–40 days, which led to significant improvements in vaginal atrophy symptoms [17].

Conversely, conflicting evidence exists regarding the efficacy of laser therapy in oncological patients. In the single-arm LAAVA study, 26 post-menopausal patients with early BC underwent vaginal CO2 laser treatment, resulting in a significant improvement in reported symptoms at 12 weeks from treatment beginning (dryness, itching, burning, dysuria, and dyspareunia) [18]. Conversely, the phase III LIGHT trial, which involved 84 post-menopausal patients with early BC receiving an aromatase inhibitor (AI), randomized participants to either 5 months of vaginal CO2 laser therapy or a sham laser treatment. This trial did not observe a significant improvement in GSM symptoms with the use of CO2 laser therapy at the 6-month follow-up visit from treatment start [19]. Despite approval by both the FDA and EMA for treating GSM in BC patients, it should be noted that vaginal laser therapy currently has limited evidence supporting its efficacy. Additionally, it is an expensive procedure, and given its relatively recent emergence, many gynecologists may still lack confidence in utilizing it.

A different form of treatment, which still relies upon the use of light to modulate vaginal tissue is photobiomodulation (PBM), which in the general population has shown to relieve GSM symptoms with similar results with respect to CO2 laser therapy [20]. Currently, there are no definitive data regarding the safety and efficacy of this approach specifically in BC patients.

A newly introduced therapeutic approach is represented by the combination of vaginal oxygen and hyaluronic acid. In a recently published study, 40 patients with early BC experiencing vaginal atrophy underwent treatment every 15 days using vaginal oxygen along with a 2 % solution of hyaluronic acid for a total of 5 cycles. The experimental treatment led to a significant improvement in dyspareunia (*p-value* <0.001), VHI (*p-value* <0.001), and female sexual function index (*p-*

Table 1
Pharmacological strategies for the management of genitourinary syndrome of menopause (GSM) in breast cancer (BC) patients.

Pharmacological Interventions	*non-hormonal strategies*	Agents	Current Regulatory Approval	References
		Vaginal moisturizers	FDA/EMA approved[d]	Bygdeman et al., 1996 Nachtigall et al., 1994 Loprinzi et al., 1997
		Vaginal lubricants	FDA/EMA approved[d]	Merlino et al., 2023 Hickey et al., 2016
		Vaginal pH-balanced gels	FDA/EMA approved[d]	Lee et al., 2011
		Vitamin D or E vaginal suppositories	FDA/EMA approved[d]	Keshavarzi et al., 2019
		Vaginal lidocaine 4 % solutions	FDA/EMA approved[d]	Goetsch et al., 2015
		Vaginal laser therapy	FDA/EMA approved[d]	Zerbinati et al., 2015 Pearson et al., 2019 Mension et al., 2023
		Vaginal oxygen and hyaluronic acid	Not FDA/EMA approved	Massarotti et al., 2023
	hormonal strategies	**Agents**	**Current Regulatory Approval**	**References**
		Systemic estrogens	Not FDA/EMA approved	Jacobson et al., 2021 Baber et al., 2016 Holmberg et al., 2004 Holmberg et al., 2008 von Schoultz et al., 2005
		Tibolone	Not FDA/EMA approved	Kenemans et al., 2009 Sismondi et al., 2011
		Ospemifene	FDA/EMA approved[ad]	Lilue et al., 2020 Archer et al., 2019 Eigeliene et al., 2016 DeGregorio et al., 2013
		Bazedoxifene	Not FDA/EMA approved	Bachmann et al., 2010 Kagan et al., 2010
		Estrogen-containing vaginal products	FDA/EMA approved[b]	Dew et al., 2003 Le Ray et al., 2012 Cold et al., 2022 Kendall et al., 2006 Wills et al., 2012 Ponzone et al., 2005 McVicker et al., 2023
		Promestriene	Not FDA/EMA approved	Del Pup et al., 2013 Espitia De La Hoz, 2017–2018 Almodovar et al., 2013
		Vaginal DHEA (prasterone)	FDA/EMA approved[cd]	Mension et al., 2022 Barton et al., 2018

Abbreviations: FDA = Food and Drug Agency; EMA = European Medical Agency; DHEA = dehydroepiandrosterone.

[a] Ospemifene can be prescribed for the management of GSM symptoms in patients with a history of breast cancer that have completed all active treatments.

[b] Estrogen-containing vaginal products mostly represent a second line option; FDA has approved only the use of estradiol-containing products for breast cancer patients, but has not approved the use of estriol-containing products; the approval granted by EMA does not include a specific focus on BC patients.

[c] Prasterone data sheet includes a warning for use in breast cancer patients.

[d] Level of evidence: 2.

value <0.001), thus representing a promising treatment for these patients [21].

Thereby, different local non-hormonal treatment options can be considered for the management of gynecological adverse events occurring in BC patients, including vaginal moisturizers and vaginal lubricants (in case of regular sexual activity), vaginal lidocaine 4 % (for patients reporting mostly dyspareunia), vaginal pH-balanced gels and vitamin D and E vaginal suppositories. Another potential option is represented by laser therapy. Finally, among emerging approaches, intravaginal oxygen combined with hyaluronic acid has shown promise in improving a broad range of gynecological symptoms in BC patients.

Systemic hormonal strategies

Considering that the symptoms of GSM derive from the abrupt decline in circulating estrogen levels induced by menopause, whether physiological or iatrogenic, the use of systemic or topic estrogens would appear as the most appropriate therapeutic strategy for mitigating symptom burden.

Despite demonstrating considerable efficacy in addressing GSM-related symptoms, systemic hormonal therapies (SyHT) are not recommended for use in BC patients according to international guidelines due to the increased risk of BC recurrence [22,23].

In the HABITS trial, 447 early BC patients experiencing menopause-related symptoms were randomly assigned to receive either hormone replacement therapy (HRT) or symptomatic non-hormonal therapy. Patients in the experimental arm had the option to receive sequential estrogen-progestagen therapy or continuous estrogen alone. After approximately 2 years of median follow-up, a significantly increased risk of BC recurrence was observed among patients exposed to HRT (26 versus 7 new BC events in the HRT and non-HRT arms, respectively; HR 3.5, 95 % CI 1.5–8.1), leading to the premature termination of the trial [24]. This finding was confirmed also at the 4-year follow up (39 versus 17 new BC events in HRT and non-HRT arms, respectively; HR 2.4, 95 % CI 1.3–4.2, *p-value* 0.003). Notably, the highest, although statistically non-significant, risk was reported for patients concurrently on Tam treatment (HR 4.7, 95 % CI 1.4–16.2, *p-value* 0.015) [25]. Contrasting results were initially reported by a parallel study, the Stockholm trial, in which 378 early BC patients experiencing menopausal symptoms were randomized to receive HRT (either estradiol plus medroxyprogesterone acetate or estradiol valerate) or non-HRT. After a median follow up of 4 years, no significant increase in the risk of BC recurrence was noted in the experimental arm (11 versus 13 new BC events in HRT and non-HRT arms, respectively; HR 0.82, 95 % CI 0.35–1.9).

Following the publication of the HABITS trial results, also the

Stockholm trial was prematurely halted. Subsequently, a joined analysis of both trials led the authors to ultimately conclude that HRT was associated with an increased risk of BC recurrence [26].

Apart from systemic estrogens, various other agents have been investigated in this setting, including selective estrogen receptor modulators (SERMs) like tibolone, ospemifene, and bazedoxifene.

Specifically, an increased risk of BC recurrence emerged among patients treated with tibolone, a steroid hormone with estrogenic, progestogenic, and androgenic properties. In the LIBERATE trial, 3148 patients with early BC reporting vasomotor symptoms, were randomized to receive either tibolone or a placebo.

After a median follow up of 3 years, although tibolone treatment proved to be effective in reducing the severity of vasomotor symptoms and vaginal dryness, as well as in improving bone density, it also revealed an increased risk of BC recurrence in the experimental arm (15.2 % versus 10.7 % of patients experiencing disease recurrence in tibolone and placebo arms, respectively; HR 1.4, 95 % CI 1.14–1.7, *p-value* 0.001), leading to the premature termination of the trial [27,28].

Ospemifene is a SERM that exerts estrogenic properties on the vaginal epithelium and bone tissue while displaying no effect on the endometrium. It also exhibits an anti-estrogenic action on the breast [29,30]. Treatment with ospemifene has demonstrated to improve all indicators of vaginal atrophy and the severity of vaginal dryness among post-menopausal patients [29,30]. However, safety concerns persist regarding its usage in BC patients. While preclinical and clinical trials have affirmed its anti-estrogenic effects on breast tissue and there is currently no evidence indicating an increased risk of BC recurrence, no trials have specifically investigated the efficacy and safety of ospemifene in BC patients [31,32]. Concerning this patient group, the consideration of ospemifene for GSM symptoms should occur after completing all definitive treatments, including adjuvant ET. Its approval for this indication is granted by the EMA, but not by the FDA. Presently, there are no ongoing trials evaluating the safety of ospemifene administration in BC patients undergoing adjuvant ET.

Two randomized clinical trials have assessed the efficacy of bazedoxifene in managing GSM among post-menopausal patients, demonstrating favorable outcomes when bazedoxifene is combined with equine estrogens [33,34]. However, owing to insufficient data concerning its effectiveness and safety in BC patients, bazedoxifene is not approved for use in this patient category, neither by the FDA nor by the EMA.

In summary, systemic estrogens are not recommended for managing sexual health dysfunctions in BC patients due to the increased risk of BC recurrence associated with their use in this category of patients. Regarding SERMs, treatment with tibolone has been linked to an increased risk of BC recurrence and is therefore not recommended in this setting. Conversely, ospemifene may be considered a safe and effective option for managing gynecological symptoms, provided it is used after all definitive treatments, including adjuvant ET, have been completed. Current data on the safety of bazedoxifene in this setting remain insufficient.

Local hormonal strategies

Several studies have investigated the role of local hormonal therapies for the management of GSM.

Low-dose vaginal estrogens have proven effective in alleviating GSM symptoms and can be administered in different formulations such as vaginal creams, tablets, or rings, and at different dosages. The most commonly used products are those containing estradiol and estriol. It is worth noting that estriol is not FDA-approved and can only be prescribed in the USA through an off-label request. Despite their effectiveness, many medical oncologists are hesitant to prescribe local hormonal therapy due to safety concerns for BC patients [35–37]. A cohort study evaluated 1472 women with early BC, among whom approximately 5 % reported GSM. These patients were treated with vaginal hormone therapy (VaHT) with estriol-containing creams or suppositories, or estradiol-containing tablets. The study found that this treatment did not lead to an increased risk of BC recurrence (HR 0.57; 95 % CI 0.20–1.58, p-value 0.28) [38]. The safety of VaHT was further assessed in a case-control study involving 13,749 early BC patients, 80 % of whom underwent Tam therapy and 20 % received an AI. Within this study, 2.1 % of the patients received VaHT through vaginal creams or tablets containing estrogens concurrently with tamoxifen or AIs, and this combination did not show an increased risk of BC recurrence (RR 0.78; 95 % CI 0.48–1.25) [39]. Similarly, a Danish observational study observed 8461 post-menopausal early BC patients who had received or had not received adjuvant ET (with Tam or AI). These patients were treated with SyHT or VaHT, or no therapy for GSM. Over time, the study evaluated the risk of BC recurrence in these groups. Notably, the use of systemic or local HRT was not associated with an increased risk of BC recurrence [(RR for BC recurrence with SyHT 1.05; 95 % CI 0.62–1.78), (RR with VaHT 1.39; 95 % CI 1.04–1.85)], or mortality [(RR for BC mortality with SyHT 0.94; 95 % CI 0.70–1.26), (RR with VaHT 0.78; 95 % CI 0.71–0.87)] [40]. However, a subgroup analysis within this study showed that for patients receiving an AI, treatment with SyHT or VaHT was associated with an increased risk of BC recurrence (RR 1.39; 95 % CI 1.04–1.85), albeit not in mortality, whilst no additional risk was observed in those patients receiving adjuvant treatment with Tam [40]. Notably, the use of VaHT has been shown to slightly increase serum estrogen levels in the first few weeks from treatment start [41]. AI function is to suppress the activity of the enzyme “aromatase”, which converts androgens in estrogens, and this is the primary mechanism of estrogen synthesis in menopause. Thereby, an even slight increase in serum estrogen levels, could explain the increased risk of BC recurrence reported by this trial. Conversely, Tam is a SERM and, thus, it competes with endogenous estrogens to bind to the estrogen receptor and its function is presumably not influenced by the small increase in serum estrogens that can occur with the use of VaHT [40].

As the primary aim of ET in early BC is to sustain suppressed systemic estrogen levels, concerns arise regarding the use of VaHT due to inconclusive available evidence on its potential to increase serum estrogen concentrations, especially in post-menopausal patients treated with an AI.

Indeed, two prospective clinical trials described increased serum estrogen levels in BC patients undergoing adjuvant ET when treated with VaHT. However, these findings were constrained by the limited cohorts sizes and relatively short follow-up periods [42,43]. Conversely, a comprehensive review that synthesized the evidence from various clinical trials indicated that the use of products containing either 25 μg of estradiol twice weekly or 0.5 mg of estriol twice weekly did not seem to notably increase systemic estrogen levels [44]. More recently, a large cohort study has evaluated a total of 49,237 early BC patients, of which 5 % received VaHT and about 1 % received SyHT. In this study, the use of VaHT was not associated with an increased risk of BC-associated mortality (HR 0.57; 95 % CI 0-34-0.96), irrespective of the duration of the exposure or the dosage of estrogens contained in the preparations [45]. Thereby, the consideration of employing low-dose vaginal estrogens to alleviate GSM in early BC patients could be contemplated, particularly given their proven clinical benefits after unsuccessful non-hormonal strategies. However, this decision warrants thorough discussion with the patient, acknowledging the current lack of definitive data regarding its safety.

Promestriene, a synthetic estrogen, has shown efficacy in treating vaginal atrophy in post-menopausal patients without causing systemic estrogenic effects, a finding that has been confirmed with the use of mass spectrometry [46]. Its efficacy and safety have also been investigated in BC patients. For example, in a randomized clinical trial conducted in Colombia, 92 post-menopausal patients with HER2-positive early BC, having completed all definitive therapies (including adjuvant ET for 46 % of the patients) and reporting symptoms of GSM, were randomly assigned to receive either vaginal promestriene or a placebo. This trial revealed that promestriene treatment significantly reduced the dyspareunia severity and enhanced vaginal lubrication without increasing

systemic estradiol levels compared to the placebo [47]. Additionally, in patients with luminal-like early BC, vaginal promestriene exhibited minimal systemic estrogenic effects [46]. However, preclinical data have indicated that promestriene exposure could induce the proliferation of breast cancer cells expressing hormone receptors, especially under conditions of estrogen deprivation. Hence, caution is advised when considering its use for managing GSM in patients undergoing treatment with an AI [48].

Given the expression of androgen receptors in the vaginal mucosa, the application of vaginal testosterone has been evaluated in this setting. Specifically, two randomized clinical trials enrolled early BC patients undergoing treatment with AIs who reported symptoms of vaginal atrophy. These patients were treated with testosterone-containing vaginal creams or were left untreated. The use of these products led to a significant improvement of reported symptoms without a significant increase in systemic estrogen levels, which could be attributable to the inhibition of testosterone conversion into estrogens by the activity of AI [49,50]. Thereby, testosterone-containing creams have shown to exert a beneficial effect over GSM in BC patients. Notably, there is growing evidence concerning the role of circulating androgens and androgen receptor signaling in BC growth and proliferation, both in hormone receptor-positive and hormone receptor-negative disease [51]. Thereby, the use of androgen-containing products for the management of GSM should be considered with caution. However, it is essential to note that their use is currently not authorized by either the FDA or EMA.

Dehydroepiandrosterone (DHEA) is a steroid hormone that can convert into both testosterone and estradiol, exhibiting efficacy in alleviating the symptoms of GSM. However, a study utilizing mass spectrometry revealed a slight increase in systemic estradiol levels upon the use of vaginal DHEA [36,52]. In the VIBRA study, 10 early BC patients undergoing treatment with AI and experiencing GSM were treated with vaginal ovules containing DHEA. After a 6-month follow-up, significant symptom improvement was reported, while maintaining low systemic estradiol levels [53]. In a randomized clinical trial involving 464 post-menopausal patients with BC or gynecological cancers experiencing GSM symptoms, participants were randomized to receive DHEA 3.25 mg or 6.5 mg per day versus a vaginal moisturizer for 12 weeks. All patients observed an improvement in vaginal symptoms regardless of the DHEA dose; however, those receiving 6.5 mg per day showed an increase in systemic estradiol levels [54]. Presently, vaginal products containing DHEA (mainly prasterone) stand as the sole androgen-based vaginal treatments approved by the FDA and EMA for managing GSM. Nonetheless, their data sheets include a cautionary warning regarding use in BC patients.

To conclude, in case of failure of local non-hormonal treatment options, VaHT could be considered, following an exhaustive discussion with the patient regarding both the efficacy and safety of these agents. Notably, there is currently no definitive evidence on the risk related to an increase in serum estrogen concentrations, especially in post-menopausal patients treated with an AI. Among other available options, promestriene can significantly improve gynecological symptoms in BC patients, although it should be used with caution in patients treated with AI. Finally, vaginal androgen-based products could be considered, although their use should be evaluated carefully in BC patients.

Non-pharmacological interventions

Lifestyle modifications play a crucial role in managing sexual health dysfunctions. These include adopting a healthy diet, losing weight, and engaging in regular physical activity, possibly under the guidance of nutritionists and personal trainers [36]. Additionally, smoking cessation is recommended, as smoking has been associated with a higher risk of atrophic vaginal changes [55].

Moreover, patients are encouraged to maintain regular sexual activity, as this can improve blood flow to the genital area and vaginal pH, helping to keep the tissue healthy and elastic [56].

Furthermore, it is important to acknowledge that the term GSM encompasses different symptoms that extend beyond mere anatomical aspects, affecting the emotional well-being of patients. In fact, cancer patients frequently experience loss of libido, body image dysperception, and communication issues with their partners. This aspect is frequently underreported during follow up visits, potentially attributable to the limited time available, concerns about patients' discomfort and difficulty in indicating appropriate treatment strategies [57]. In order to overcome these barriers, it is highly recommended for health care practitioners to be appropriately trained on the topic and improve their communication skills and encourage their patients in expressing eventual sexual health concerns [57]. Various forms of personalized face-to-face therapy have proven to be effective in managing these symptoms, with higher impact interventions being mostly couple-oriented [58,59]. Group interventions can also be considered. For example, in a small study that enrolled 20 BC patients, a 4-h long group intervention focused upon sexual health rehabilitation, body awareness exercises, and mindfulness-based cognitive therapy skills, followed by a phone call delivered after the group session was associated with a significant improvement in sexual health and psychological distress [60].

Also cognitive behavioral therapy sessions, whether individual or with partners involved, have been investigated in this setting. In particular, evidence from a multicenter, randomized clinical trial indicates that cognitive behavioral therapy (with the guide of a sexologist) significantly alleviates different GSM symptoms, including but not limited to sexual desire, distress, body image concerns, vaginal lubrication, and discomfort during sexual intercourse [61]. Moreover, a phone-counseling program encompassing 16 phone calls 45-min long, delivered by trained psycho-oncologists, was found to positively impact upon sexual health dysfunctions and overall personal growth [62]. A Korean study, instead, investigated the efficacy of a sexual life reframing program on different forms of sexual health dysfunctions reported by BC patients [63]. The program lasted a total of 6 weeks and encompassed 2-h long sessions and it was ultimately associated with an improvement in sexual satisfaction among involved patients [63].

Finally, BC patients commonly exhibit reduced pelvic floor muscle strength and impaired relaxation capacity, significantly impacting their sexual functions [64]. Thereby, interventions like pelvic floor muscle training and relaxation techniques may aid in improving pelvic floor musculature function and alleviating GSM symptoms. However, to date, no trial has specifically assessed the role of pelvic floor muscle therapy in BC patients experiencing GSM.

Conclusions and Future Perspectives

Sexual health issues represent one of the major causes of quality of life impairment among BC survivors, potentially affecting treatment adherence and compliance. In the general population, hypoestrogenism-related symptoms are typically addressed through systemic estrogen administration. However, this approach is contraindicated in BC patients due to concerns about increased risk of disease recurrence, thus complicating the management of sexual health problems in this specific patient group, urging the investigation of alternative pharmacological and non-pharmacological measures.

Despite recent attention toward addressing BC-related sexual health problems, optimal management remains elusive. Future research agenda should prioritize a multi-disciplinary and multi-stakeholder approach, tailoring personalized strategies. Central to this effort is the imperative of heightened education and awareness among both patients and practitioners. In this context, structured ongoing initiatives are recognizing sexual health problems as integral to survivorship care, demanding priority attention. Indeed, a recent consensus by the European Society for Medical Oncology (ESMO) endorsed the implementation of evidence-based frameworks in survivorship care and research, acknowledging persistent unmet needs in cancer survivors, particularly among BC patients [65].

Current barriers to delivering the highest-quality survivorship care, education, and research include the absence of robust longitudinal

databases focused on core survivorship issues, challenges in discerning true cancer/treatment-associated late effects due to the lack of healthy controls groups, a paucity of international interventional studies, and limitations in evidence assessing the feasibility and impact of reconciling different care models. Therefore, future research in the realm of BC sexual health should proactively address these gaps, aiming for a holistic, patient-centered approach.

Conflicts of interest

L.C. declares no competing interests. F.M. reports personal fees from Roche, Novartis, Gilead, Seagen, Pfizer. V.G. reports personal fees for advisory board membership for AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Exact Sciences, Gilead, Merck Serono, MSD, Novartis, Pfizer, Olema Oncology, Pierre Fabre; personal fees as an invited speaker for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK, Novartis, Roche and Zentiva; personal fees for expert testimony for Eli Lilly. 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.

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CRediT authorship contribution statement

Linda Cucciniello: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Federica Miglietta:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Valentina Guarneri:** Writing – review & editing, Formal analysis, Conceptualization. **Fabio Puglisi:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

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