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MANAGEMENT OF SEXUAL AND REPRODUCTIVE PROBLEMS IN BREAST CANCER SURVIVORS

Iurii ARIAN[1,2], Dumitrita BIVOL[1], Daniela MACHIDON[1], Ion DUMBRAVEANU[1,2]

[1]Laboratory of Andrology, Functional Urology, and Sexual Medicine, Chisinau, Republic of Moldova
[2]*Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Corresponding author: Iurii Arian, e-mail: iurii.arian@usmf.md

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Keywords: *breast cancer survivors, reproductive health, sexual health, sexual disorders, sexual therapy.*

Introduction. *Breast cancer is the most common form of cancer in women and is a threat to female sexuality, considering the mammary glands' significance in sexuality, attractiveness, and sexual satisfaction. Female sexual disorders, which involve disturbances in sexual desire, attraction, arousal, orgasm, and genito-pelvic pain, are common among middle-aged breast cancer survivors (BCS).*

Material and methods. *A systematic and structured search of the specialty literature was conducted using PubMed, SCOPUS, EMBASE, and Web of Science databases with keywords such as breast cancer survivors", "sexual disorders", and "reproductive health" to find studies relevant to the targeted hypothesis. Works were selected according to the following criteria: full-text articles, publications in English, covering the period 2000-2023.*

Results. *Patients with sexual dysfunctions may benefit from a variety of treatment approaches, such as pharmaceutical, physical, and psychological ones. Studies show that local strategies, such as vaginal estrogens and DHEA, vaginal moisturizers, aqueous lidocaine, vaginal dilators, intravaginal laser, and radiofrequency, as well as psychotherapeutic strategies, such as cognitive-behavioral therapy and couple's therapy based on sexual health, improve sexual function.*

Conclusions. *Identifying and managing sexual dysfunction requires a higher level of awareness, interpersonal interaction, and education among physicians and other health care practitioners. To provide appropriate care and prevent the condition from getting more severe, a systematic assessment of sexual function in BCS patients may be helpful in early diagnosis of sexual disorders.*

Cuvinte-cheie: *supraviețuitoare, cancer mamar, sănătate reproductivă, sănătate sexuală, tulburări sexuale.*

MANAGEMENTUL PROBLEMELOR SEXUALE ȘI REPRODUCTIVE LA SUPRAVIEȚUITOARELE CANCERULUI MAMAR

Introducere. *Cancerul mamar este cea mai răspândită formă de cancer la femei și reprezintă o amenințare pentru sexualitatea feminină, deoarece marea majoritate a acestora consideră glandele mamare importante în sexualitate, atractivitate și satisfacție sexuală. Tulburările sexuale feminine, care implică perturbări ale dorinței sexuale, atracției, stimulării, orgasmului și durerea genito-pelvină, sunt frecvente la supraviețuitoarele cancerului mamar de vârstă mijlocie.*

Material și metode. *S-a efectuat o cercetare sistemică și structurată a literaturii de specialitate, utilizând bazele de date PubMed, SCOPUS, EMBASE și Web of Science cu cuvintele-cheie „supraviețuitori ai cancerului de sân", „tulburări sexuale" și „sănătate reproductivă" pentru a găsi studii relevante ipotezei vizate. Au fost selectare lucrări conform următoarelor criterii: articole integrale, publicații în limba engleză, perioada 2000-2023.*

Rezultate. *Pacientele cu disfuncții sexuale pot beneficia de o varietate de abordări terapeutice, cum ar fi cele farmaceutice, fizice și psihologice. Studiile arată că strategiile locale, precum estrogenii vaginali și DHEA, cremele hidratante vaginale, lidocaina apoasă, dilatatoarele vaginale, laserul intravaginal și radiofrecvența, precum și strategiile psihoterapeutice, cum ar fi terapia cognitiv- comportamentală și terapia de cuplu bazată pe sănătatea sexuală, îmbunătățesc funcția sexuală.*

Concluzii. *Identificarea și gestionarea disfuncției sexuale necesită un nivel mai înalt de conștiință, interacțiune interpersonală și educație în rândul medicilor și altor practicieni din domeniul sănătății. Pentru a oferi îngrijiri adecvate și pentru a preveni agravarea afecțiunii, o evaluare sistematică a funcției sexuale pentru supraviețuitoarele cancerului mamar poate fi utilă în diagnosticarea precoce a tulburărilor sexuale.*

INTRODUCTION

Out of all the cancers that affect women, breast cancer has the highest incidence rate. Based on statistical data, breast cancer has become a leading cause of death among female patients. Fortunately, more women are surviving their diagnoses, likely due to earlier detection and improved treatments. Reports indicate that women with breast cancer have a 5-year survival rate of 76-92% following systemic treatment (1). Consequently, more than three million women have been diagnosed with a history of breast cancer, representing the largest group of cancer survivors in the United States (41% of the total cancer survivor population) (2), with over 2.3 million female cancer survivors under the age of 60 (3). As such, managing the long-term health of survivors has become crucial. Sexual health is one aspect that often suffers after surviving breast cancer, due to anxiety, stress, or changes in body image following breast cancer therapy. Female sexual dysfunction can broadly be classified into three categories: genitopelvic pain or penetration difficulties, orgasmic disorder, and sexual desire or arousal disorder. According to the Diagnostic and Statistical Manual 5th Edition (DSM-5) (4), a woman is diagnosed with a sexual disorder if she experiences recurrent symptoms that last at least six months and cause significant distress. A study involving 83 women who had survived breast cancer for three years used the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale-Revised (FSDS-R) for assessment. According to the Malay Version of the Female Sexual Function Index-6, 73.4% (n=69) of the 94 female patients (aged 16–65 years) who were married, had a partner, had breast cancer, and had undergone breast surgery reported experiencing sexual dysfunction (5). The frequency of sexual issues remained significant 5 and 10 years after a cancer diagnosis. In another study, Ganz and colleagues found that nearly 760 women who had previously participated in a poll returned for a follow-up survey, with an average interval between survey points of 6.3 years. While physical and emotional functioning had returned to normal, sexual function remained impaired, evidenced by a decrease in sexual engagement with a partner (from 65% to 55%), persistent vaginal dryness, and urinary incontinence (6).

On the other hand, survivorship treatment often fails to adequately address sexual health issues, and few BCS receive sexual function education and information from cancer specialists (7). Moreover, individuals may feel hesitant or embarrassed to discuss sexual issues with healthcare providers (8). To effectively understand the problems and challenges faced by women and offer solutions, midwives and other healthcare professionals should assess, educate, and advocate for women's sexual health within an environment of trust, intimacy, and attentive communication (9, 10). To improve sexual health after breast cancer, various pharmaceutical and behavioral strategies have been explored. Notably, enhancements in sexual function have been observed in women who participate in cognitive-behavioral therapy (CBT), along with pharmaceutical and non-pharmaceutical remedies.

Psychoeducational programs, improved communication, counseling for women (both individually and in couples), group therapy, and couple therapy have all been shown to enhance well-being and promote a positive body image (9). Community midwives must have knowledge of and training in addressing the experiences of women diagnosed with breast cancer. Women are typically more inclined to express their concerns in environments where they feel relaxed.

In this review, *we aim to analyze* existing studies that explore the management of difficulties among individuals who have survived breast cancer. Our goal is to compile information that enhances understanding and awareness of health for both breast cancer survivors and their healthcare professionals.

MATERIAL AND METHODS

Full-text papers, English-language literature, narrative, and systematic review articles were the criteria used to specifically select bibliographic sources for conducting a systematic and structured search. Regarding publication timeframes, papers published between 2000 and 2023 were included. To find studies relevant to the targeted issue, we utilized databases such as PubMed, SCOPUS, EMBASE, and Web of Science.

After analyzing the bibliographic resources using the following keywords: "sexual disorders," "sexual therapy," "breast cancer survivors," "repro-

ductive health," and "sexual health," we located 160 items. Articles evaluating non-gynecological tumors and those examining men's sexuality were excluded. Ultimately, we selected 30 articles that we deemed appropriate for the proposed research topic.

To elucidate particular and complex topics, additional sources of knowledge were consulted in accordance with the established criteria. Excluded from the bibliography were similar studies, papers that were not fully accessible or aligned with the study's objectives, comments, letters, case reports, case series, and articles lacking sufficient data.

RESULTS

Impact of treatment on sexual health

As survival rates increase, addressing the long-term wellness issues of survivors becomes crucial. The multifactorial etiology of sexual dysfunctions in breast cancer survivors encompasses the deleterious effects of radiation, chemotherapy, endocrine therapy, and surgery on a woman's sexual health and function (fig. 1).

Surgery

Mastectomies or breast-conserving surgeries are currently the most prevalent surgical procedures for breast cancer. Studies have shown that a complete mastectomy impacts sexual function more than breast-conserving surgery (11). Women treated with mastectomy reported greater life disturbance and markedly worse ratings in the areas of body image, role, and sexuality. Even more concerning is that sexual functioning does not improve over time. The psychological effects of breast loss and surgical scars can be severe. Women's breasts are significant secondary sexual traits that influence their self-esteem, body image, sexual enjoyment, and stimulation (12).

Chemotherapy

Chemotherapy treatment can lead to ovarian failure and early menopause, resulting in symptoms such as decreased sexual desire, vaginal dryness, difficulty engaging in sexual activities, and other unpleasant side effects. Ultimately, these issues can reduce the frequency and intensity of orgasms (13). Furthermore, taxanes and anthracyclines may adversely affect general bodily functions, including libido, arousal, and perceptions of attractiveness. Intense fatigue, hair loss, gastrointestinal distress, and myelosuppression are common physical side effects of chemotherapy.

Radiation therapy (RT)

Reduced sexual function has been associated with locoregional complications caused by radiation therapy (RT), such as lymphedema, discomfort, and reduced flexibility in the arms and shoulders, as well as chronic breast pain (14 - 17). Additionally, radiation treatment can permanently alter the breast. Pores may become enlarged and more visible, and skin may darken slightly. The skin might become firmer and thicker than before treatment and may exhibit increased or decreased sensitivity. Some side effects may persist long after treatment. A recent study of over 600 patients who underwent implant breast reconstruction found that 219 had previously received RT. Those who underwent RT reported lower health-related quality of life and lower satisfaction compared to those who did not (15). Patients who received postoperative RT showed significant declines across all dimensions (satisfaction with breasts and outcomes, emotional well-being, sexual wellness, and physical wellness).

Endocrine therapy

Hormonal treatment is primarily used to limit tumor progression in individuals with hormone receptor-positive breast cancer. Endocrine therapy inhibits the growth of estrogen-dependent breast cancer cells by reducing estrogen levels in the body or blocking the interaction between estrogen and hormone receptors. This involves taking an aromatase inhibitor (AI) for five years or tamoxifen for five years, followed by an additional five years of either tamoxifen or an AI (18).

These medications have been linked to the development or exacerbation of menopausal symptoms. According to a survey by Morales et al. involving more than 180 women, both agents significantly increased the frequency and intensity of vaginal dryness, night sweats, and hot flashes. The use of aromatase inhibitors often results in vaginal dryness. Unlike hot flashes, vaginal symptoms generally worsen over time (19). Tamoxifen significantly reduced sexual attraction, while aromatase inhibitors (AIs) dramatically increased the risk of dyspareunia, indicating that both agents can negatively impact female sexual health, albeit in different ways. Furthermore, they found that toxicities were substantially more common among younger women.

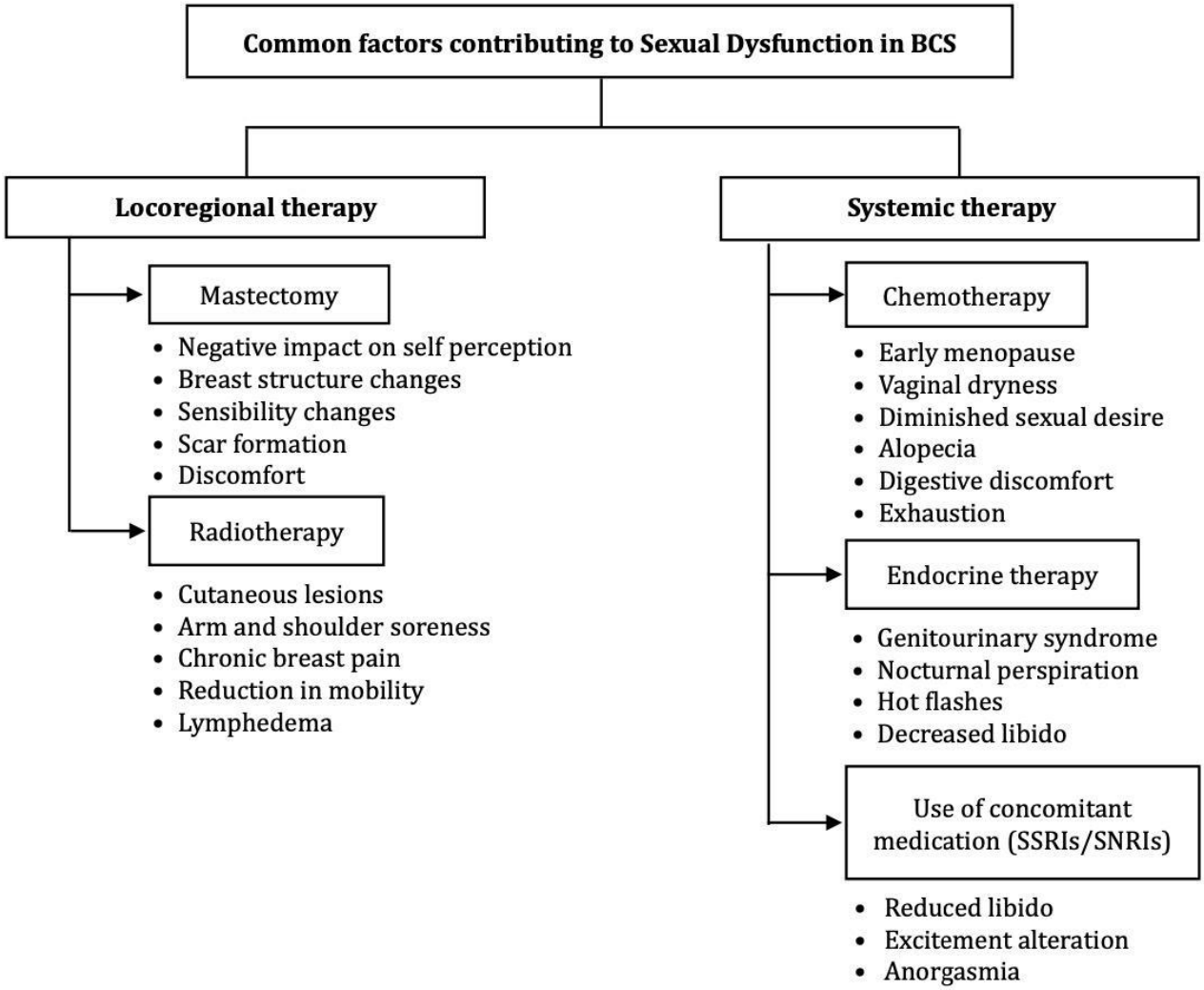

Figure 1. Common factors contributing to sexual dysfunction in BCS.

Management of sexual dysfunction

Patients should be informed about the potential effects of breast cancer treatments on their sexuality and any side effects. This topic should be discussed openly and candidly during visits, and patients should be offered solutions or further information if they need assistance. In some cases, having more treatment options could reduce the likelihood of female sexual dysfunctions (tab. 1).

Vaginal products interventions

The hemodynamic processes involved in the sexual response are significantly influenced by estrogens. Estrogen deficiency not only leads to the shrinkage of the labia majora and minora but also results in decreased clitoral tumescence and insufficient vaginal lubrication. Consequently, up to 50% of affected women experience dyspareunia, and a decline in clitoral sensitivity affects up to 20% of these women. Clinically significant vaginal atrophy can occur in postmenopausal patients when blood estradiol levels fall below 73 pmol/L. The most effective treatment for vaginal atrophy is the direct application of estrogen medicine (20), a commonly used routine therapeutic option. Numerous meta-analyses have shown that topical estrogen therapy can improve symptoms and signs of vaginal atrophy regardless of the mode of administration (21, 22). Estriol, a low-potency, short-acting estrogen, is irreversibly converted to either estradiol or estrone. It is widely recognized that estriol is safe for endometrial hyperplasia and effective for treating vaginal atrophy (23). Estrogen replacement therapy can be administered through oral pills, transdermal patches, vaginal rings, and transdermal gel. Oral estrogen is converted to estrone in the intestinal environment, which is then transformed to estradiol in the liver, reducing the estrogen level in the serum by about 30%. The serum level of estradi-

ol with the transdermal method is comparable to that of the oral route, as it bypasses the initial liver pass. Research indicates that the use of the transdermal form does not correlate with an increase in breast mammography density (24). Estriol can specifically increase blood flow and the regeneration of the vaginal epithelium, and while it may be less stimulating to the breast and endometrium, this medication is also used for symptoms of genital degeneration. An ultra-low dose of 0.005% estriol vaginal gel effectively treated the symptoms and signs of vulvovaginal atrophy. These outcomes, along with minimal fluctuations in hormone levels during treatment, support the use of an ultra-low dose of 0.005% estriol vaginal gel as a potential treatment for vulvovaginal atrophy in women receiving NSAIDs for breast cancer who require vaginal estrogen therapy. As a final metabolite with a low binding affinity for the estrogen receptor, estriol cannot be converted back into other estrogenic precursors. Additionally, estriol has a preference for binding to β (urogenital) estrogen receptors over α (breast) estrogen receptors, making it a hormone with lower potency and estrogenic potential compared to estradiol (25).

A controlled clinical study evaluated dehydroepiandrosterone (DHEA) as an adjunct hormonal therapy. It has been found that vaginal DHEA is a safe and effective treatment for menopausal women experiencing symptoms of vaginal atrophy. According to several preclinical studies, DHEA is believed to act on the nerves within the vaginal wall fibers, enhancing their sensitivity during sexual activity. This mechanism also explains why intravaginal application of DHEA does not lead to systemic changes in the levels of androgenic hormones or DHEA metabolites, such as testosterone and estradiol. Many of the potential side effects of DHEA can be avoided since it does not cause significant systemic hormonal changes. Furthermore, the local therapeutic effects against vaginal atrophy can be achieved through intravaginal DHEA administration without significant increases in serum estrogen levels, thus minimizing the risk of breast cancer.

Vaginal moisturiser

Vaginal moisturizers are particularly beneficial for individuals when applied vaginally. In a study involving 86 participants, a 12-week therapy using a pH-balanced gel for the vagina was compared to a placebo. Unlike the placebo, the vaginal gel significantly lowered vaginal pH and improved vaginal maturation. Additionally, the treatment reduced dyspareunia and vaginal dryness (26). A similar study on the efficacy of a vaginal moisturizer based on polycarbophils found that applying a polycarbophil-based vaginal moisturizer at least twice a week enhances vaginal dryness, pH, dyspareunia, frequency, and sexual satisfaction, according to clinical trial results.

Unlike lubricants, vaginal moisturizers such as Replens are absorbed by the skin rather than remaining on the surface. The primary purpose of moisturizers is to attract and retain moisture in the skin's tissue. Like lubricants, vaginal moisturizing products have dual functions: they can either increase or decrease desire. Initially, the use of a vaginal moisturizer can alleviate discomfort and itching in the short term. Secondly, regular application of a vaginal moisturizer maintains the softness and flexibility of vaginal tissue, reducing its susceptibility to damage such as tearing, thus helping to restore its integrity. A vaginal moisturizer can also alleviate symptoms of vaginal atrophy and the discomfort caused by vaginal dryness.

Aqueous lidocaine

For individuals experiencing discomfort during penetrative sexual activities, particularly if the pain is localized to the vulvar vestibule, aqueous lidocaine is one potential treatment option. In a randomized experiment involving 46 breast cancer survivors, applying lidocaine topically to the vestibule three minutes before planned penetrative activities, followed by the application of silicone lubricant, led to a reduction in dyspareunia. After open-label use, 90% of the participants reported a return to comfortable penetration (27).

Vaginal dilators

Vaginal dilators can be instrumental in overcoming pelvic floor muscle reflexes, aiding in the increase of vaginal flexibility. Medical professionals often recommend the use of vaginal dilators for this purpose. It is advised that women begin with the smallest, most comfortable size and gradually progress to larger sizes until they reach a level of satisfaction. Dilators function by gently stretching and widening vaginal tissue over time. This process enhances flexibility and can significantly reduce discomfort experienced during sexual activity.

Intravaginal laser and radiofrequency

To enhance the long-term wellness of women with breast cancer, safe and effective non-hormonal treatments are essential. Recently, non-pharmacological therapy alternatives for managing GSM have been suggested, including the use of intravaginal energy-based techniques such as radiofrequency and laser. The short-term data available indicate that both erbium lasers and CO_2 lasers are successful in treating the most prevalent symptoms of GSM. Their primary mechanism of action involves heat effects, which cause collagen fibers in the vaginal epithelial tissue to change shape.

A comprehensive analysis of trials compared the effectiveness of fractional CO_2 laser treatment with standard estrogen therapies such as conjugated estrogens, estriol, and promestriene. The results showed that both treatments were effective in alleviating signs and symptoms associated with genitourinary syndrome of menopause (GSM), as measured by the VAS, VHI, VMI, and FSFI scores (28).

In a randomized trial conducted by Gold et al., the efficacy of vaginal erbium laser treatment versus hyaluronic acid in women experiencing urogenital atrophy after breast cancer surgery (BCS) was examined. The study included 43 participants who reported symptoms such as dryness, dyspareunia, urgency/dysuria, or recurrent urinary tract infections. Participants were randomly assigned to receive either two sessions of vaginal erbium laser treatment spaced 30 days apart or daily hyaluronic acid vaginal suppositories for 10 days, followed by three times a week for a duration of 12 weeks. After a follow-up period of 12 weeks, both treatment groups showed improvements in the Vaginal Health Index (VHI) without any significant difference in efficacy between the erbium laser and hyaluronic acid treatments (29).

Cognitive behavioral therapy (CBT)

Enhancing sexual well-being in BCS has been achieved through various psychotherapy and educational programs, especially those targeting sexual dysfunction. Sexual counselors, family and marriage psychologists, sex psychologists, and other mental health professionals offer educational courses in cognitive behavioral therapy (CBT), psychological therapies, and other supportive services.

Table 1. The primary therapy for Sexual Dysfunction in BCS.

Local Strategies		Psychotherapeutic Strategies	
Type of treatment	**Outcome**	**Type of treatment**	**Outcome**
Vaginal Estrogen	Better vaginal histology and symptom relief	Cognitive behavioral therapy (CBT)	Rise in sexual activity, remission in urine manifestations
Vaginal DHEA	Increasing sensitivity during sexual intercourse and enhancing sexual pleasure	Couple therapy based on sexual health	Enhance sexual wellness
Vaginal moisturizers	Improvement of vaginal pH, reduction of dyspareunia, vaginal dryness and improvement of sexual pleasure and frequency		
Aqueous lidocaine	Decreased dyspareunia and improvement of pleasant penetration		
Vaginal dilators	Lower discomfort during sexual intercourse		
Intravaginal laser and radiofrequency	Improvement of Genitourinary syndrome, less burning sensations and itching		

In one study, 422 individuals were randomly selected to participate in either cognitive-behavioral therapy (CBT) alone or CBT combined with physical activity. CBT included six weekly group sessions focused on managing hot flashes and night sweats, as well as addressing issues related to appearance, sexuality, and mental health, alongside relaxation techniques. The physical ac-

tivity component aimed for 2.5 to 3 hours of weekly exercise over 12 weeks. Compared to the control group, patients in the CBT plus physical exercise group exhibited a noticeable increase in sexual activity. Conversely, patients in the CBT alone group experienced a significant and lasting improvement in their urinary symptoms (30). These findings suggest that CBT can be an effective treatment for breast cancer survivors facing sexual health issues.

DISCUSSIONS

Studies have strongly supported the regular use of vaginal moisturizers as an effective means to enhance sexual pleasure and frequency, alleviate dryness and dyspareunia, and improve vaginal pH (26). Additionally, vaginal hormonal products have shown to be more effective than moisturizers in enhancing sexual function (21, 22). It has been established that various counseling and educational techniques, especially those targeting sexual dysfunction, improve sexual health in BCS (30). Vaginal laser therapy presents an excellent option to repair tissues and prevent estrogen exposure, offering a solution to bridge the gap. The results provide short-term reassurance, indicating that erbium lasers and CO_2 lasers are equally effective in treating the most common symptoms of GSM (28). Furthermore, a study has found that in 90% of breast cancer survivors, painful penetration can be avoided, and severe dyspareunia may be relieved by the application of self-administered lidocaine compresses to the vestibule (27).

Despite the high prevalence of sexual dysfunction and its significant impact, there are no established treatment protocols for affected patients. Considering the complex nature of sexual dysfunction and its profound effects on various aspects of a patient's quality of life, a combination of pharmacological and psychological approaches might offer suitable therapeutic options.

CONCLUSIONS

1. Sexual dysfunction issues have become a clear challenge for patients in this community as more women continue to survive breast cancer diagnosis and treatment. It is becoming increasingly evident that addressing sexual issues is crucial to offering the best possible care to patients with breast cancer.
2. A multidisciplinary team, including oncologists, nurses, psychologists, psychiatrists, and sex therapists, should ideally address concerns related to sexual health. If medical professionals are not equipped to manage this issue, a referral to a sexologist or specialized physician is recommended. The principal areas for future research focus on specific therapeutic options for BCS.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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