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INTERVENTIONS FOR SEXUAL DYSFUNCTION IN WOMEN WITH BREAST CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To analyze the effectiveness of interventions performed in women with breast cancer for the improvement of sexual dysfunction. **Materials and Methods:** This was a systematic review of the literature following the PRISMA guidelines. Bibliographical searches were carried out in the Medline, LILACS, Ibecs, BDenf, Scopus, Web of Science and CINAHL databases. The following inclusion criteria were considered: primary study with an experimental and randomized design; recruitment of women with breast cancer; addressing the effectiveness of an intervention to improve sexual dysfunction; with a Jadad's scale score equal to or greater than three; published in English; and with the full text available online. Nine articles were included in the final review **Results:** The included studies focused on interventions with educational technologies (peer counseling program, cognitive behavioral therapy, *Trendils* website) as well as with pharmacological methods (bupropion, water- and silicone-based lubricants, pH-balanced vaginal gel, intravaginal testosterone cream and estradiol-releasing ring). **Conclusion:** There is evidence to support the use of educational technologies, such as cognitive-behavioral therapy and self-help groups, as effective strategies for improving sexual dysfunction in breast cancer survivors and of intravaginal testosterone cream and estradiol-releasing vaginal ring in breast cancer patients.

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INTRODUCTION

According to the International Agency for Research on Cancer, breast cancer has an estimated incidence of 2,088,849 cases worldwide by 2018, which accounts for 11.6% of all cancer types (INTERNACIONAL AGENCY FOR RESEARCH ON CANCER, 2019). In Brazil, the National Cancer Institute estimates 59,700 new cases for each year of the 2018-2019 biennium, with an estimated risk of 56.33 cases per 100,000 women (INSTITUTO NACIONAL DE CÂNCER JOSÉ ALENCAR GOMES DA SILVA, 2017). Estimates for subsequent years indicate an increasing trend in the number of cases. Hence, several studies have been developed to determine the impact of breast cancer diagnosis and treatment on the sexual well-being of affected women (MACEDO *et al*., 2018). Sexual changes are a common condition in women with breast cancer (BC) which may be aggravated by factors such as diagnosis; treatment; age (usually affecting younger women who have not experienced menopause); disease grading; issues in the marital relationship; and alterations in the body image due to the alopecia and/or more radical surgical procedures. Sexual changes take place when organic factors of the sexual response undergo physiological or psycho-organic changes and manifest as a persistent or recurrent disorder related to sexual desire, subjective or genital arousal, orgasm and/or pain in sexual intercourse (MALE *et al*., 2016). The literature has pointed out that most women with breast cancer are not satisfied with the quality and frequency of care they receive from health professionals regarding sexuality. This is mainly because most professionals do not address the complaints or difficulties related to the sexuality of these patients due to stigma about the topic or lack of knowledge on how patients should proceed in specific situations (DOW *et al*., 2015). In this systematic review, we analyzed the effectiveness of interventions carried out in women with breast cancer for the improvement of their sexual dysfunction. The findings reported herein may provide evidence to support intervention guidelines by health professionals in oncology. This study attempted to answer the following focused question: which

interventions are effective for the improvement of sexual dysfunction in women with breast cancer?

MATERIALS AND MÉTODOS

This systematic review of the literature (MANCINI *et al*., 2014) was designed and executed in accordance with the PRISMA (LIBERATI *et al*., 2009) flowchart (Figure 1). Bibliographical searches were carried out in PubMed, LILACS, IBECS, BDENF, Scopus, Web of Science and CINAHL databases between April 9 and 10, 2018, using the keywords: "breast cancer", "treatment", "therapy", "pharmacological intervention", "hormonal therapies", "alternative therapies", "sexual dysfunction " and "sexual", which were combined with Boolean operators ("AND" and "OR"). The following search strategies were used: "breast cancer" AND "sexual dysfunction"; "breast cancer" AND "sexual dysfunction" AND "treatment" OR "therapy"; and "breast cancer" AND "sexual" AND "pharmacological intervention" OR "hormonal therapies" OR "alternative therapies". Studies that meet the following inclusion criteria were considered eligible: primary study with an experimental and randomized design; recruitment of women with history of, or active, breast cancer; addressing the effectiveness of an intervention to improve sexual dysfunction; with a Jadad's scale (JADAD *et al*., 1996) score equal to or greater than three; published in English, Portuguese or Spanish; and with the full text available online. No temporal limitation was used, and gray literature was excluded.

Two examiners independently assessed the methodological quality of the included experimental and randomized studies using the Jadad's scale (JADAD *et al*., 1996). The Jadad score ranges from zero to five based on methodological criteria of a randomized clinical trial, namely: Was the study randomized? Is the randomization described adequately? Was the study double-blinded? Is the described allocation concealment appropriate? Is there a description of sample losses and withdrawals? Each criterion of this scale can be judged as "yes" (1 point) or "no" (0 point). Scores lower than three indicate a poor methodological quality of the study, with hardly generalized outcomes (JADAD *et al*., 1996). To include high-quality studies in this systematic review, the articles scoring less than three were excluded from the analysis. The data were extracted into standardized Microsoft Office Excel worksheets by one examiner and checked for completeness and accuracy by other two examiners. Disagreements or inconsistencies were resolved through discussion and consensus among the three examiners. The following information was extracted from all studies: publication information (title, journal, author, country, language, year of publication), institution where the study was carried out, type of publication (nursing, medicine, psychology or multiprofessional), methodological characteristics of the study, and assessment of methodological rigor using the Jadad's scale (JADAD *et al*., 1996). Figure 1 illustrates the selection process of the articles in this systematic review, as re-commended by the PRISMA Group (LIBERATI *et al*., 2009).

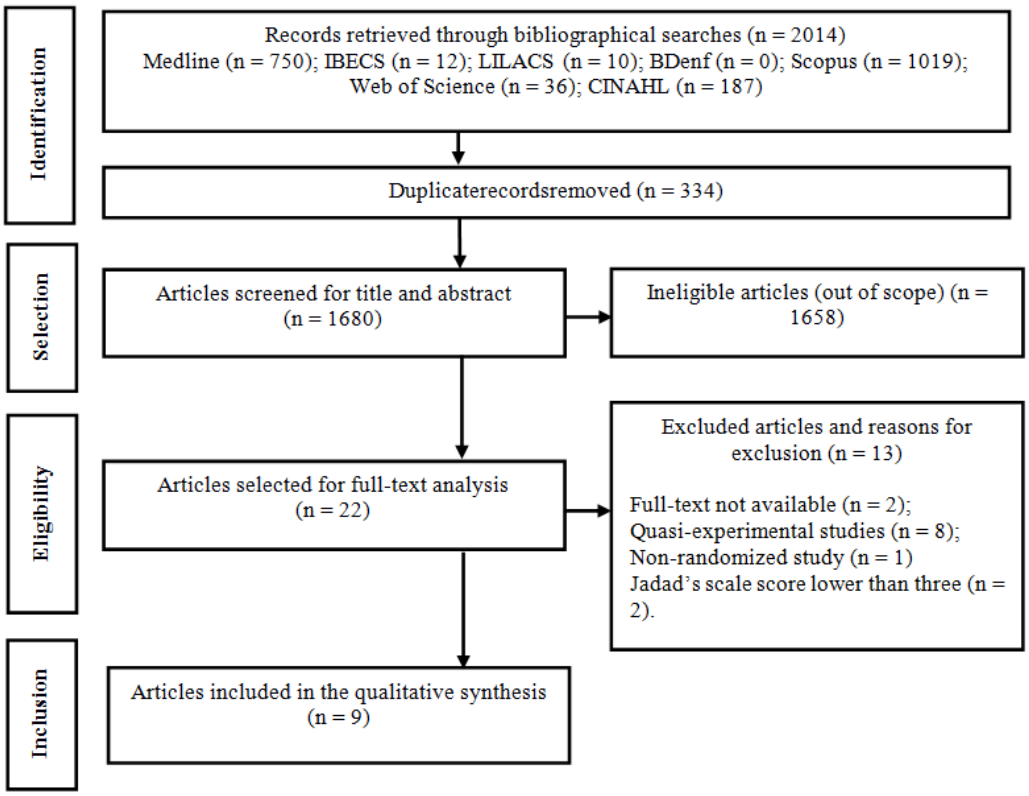

Figure 1. Flowchart of the Search Strategy and Study Selection Based on the PRISMA Guidelines

After the removal of duplicate records (N = 334), two examiners independently screened the titles and abstracts of retrieved articles for eligibility. In case of inconsistency, a third examiner was requested for analysis. Following the preliminary screening, a full-text analysis of selected studies was carried out to check for inclusion and exclusion criteria.

RESULTS

A total of twenty-two studies met the initial eligibility criteria and were included for analysis. After a full-text analysis, only nine studies were included in the final review. Most articles were published between 2013 and 2017, with approximately half of them published in 2017. Five studies were carried out

in the United States and the remaining in the Netherlands, Brazil, Australia and South Korea. As for methodological quality, seven and one of the nine selected articles obtained Jadad scores equal to three and four, respectively. The highest score was given to a study that compared the use of water-based versus silicone lubricant for vaginal dryness and dyspareunia in breast cancer survivors. The sample size of the selected studies ranged from 38 to 186 participants, with a minimal, mean and maximal dropout rate of 9.6%, 24.7% and 47.2%, respectively. Six studies (SCHOVER *et al*., 2011; HICKEY *et al*., 2016; HUMMEL *et al*., 2017; SCHOVER *et al*., 2013; NUÑEZ *et al*., 2013; GREVEN *et al*., 2015) were composed of breast cancer survivors, and two of these were composed specifically of individuals who had undergone hormonal therapy. Two studies (ADVANI *et al*., 2017; MELISKO *et al*., 2018) recruited post-menopause breast cancer women undergoing hormonal therapy. Lastly, one study (KIM *et al*., 2017) included breast cancer patients undergoing chemotherapy who had not menopaused yet. The included studies were classified as for intervention length into short-term (up to 8 weeks; n = 3; 33.3%) (SCHOVER *et al*., 2011; HICKEY *et al*., 2016) and long-term (between 9 and 24 weeks; n = 6; 66.6%) (HUMMEL *et al*., 2017; Melisko *et al*., 2017). Six studies used the Female Sexual Function Index (FSFI) to measure participants' sexual function (SCHOVER *et al*., 2011; HUMMEL *et al*., 2017; SCHOVER *et al*., 2013; GREVEN *et al*, 2015; ADVANI *et al*., 2017; KIM *et al*., 2017). Other scales used in the selected studies were the Fallowfield Sexual Activity Questionnaire Discomfort (subscale SAQ-D12), Arizona Sexual Experience Scale (NUÑEZ *et al*., 2013) and the Cancer Rehabilitation Evaluation System (sexual interest and sexual dysfunction subscales and single-item sexual satisfaction) at baseline (MELISKO *et al*., 2017).

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One study (ADVANI *et al*., 2017) investigated the hypothesis that combining sexual counseling, vaginal moisturizers, lubricants, dilatation and pelvic floor muscle exercises, would prevent further deterioration of sexual function as compared to usual care. Participating women were randomized into three treatment groups. All groups received a handout on how to manage sexual side effects and only the CG received no additional care. The two IGs underwent the following treatment regimens: a six-month supply of a vaginal moisturizer (one based on hyaluronic acid and the other based on prebiotics); water-based lubricant; vaginal dilator; access to a password-protected educational website, which provided detailed information on sexual issues related to women with cancer; and telephone-based training. In addition, six telephone calls with a coach were scheduled for participants from both IGs during the 12-week treatment, in addition to three monthly follow-up calls. The calls lasted from 15 and 30 minutes and included inquiries about the frequency of sexual activities, lubricant use and product satisfaction (Figure 2). One of the included studies (HUMMEL *et al*., 2013) evaluated the effect of internet-based cognitive-behavioral therapy on sexual functionality and intimacy in relationships among breast cancer survivors with sexual dysfunction. IG participants underwent internet-based cognitive-behavioral therapy, which consisted of weekly sessions guided by therapists, psychologist or sexologist, with a maximum duration of 24 weeks. The GC received an information handout addressing sexuality issues following breast cancer treatment and, after six weeks, they received a call from the therapist to briefly discuss any issues related to the handout (Figure 2). Another study (NUÑEZ *et al*., 2013) determined the efficacy of bupropion 150 mg for the frequency and severity of heat waves (sudden heat sensation) and for sexual dysfunction, depression, and quality of life. Patients were randomized to receive 4-week treatment with bupropion or placebo, followed by a washout week and 4 weeks of crossed treatment. A recent study (KIM *et al*., 2017) evaluated whether a pH-balanced vaginal gel containing lactic acid was more effective than a placebo (lactate-free gel) in improving dyspareunia and sexual function in premenopausal women diagnosed with breast cancer who underwent adjuvant chemotherapy and had an active sexual life but presented with symptoms of dyspareunia. The patients were instructed to apply 3 ml of gel with a vaginal applicator three times a week at bedtime and additionally during sexual intercourse for 8

weeks (Figure 2). One selected study (GREVEN *et al*., 2015) assessed the impact of ArginMax on sexual function and quality of life of cancer survivors with sexual complaints. ArginMax is made up of extracts of L-arginine, ginseng, ginkgo and damiana, multivitamins and minerals. Participants were instructed to take three capsules of ArginMax (IG) or placebo (CG) 2 times a day for 12 weeks and to keep records of the number of capsules consumed daily (Figure 2).

Other authors (MELISKO *et al*., 2017) evaluated the impact of intravaginal testosterone cream administration and estradiol-releasing vaginal ring on quality of sexual life and vaginal atrophy. Participants were instructed to administer daily 0.5 mg of the intravaginal testosterone cream (1%) by means of a calibrated applicator for two weeks, then three times a week for 10 weeks. The estradiol-releasing vaginal ring (2 mg) is a silicone vaginal ring which releases 0.75 μg of estradiol every 24 h for 90 days. The ring was applied by the participants themselves or by a researcher on the first day of the experiment (Figure 2). Lastly, another study (HICKEY *et al*., 2016) compared the efficacy and acceptability of a water and silicone lubricants for sexual discomfort. Both lubricants were of intravaginal application, which had as mechanism of action to maintain the pH and hydration of vaginal surfaces to lessen friction (Figure 2). The selected studies used two educational technologies, Cognitive Behavioral Therapy (HUMMEL *et al*., 2017) and Trendils (SCHOVER *et al*., 2013) Program, which despite presenting distinct strategies, used the internet as a tool. Both strategies had a significant relationship with the improvement of sexual function. It is noteworthy that these studies (SCHOVER *et al*., 2011; HICKEY *et al*., 2016) had health professionals trained as counselors, unlike the SPIRIT Program (SCHOVER *et al*., 2011) proposal, which adopted peer counseling and did not obtain a statistically significant difference between the groups. All the studies used mixed linear models to evaluate intra- and inter-group differences throughout the experimental period (Figure 2).

The hyaluronic acid-containing vaginal moisturizer was found to have a positive effect on sexual function, although for a limited time, as no significant difference in sexual function was observed after 12 months. On the other hand, intervention groups receiving combined care had less sexual distress ($P = .02$) than those with usual care. The authors used covariance analysis (ANCOVA) to check for differences between groups at 6 and 12 months (ADVANI *et al*., 2017). A linear regression model revealed that while there was no difference between the effects of water and silicone lubricants on sexual function, the latter was more effective for vaginal lubrication (HICKEY *et al*., 2016) (Figure 2). The use of a pH-balanced vaginal gel did not significantly improve sexual function in comparison to the placebo group. However, women who used it showed a significant increase in vaginal health conditions, with a lower vaginal pH ($P < .01$) and a higher vaginal maturation index ($P = .01$). The authors of this study used the Student's t test and the Mann-Whitney U test to compare continuous variables and

the Chi-square test to compare categorical variables between the two groups (KIM *et al*., 2017) (Figure 2). Both the intravaginal testosterone cream and the estradiol-releasing ring caused a significant improvement in sexual function, although the latter was related to higher scores of sexual satisfaction (MELISKO *et al*., 2017). The study investigating the impact of ArginMax on sexual function found no significant effects of this nutritional supplement when compared to a placebo. To evaluate the differences between groups, the authors used a mixed-effect repeated-measures analysis of variance (RMANOVA) (GREVEN *et al*., 2015). The statistical analysis indicated that bupropion did not have significant effects on sexual function when compared to a placebo (NUÑEZ *et al*., 2013) (Figure 2).

DISCUSSION

Even though sexual dysfunction represents a common problem, it is still poorly studied among women with breast cancer (CORNELL *et al*., 2017). Female sexual dysfunction (FSD) is characterized as distress related to sexual pain, arousal, desire and/or orgasmic dysfunction (KRAKOWSKY *et al*., 2018). This is the first systematic review of interventions to improve sexual dysfunction in women affected by breast cancer. Although most of the studies did not present statistically significant outcomes, there were interventions with potential to improve sexual dysfunction among surviving and breast cancer patients and to thereby promote their sexual well-being. According to the studies included in this review, non-pharmacological interventions (e.g. internet-based educational strategies and professional counseling through cognitive-behavioral therapy (HUMMEL *et al*., 2017) and the Tendrils program (SCHOVER *et al*., 2013) were more effective in improving sexual dysfunction in breast cancer survivors. Internet-based resources can play an important role in bonding patients to healthcare and other professionals under similar circumstances; or as an educational tool, as it increases patients' knowledge about the condition (MCALPINE *et al*., 2015). In addition, online interventions by qualified professionals such as psychologists or therapists in cancer patients experiencing sexual difficulties may be more effective than face-to-face interventions (KANG *et al*., 2018). These findings are consistent with those observed in this review. In most studies, counselors were health professionals (physicians, psychologists and sexologists), who interacted with patients to elucidate questions and monitor their evolution throughout the experimental period. Other authors reiterate that women with breast cancer and their partners report the need for psychosexual support through information and practical advice (VERMEER *et al*., 2016). Changes in sexuality and intimacy affect many women with breast cancer and are mainly caused by the stigma of diagnosis and adverse effects of treatment, as well as other factors such as age, disease stage, marital relationship problems, and changes in their body image (MALE *et al*., 2016). These problems may occur for a limited or a lasting period. Study conducted with women who survived breast cancer verified that problems in sexuality prevail for a long period, directly interfering in their quality of life (DOW *et al*., 2015). Sexual dysfunction in female cancer survivors is a multifactorial issue involving sociocultural, psychological, biological and relationship factors. Medical treatments such as surgery, hormonal manipulation, and chemotherapy and radiotherapy seems to have a major impact on sexual health (GAMBARDELLA *et al*., 2018). According to the studies included in this review, hormonal methods (e.g., intravaginal testosterone cream and estradiol-releasing ring) were effective in improving sexual dysfunction in postmenopausal women in the early stage of breast cancer who were using aromatase inhibitors. The authors further investigated the risk of persistent elevation of estradiol in these patients and concluded that a 12-week protocol is considered safe. Further research is needed to understand the variability of estradiol susceptibility under these circumstances (MELISKO *et al*., 2017).

Figure 2. Sample Size and Characteristics of Experimental Interventions

Authors, Year of Publication and Study Quality	Final Sample Size (*n*)*	Study Population	Intervention	Comparative Arm	Frequency and Length of Intervention	Protocol and Follow-up Length	Main Outcome(s)
Schover et al, 2011, Jadad's score: 3	185 CG: 89 IG: 96	African Americans with at least 1 year post-diagnosis of breast cancer and hormone therapy	Peer Counseling Program plus three face-to-face counseling sessions	Peer Counseling Program	Three 60-to-90-minute sessions	6 weeks Partial: 6 weeks and 6 months End: 1 year	There was no statistically significant difference between the groups (P = .630)
Hummel et al, 2017. Jadad's score: 3	169 CG: 85 IG:84	Breast cancer survivors (6 months to 5 years) Age: 18-65 years With sexual dysfunction	Cognitive-Behavioral Therapy	Informative handout	Once a week	24 weeks Partial: 10 weeks End: Post-therapy	IG showed a significant improvement in general sexual function (P = .031)
Schover et al, 2013, Jadad's score: 3	38 CG: 16 IG: 22	1 to 7 years after diagnosis of breast cancer or gynecological diagnosis	Tendrils website: "Sexual renewal for women after cancer".	Tendrils website: "Sexual renewal for women after cancer" plus three counseling sessions	Three sessions	12 weeks Partial: 12 weeks and 3 months End: 6 months	There was an improvement in sexual function (P < .001) in IG
Advani et al, 2017, Jadad's score: 3	45 IG_1: 13 IG_2: 12 CG: 20	Estrogen positive breast cancer; Post-menopaused; In recent use (<4 weeks) of aromatase inhibitor; Sexual partner for at least 6 months or attempted sexual activity in the last 12 months.	IG_1: Hyaluronic acid-containing vaginal moisturizer IG_2: Prebiotic vaginal moisturizer	Usual care	Once a day during the first week, then two to three times a week.	24 weeks Partial: 6 months End: 12 months	Although IG_1 showed a significant improvement in sexual function at 6 months (P = .04), there was no statistically significant difference between groups at 12 months
Nuñez et al, 2013. Jadad's score: 3	49 CG: 24 IG: 25	Breast cancer survivors without history of active disease; Subjected to hormone therapy for at least 3 months; With severe complaints of heat waves.	Bupropion 150mg	Placebo	One capsule/day for three days, followed by two capsules/day for four weeks.	10 weeks Partial: 4 weeks End: 10 weeks	There was no statistically significant difference between the groups (P = .497)
Kim et al, 2017, Jadad's score: 4	107 CG: 57 IG: 50	Age over 20 years; Diagnosed with primary breast cancer before menopause; Who received adjuvant chemotherapy; Sexually active (at least 1 intercourse / month); with dyspareunia.	pH-balanced vaginal gel	Placebo	3ml, 3x/week at bedtime or during sexual intercourse for eight weeks.	8 weeks Partial: before treatment End: 8 weeks	There was no statistically significant difference between groups (P = .93).
Greven et al, 2015, Jadad's score: 3	186 CG: 92 IG: 94	Female Cancer Survivor Sexual complaints (after 6 months of treatment)	ArginMax	Placebo	Three capsules daily in the morning and at night	12 weeks Partial: 4 and 8 weeks End: 12 weeks	There was no statistically significant difference between groups (P = .827).
Melisko et al, 2017, Jadad's score: 3	68 CG: 33 IG: 35	Post-menopausal women in early stage of breast cancer; Treated for at least 30 days with aromatase inhibitor; Symptoms of vaginal dryness, dyspareunia and decreased libido.	Intravaginal Testosterone Cream (0.5 mg)	Estradiol-releasing vaginal ring (2mg)	Once a day for two weeks, followed by three times a week for 10 weeks.	12 weeks Partial: 4 weeks End: 12 weeks	There was an improvement in mean sexual dysfunction in patients in both groups (P < .001)
Hickey et al, 2016, Jadad's score: 5	38 CG: 19 IG: 19	Breast cancer survivor; Sexually active; with vaginal dryness or dyspareunia.	Silicone lubricant	Water lubricant	Before and during sexual intercourse at least two times a week	4 weeks Partial: 4 and 8 weeks End: 12 weeks	There was no statistically significant difference between the groups (P = .06)

*CG=Control Group; IG=Intervention Group.

The American Society of Obstetricians and Gynecologists recommends that non-hormonal options be prioritized in cases of patients with a history of estrogen-sensitive breast cancer. Therefore, it is suggested that vaginal estrogens are reserved only for patients who do not respond to non-hormonal treatment for the improvement of sexual dysfunction, and only after consultation with the oncologist. This indication should be preceded by an informed decision-making process and consent in which the patient has the information and all resources necessary to consider the potential benefits and risks of low-dose vaginal estrogen administration (AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGISTS, 2016).

The vaginal testosterone cream may be an effective alternative for the treatment of sexual dysfunction in women with breast cancer rather than vaginal estrogen administration (DAHIR *et al*., 2014). One study reported increased libido and sexual satisfaction in breast cancer patients and survivors following treatment with the vaginal testosterone cream (KRYCHMAN *et al*., 2007), although the cardiovascular risks of testosterone in this population remain to be determined (WHITE *et al*., 2012). Thus, although its use seems to be promising, there is still a need for further research to fully support a change in clinical practice, as the available evidence is very limited (LEMKE *et al*., 2017). Furthermore, among women who have undergone BC treatment, sexuality may be experienced in different ways. BC treatment involves several repercussions, and the occurrence of sexual dysfunctions should be analyzed by professionals during the patients' therapeutic sessions (MACEDO *et al*., 2018). Women with breast cancer need the information, support, and practical strategies provided by professionals to help manage cancer-related sexual changes and treatment. Healthcare professionals should evaluate the therapeutic effects on sexuality of breast cancer survivors. Therefore, breast cancer should be managed as a systematic approach with multidisciplinary contributions (GAMBARDELLA *et al*., 2018). Health professionals need to have qualified expertise in this specific area, which requires study, humanization, and autonomy when performing clinical monitoring, emotional support, and holistic care, contributing to a better quality of life of women with breast cancer (CESAR *et al*., 2017). In this context, interventions should be implemented early and continuously to prevent sexual dysfunction and promote the sexual well-being of women with breast cancer.

One of the major limitations of this systematic review consisted of the small sample size of selected studies. In addition, while the primary focus of this review was on interventions to improve sexual dysfunction in women with breast cancer, most studies recruited only breast cancer survivors. Thus, the outcomes reported herein may not be extrapolated to individuals undergoing therapy for breast cancer. Although this review did not address a specific professional category, the outcomes may guide the multiprofessional team's decision-making on pharmacological and non-pharmacological interventions. From this, the multiprofessional team can choose the most appropriate strategy with autonomy and based on the patient's clinical condition. Despite these limitations, this systematic review listed some effective interventions for the improvement of sexual dysfunction in women affected by breast cancer, which can be used through different approaches by the multiprofessional healthcare team.

Conclusion

There is evidence to support the use of educational technologies, such as cognitive-behavioral therapy and self-help groups, as effective strategies for improving sexual dysfunction in breast cancer survivors and of intravaginal testosterone cream and estradiol-releasing vaginal ring in breast cancer patients. This review may enable nurses to explore the remaining gaps in nursing practice and research on the sexuality of women with a history of or ongoing breast cancer. In addition, nurses are strategic professionals to identify and intervene early in sexual dysfunction in breast cancer women and survivors to improve their quality of life. The outcomes reported herein may support not only nurses but also other health professionals while choosing an effective intervention to improve patient's sexual dysfunction.

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