Efficacy and Safety of Treatments to Improve Dyspareunia in Breast Cancer Survivors: A Systematic Review

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Keywords

Dyspareunia · Female sexual dysfunction · Breast cancer ·
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Abstract

Objective: To analyse all available evidence to validate the effectiveness of a local intervention in the treatment of dyspareunia in breast cancer survivors (BCS). **Methods:** We searched the Institute of Scientific Information Web of Knowledge, MEDLINE, PubMed, Scopus, and Cochrane databases for all articles published in peer-reviewed journals up to April 2019. The PICOS standards were: (population) BCS with dyspareunia; (intervention) any type of vulvovaginal treatment; (main outcome) frequency and severity of dyspareunia; (study design) clinical studies. **Results:** The literature search strategy identified 252 articles, of which 233 were excluded at various stages of the search. Finally, we systematically reviewed 19 studies, 8 with local hormonal therapies, 7 with local non-hormonal therapies, 3 with laser therapy, and 1 with other interventions. Of the studies, 7 were randomized control trials and 11 were prospective observations.

Most of the interventions were shown to be effective and safe in the improvement of dyspareunia. **Conclusion:** In addition to the traditional options already analysed in other current reviews, other interesting options are highlighted (such as laser or local dehydroepiandrosterone [DHEA]). Further work on dyspareunia should make use of high-quality trials with large numbers of samples to obtain evidence that could adequately demonstrate key methodological characteristics and harmful effects.

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Introduction

Breast cancer (BC) is the most common type of cancer (accounting for 28.7% of all cancers) and has the highest mortality rate (15.5%) of all cancers affecting women [1]. However, the number of BC survivors (BCS) has also increased due to early detection programs and improved

The study was registered at www.propero.org (CRD42019127832).

Fig. 1. Flow chart of the literature search.

treatments; therefore, BC has the highest survival rate among all cancers affecting women [2].

In BCS, sexual health is affected after treatment, having an impact on all phases of sexual response, with vaginal atrophy being particularly problematic. In this regard, dyspareunia is common in BCS, particularly in those women who are treated with aromatase inhibitors (AIs) [3].

In previously published articles on sexual health in BCS, we recommended that an adequate sexual health approach in BCS should be delivered through a multidisciplinary team, in order to minimize female sexual dysfunction (FSD) and relationship issues [4].

Overall, there are few randomized controlled trials (RCTs) evaluating treatments for dyspareunia in BCS women, and those that exist comprise small sample sizes and report mixed results. The most recommended option is the use of vaginal moisturizers and lubricants. Only after consultation with the patient's oncologist and comprehensive counselling about potential risks should local oestrogen treatment be used [4]. However, in recent years new therapeutic options have emerged for the treatment of postmenopausal vaginal symptoms that deserve to be evaluated in these women.

The purpose of this systematic review is to analyse all available evidence to validate the effectiveness of local interventions in the treatment of perimenopausal and postmenopausal BCS with dyspareunia.

Methods

Selection of Studies

We searched the Scientific Information Web of Knowledge (MEDLINE, PubMed, Scopus, and Cochrane databases) for all articles (in any language) published in peer-reviewed journals up to April 2019. The search criteria were applied to each database and combined with the available database-specific filters. Other publications were identified by manually searching through a reference

list of papers highlighted by the search as well as key reviews. Press reports published in peer-reviewed journals and reports available online prior to publication were also considered.

The PICOS (Population, Intervention, Comparators, Outcomes, Study Design) criteria were developed a priori to guide the scope of the review, along with the procedures, selection, and synthesis of the literature search.

The selection criteria were as follows: (Population) patients with BC and dyspareunia; (Intervention) any type of pharmacological or local (vaginal) treatment; (Outcome) primary outcome: change in frequency, severity, and average mean scores of sexual symptoms measured with a validated instrument, secondary outcomes: quality of life; and (Study Design) clinical studies. Any complete article that met the inclusion criteria was reviewed in detail. Other related papers are for reference purposes only.

Exclusion criteria were other aetiologies of FSD, prevention (or treatment) of FSD, and the presence of other female cancers.

Assessment of Study Quality and Data Synthesis

We conducted a systematic review in accordance with PRISMA [5]. Qualitative and quantitative data were extracted from the papers included in the review using standardized data extraction tools from Jadal and CONSORT. The authors conducted an independent search, screening studies to include, extract, and examine data, and to synthesize the results. These authors independently evaluated the adequacy of the study design and the main methodological features in order to determine the validity of the study. The extracted data include the specific details about interventions, populations, research methods, and outcomes that are relevant to the reviewed questions and specific objectives. Disagreements were resolved through discussion and consensus.

Data Extraction

Two independent reviewers extracted the data from the included studies by using a specifically developed data extraction form based on the selection criteria. The extracted information includes a description of the study, participants, and findings based on the above outcomes. When there were no data (methods or results) of interest in the published paper, we contacted the author by email.

Results

As shown in Figure 1 (PRISMA flow chart), the literature search strategy identified 252 articles. Of these, 233 were excluded at different stages of the search. Finally, we systematically reviewed 19 studies, 8 of which were concerned with treatments based on local hormonal therapy [6–13], 7 with local non-hormonal therapy [14–20], 3 with laser [21–23], and 1 with other interventions [24].

Of the studies, 7 were RCTs [12, 13, 15–19] and 11 were prospective observational studies [6–11, 14, 20, 22–24]. Except for one [18] double-blind and random sequence generation, all RCTs were collected; allocation concealment was evident in only 2 RCTs [13, 17]. One of the RCTs is a crossover study that includes the flushing phase [17]. Meta-analysis was not possible due to the heterogeneity and small sample size of the included studies.

A summary of the main features of the selected studies (study design, population, intervention, objective, and

Table 1. Summary of findings

Authors	Study design	Population	Intervention	Objective	Main results
<i>Hormonal local interventions</i>					
Kendall et al. [6], 2006	Prospective cohort study	6 postmenopausal BC on AI with dyspareunia Age: 52 years (51–59)	– Oestradiol 25 µg 12 weeks	Primary: oestrogen levels Secondary: dyspareunia	5/6 improved but significant rise in oestradiol levels
Biglia et al. [7], 2010	Prospective cohort study	26 postmenopausal BCS with GSM Age: 54.1 vs. 46.1 years	– Oestradiol 0.25 mg (<i>n</i> = 10) – Oestradiol 12.5 µg (<i>n</i> = 8) – Polycarbophil-based moisturizer 2.5 g (<i>n</i> = 8) 12 weeks	Primary: efficacy on vaginal symptoms Secondary: oestrogen levels	Both LET are effective for VVA (<i>p</i> < 0.01) Minimal increase of oestrogen levels.
Pfeiler et al. [8], 2011	Prospective cohort study	10 BC on AI with dyspareunia Age: 65 years (50–77)	– Oestradiol 0.5 mg (<i>n</i> = 10) 2 weeks	Primary: oestrogen levels Secondary: dyspareunia	6/10 improved but significant decline in FSH levels
Witherby et al. [9], 2011	Prospective cohort study	21 postmenopausal BC women on AI with VVA Age: 56–57 years (45–69)	– Testosterone 4 weeks	Primary: oestrogen levels Secondary: dyspareunia	Improved dyspareunia (<i>p</i> < 0.001)
Dahir et al. [10], 2014	Prospective cohort study	13 postmenopausal BC women on AI with dyspareunia Age: 59.67 years	– Testosterone 4 weeks	Primary: sexual health FSFI	Improvement in all FSFI domain (<i>p</i> < 0.001)
Donders et al. [11], 2014	Prospective cohort study	16 BC on AI with dyspareunia Age: 57 years (52–63)	– 0.03 g oestradiol + <i>L. acidophilus</i> 12 weeks	Primary: oestrogen levels Secondary: dyspareunia	Safe and efficacious (<i>p</i> < 0.01)
Melisko et al. [12], 2017	RCT NCT00698035	69 postmenopausal BC women on AI with dyspareunia Age: 56 years (37–78)	– Testosterone (<i>n</i> = 36) – Oestradiol ring –7.5 µg/day (<i>n</i> = 40)	Primary: oestrogen levels Secondary: dyspareunia + FSD	Vaginal atrophy and FSD improved in all patients
Barton et al. [13], 2018	RCT multi-centre NCT01376349	464 postmenopausal with gynaecological or BCS (97% BCS) with dyspareunia Age: 57 years (56–58)	– DHEA 3.25 mg (<i>n</i> = 149) – DHEA 6.5 mg (<i>n</i> = 147) – Placebo (plain moisturizer) (<i>n</i> = 147) 12 weeks	Primary: alleviation of the most bothersome vaginal symptoms (dryness or dyspareunia) Secondary: FSFI	All interventions improved symptoms DHEA, 6.5 mg, significantly improved FSFI (<i>p</i> = 0.005)
<i>Non-hormonal local interventions</i>					
Juraskova et al. [14], 2013	Prospective cohort study	25 postmenopausal BCS with dyspareunia Age: 51 years (37–66)	Pelvic floor muscle relaxation exercises + polycarbophil-based vaginal moisturizer + olive oil lubricant	Primary: dyspareunia and sexual functioning Secondary: quality of life	Improvements in dyspareunia, sexual function, and quality of life (<i>p</i> < 0.001)
Lee et al. [15], 2011	RCT NCT00607295	98 postmenopausal BCS with VVA Age: 45.86 years (34–53)	– pH-balanced gel (ac lactic) (<i>n</i> = 49), 45 years old – Placebo (<i>n</i> = 49), 44 years old 12 weeks	Primary: dyspareunia and vaginal symptoms Secondary: vaginal health and maturation indexes	Improvement in dyspareunia, vaginal pH, and maturation (<i>p</i> < 0.001)
Goetsch et al. [16], 2015	RCT NCT01539317	46 postmenopausal BCS with dyspareunia Age: 55 years	– Lidocaine (<i>n</i> = 23) – Placebo (<i>n</i> = 23) 2 months	Primary: dyspareunia Secondary: sexual distress	Less pain (<i>p</i> = 0.007) and sexual distress (<i>p</i> < 0.001)

Table 1 (continued)

Authors	Study design	Population	Intervention	Objective	Main results
Hickey et al. [17], 2016	RCT crossover ACTRN12611001249943	46 postmenopausal BC women with vaginal dryness or dyspareunia Age: 53.1 years	– Silicon-based lubricant ($n = 24$) – Water-based lubricant ($n = 22$) 4 weeks/crossover/4 weeks	Primary: discomfort during sexual activity Secondary: sexual pleasure and distress	No differences
Juliato et al. [18], 2017	RCT	60 BC women treated with tamoxifen with vaginal dryness. Age: 48.8 vs. 50.5 years	– Polyacrylic acid ($n = 30$) – Placebo ($n = 30$) 30 days	Primary: vaginal dryness and loss of sexual function Secondary: quality of life	Both treatments improved sexual function without differences between them
Kim et al. [19], 2017	RCT NCT00981305	136 perimenopausal BCS women with dyspareunia Age: 49.3 vs. 48.2 years	– pH-balanced vaginal gel containing lactic acid ($n = 69$) – Placebo ($n = 67$) 8 weeks	Primary: dyspareunia Secondary: vaginal pH and maturation index	No differences in dyspareunia Improvement in pH
Chatsipiros et al. [20], 2019	Open, prospective, multicentre, observational study	116 BC women with VVA/GSM (80% with sexual activity and dyspareunia) Age: 51 years (30–85)	An oil-in-water emulsion 4 weeks	Primary: VVA/dyspareunia	improvements in dyspareunia ($p < 0.0001$)
<i>Laser</i>					
Pieralli et al. [21], 2016	Prospective observational study	50 postmenopausal BCS Age: 53 years (41–66)	Fractional CO ₂ laser 3 times	Dyspareunia	Effective ($p < 0.0001$)
Gambacciani and Levancini [22], 2017	Prospective observational study	43 postmenopausal BCS with GSM Age: 50.8 years (38–70)	Erbium laser 18 months	Dyspareunia	Effective and safe ($p < 0.01$)
Becorpi et al. [23], 2018	Prospective observational study	20 postmenopausal BC women with GSM Age: 58.2 years	Fractional CO ₂ laser (1 session)	Primary: effects on vaginal immune mediators and microbiome Secondary: reduction of GSM symptoms	Effective and safe ($p < 0.001$) Absence of modifications in the vaginal microbiome
<i>Hyaluronic acid</i>					
Hersant et al. [24], 2018	Phase 2 pilot study (not controlled) NCT02966925	20 postmenopausal BCS with VVA Age: 60.8 years (55–69)	A-PRP + HA 6 months	Primary: mucosa changes Secondary: dyspareunia and FSD	All participants showed improvement in the clinical symptoms of vaginal dryness and dyspareunia ($p < 0.0001$)

AI, aromatase inhibitors; A-PRP, autologous platelet-rich plasma; BC, breast cancer; BCS, breast cancer survivors; FSD, female sexual dysfunction; FSFI, female sex function index; FSH, follicular stimulation hormone; GSM, genitourinary syndrome menopause; HA, hyaluronic acid; HSDD, hypoactive sexual desire disorder; LET, local oestrogen therapy; MHT, hormone menopausal therapy; RCT, randomized control trial; SFI, sexual function index; VAS, visual analogue scale; VHI, vaginal health index; VVA, vulvovaginal atrophy.

Table 2. Quality of studies included in the systematic review

Authors	RCT	Random	Allocation	Blind	Time from BC	Dropout, %	Adverse effects
<i>Hormonal local interventions</i>							
Kendall et al. [6], 2006	–	–	–	–	–	None	Not described
Biglia et al. [7], 2010	–	–	–	–	–	16	Not described
Pfeiler et al. [8], 2011	–	–	–	–	–	None	–
Witherby et al. [9], 2011	–	–	–	–	+	10	+
Dahir et al. [10], 2014	–	–	–	–	+	8	Not described
Donders et al. [11], 2014	–	–	–	–	–	None	–
Melisko et al. [12], 2016	+	–	+	+	+	10	+
Barton et al. [13], 2018	+	–	+	+	–	8	+
<i>Non-hormonal local interventions</i>							
Juraskova et al. [14], 2013	–	–	–	–	+	36	Not described
Lee et al. [15], 2011	+	+	–	+	–	12	+
Goetsch et al. [16], 2015	+	+	+	+	+	11	+
Hickey et al. [17], 2016	+	+	+	+	+	8	Not described
Juliato et al. [18], 2017	+	–	–	–	–	13.3	Not described
Kim et al. [19], 2017	+	+	–	+	–	7.9	+
Chatsipirois et al. [20], 2019	–	–	–	–	–	8.5	+
<i>Laser and hyaluronic acid</i>							
Pieralli [21], 2016	–	–	–	–	–	None	+
Gambacciani [22], 2017	–	–	–	–	–	14	–
Becorpi et al. [23], 2018	–	–	–	–	–	None	Not described
Hersant et al. [24], 2018	–	–	–	–	–	None	–

main outcomes) is presented in Table 1. Although the mean age and age range of the patients were reported in all articles, BC diagnosis time was described in only 4 studies [9, 10, 14, 17]. In all studies, the analysis of dyspareunia was an objective of the study, and in most of these (except for 2) this was the main objective. None of the studies had evaluated sexual behaviour prior to BC.

Most of the studies were considered to be of low to medium quality, primarily because they were not RCTs, or because of the small sample size, high dropout rates, or the fact that the adverse effects of the interventions were not described (see Table 2). All studies included heterosexual patients.

Intervention Characteristics

Hormonal therapy was used in 8 of the studies. In general, an improvement in dyspareunia was observed, but only 2 of these were RCTs [12, 13]. In most of the studies on local oestrogen therapy, the main outcome was linked to oestrogen levels. Most of them were prospective cohort studies during 12 weeks with local preparations containing oestradiol (7, 7–25 µg daily) [6, 7] or oestriol (0.25–0.5 mg daily) [7, 8]. In 2 additional prospective cohort studies, testosterone vaginal cream (150–300 µg daily) was used for 4 weeks [9, 10]. One RCT used various doses of dehydroepiandrosterone (DHEA) daily for 12 weeks, demonstrating efficacy and

safety in the treatment of dyspareunia in BCS women [13]. Most of them show that there was no significant difference in median serum oestradiol level before and after treatments, except in one study with vaginal oestradiol in BC patients under AI treatment [6]. No case of recurrence of BC was registered in any study with vaginal hormonal therapy [6–13] (for further details, see Table 1).

With regard to non-hormonal treatments, these involved the use of vaginal lubricants or moisturizers with a pH-balanced vaginal gel or similar. An improvement in dyspareunia was observed in [14, 15, 18], and placebo also improved the dyspareunia in the study by Juliato et al. [18].

In 4 prospective cohort studies, local laser or autologous platelet-rich plasma plus hyaluronic acid was reported to improve dyspareunia. Apart from the pain that some women complained during vaginal probe insertion, no adverse event related to the procedures was recorded in any case [21–24].

Discussion

Although BC is an increasingly common disease, the number of survivors is also increasing due to early diagnosis and more effective treatment. Women who receive

chemotherapy, particularly young women, are more likely to suffer from vaginal dryness, dyspareunia, decreased libido, and difficulty in reaching orgasm [25]. Among the ever-increasing health problems associated with BCS, women develop FSD, the most common and disturbing symptom of which is dyspareunia, which is often made worse by BC treatment, particularly AI. In most cases, hormonal therapy is not indicated or recommended in BCS women [26].

Why Is It Important to Conduct This Systematic Review?

Trials that assess the effectiveness of dyspareunia treatment often exclude patients with other significant health problems, such as cancer. The diagnosis of FSD is becoming more frequent, and the need for effective and safe treatment is increasing. However, despite the growing importance of this topic, there is a lack of research and clarity of ideas. This systematic review updates the evidence included in a report published by the Spanish Menopause Society [4] and now only includes interventions used to treat FSD after BC.

Strength

This systematic review summarizes the state of the art regarding existing evidence on the effectiveness of local interventions for dyspareunia. Our review has identified 19 studies that recruited 990 patients with BC who had dyspareunia as the main symptom of FSD. The advantage of this evaluation lies in the systematic approach taken towards identifying and classifying existing evidence of BCS female dyspareunia and other FSD-specific interventions.

Limitations

Due to the heterogeneity of the research, it is fundamentally impossible to conduct a meta-analysis. Most studies consistently fail to specifically define degrees of dyspareunia; criteria for degrees of severity do not include dyspareunia scores or the ability of dyspareunia to disrupt sexual function patterns. In addition, women self-diagnose and self-allocate with regard to the severity of the disorder (mild, moderate, or severe dyspareunia). The use of dryness as a diagnosis rather than a descriptor is also problematic.

Our systematic review studies differed in terms of design: some included a comparison of treatments without additional support for dyspareunia, whilst others compared interventions with active controls. Identifying the ideal care strategy for women with dyspareunia will be considered in the RCT in future studies by comparing the impact of new interventions on FSD.

Other important limitations to be noted are the small sample size of most studies, dropouts, and follow-up fail-

ures, along with the beneficial effects of placebos in many settings. Most studies have a high risk of bias because they include samples of less than 50 participants in each trial. The trials differed not only in terms of the content of the intervention, but also with regard to the measurement of the results, which limited the combined analysis. In addition, the study lacked safety data. Generally, for most of the included studies, the quality of the evidence was medium to low.

BC patients could be diagnosed with dyspareunia for a variety of reasons: none of the studies indicated whether these were present in BC or whether the disease was present before or after treatment. In addition to dyspareunia, other emotional reasons, stress, and aging itself could be underlying causes of FSD. Therefore, not all FSDs are a direct consequence of BC or its treatment. In addition, interventions and recommendations for BCS without the disease are different from those for BC women, who may even be in treatment with drugs that impair sexual health, particularly AI.

What Is Novel about Other Similar Reviews?

Other systematic reviews have not found sufficient evidence to demonstrate the effectiveness of any type of intervention (pharmacological, mechanical, psychotherapeutic, or pelvic floor exercises). In addition, for medical treatment, the possible harmful effects have not been adequately recorded [27–30].

Our review was conducted in accordance with the Cochrane Library and we agreed to include only treatments for dyspareunia, rather than preventive measures [31]. But, unlike the Cochrane Library, we have not imposed restrictions on observational studies because these include interesting options for using alternatives such as lasers or hyaluronic acid, which have not been compared in RCTs.

One of the mistakes that often occurs when developing the question in a systematic review is the failure to include all of the patient's important outcomes (such as toxicity or adverse effects). In this systematic review, we included a study to assess the effectiveness of dyspareunia treatment. Participants were women with BC who had developed dyspareunia due to BC treatment or BC itself. We only focus on the evaluation of pharmacological or local interventions.

About the Strategies

Generally, relatively few RCTs evaluated the treatment of dyspareunia after BC, while those that existed used small sample sizes and reported mixed results. The results showed significant evidence for regular use of various vaginal interventions to improve dyspareunia and dryness, and in many cases, sexual satisfaction.

Vaginal Hormonal Therapies

Local preparations containing hormones (oestradiol, oestriol, testosterone, DHEA) have been studied in an uncontrolled way, with few cases, and an insufficient time period. Moreover, few studies have analysed their safety. In fact, in most studies, the main observed outcomes were in terms of effects on oestrogen levels following the intervention. In general, these treatments provide some relief from dyspareunia and dryness, but even at low doses, a local hormonal intervention can cause systemic absorption. Unfortunately, there were no RCTs designed to assess BC recurrence with long-term hormonal intervention.

In general, vaginal hormonal therapy is available as a tablet or cream and is effective in treating genital atrophy. However, early systemic absorption is a safety issue for patients with BC when the tissue is still atrophic, and it is only recommended for women who are not responsive to non-hormonal therapy and women being treated with AIs; these therapies should be avoided or only used for a very short period of time [32].

The most interesting study in this group was one that used various doses of DHEA [13]. This study analysed a group of heterogeneous women with any type of gynaecological cancer and BC, 97% of whom had a history of BC, and some of whom received tamoxifen or AI. However, this is a large-sample multi-centre RCT demonstrating the efficacy and safety of vaginal DHEA in the treatment of dyspareunia. DHEA has been proposed as a treatment for vulvovaginal atrophy due to its intracellular transformation in oestrogen and androgen. Clinical improvement in postmenopausal women was observed following vaginal DHEA administration [33].

Considering the safety of the vaginal hormonal therapies, no case of recurrence of BC was registered in any study. Safety was the primary objective in most of them, and this was shown, as well as the absence of side effects in all of them [9–13].

Regarding oestrogenic blood levels, most studies include this value as the primary [6, 8, 9, 11, 12] or secondary objective [7]. Most of them show that there was no significant difference in median serum oestradiol level before and after treatments. However, in BC patients under AI treatment, inconsistent results are observed with vaginal oestradiol [6, 12]. Despite the safety provided by these studies, baseline elevation in oestradiol in AI patients complicates this assessment, so further study is required to understand oestradiol variability in this setting.

Vaginal Lubricants and Moisturizers

In our previous paper, non-hormonal vaginal lubricants and moisturizers were the treatment of choice for

women in BC because they improved dryness and vulvo-vaginal blood flow [4].

Although there is limited evidence in patients with BC, vaginal moisturizers and lubricants are effective in treating dyspareunia and vaginal dryness when used regularly (3–5 times a week). There are three types of vaginal moisturizers and lubricants: pectin-based, water-based, and gels containing polycarbophil.

Other Therapies

In women with dyspareunia or vaginal dryness, other alternative therapies are increasingly being studied, particularly in cases where it is not possible to use other hormonal options. This is the case with local laser treatment, which is a good choice for BCS. In the three prospective observational studies of this review, which globally analysed 113 BCS women, the efficacy and safety of laser therapy were observed even when applied only once. Along with the use of DHEA, laser is one of the non-hormonal options that we highlight in this review. Unfortunately, we do not have enough RCTs to determine their effectiveness and safety, although some trials are already in progress.

Future Research

Nonetheless, our systematic review has identified some important areas for future research, particularly in laser-related areas, and several RCTs are underway. We expect that the results will contribute towards the development of an effective and safe alternative to treating dyspareunia. Larger double-blind studies should be conducted over a longer follow-up period to assess different treatment strategies for dyspareunia, and future research should also address the effectiveness and safety of dyspareunia interventions in BCS. In addition, there should be an extension of the intervention in order to monitor compliance for more than 3 months; this is important because the increase in major symptoms occurs between 1 and 3 months and relapses occur after discontinuation of use, similar to data in the general population [34].

Conclusions

Since improvements in both the diagnosis and treatment of BC mean that more women will become BCS, a significant proportion may have dyspareunia. In addition to the traditional options that have been analysed in other reviews, other interesting options have emerged (such as laser or local DHEA). High-quality trials with large numbers of samples are required to provide further evidence of dyspareunia or other dyspareunia treatments, particularly with regard to adequately identifying key methodological characteristics and harmful effects.

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Author Contributions

N. Mendoza and R. Carrión: conception and design of the study. N. Mendoza, R. Carrión, L. Mendoza-Huertas, and A.R. Jurado: data interpretation and preparation of the manuscript. All authors approved the final version of the manuscript.

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