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FEMALE SEXUAL DYSFUNCTION AND DISORDERS (T LORENZ AND R NAPPI, SECTION EDITORS)

Dyspareunia in Women: Updates in Mechanisms and Current/Novel Therapies

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Abstract

Purpose of Review Dyspareunia could influence negatively the sexuality of pre- and postmenopausal women. Genital pain can be cause for disturbing sexual desire. We conducted a review to describe interventions to address dyspareunia.

Recent Findings We reviewed 64 articles, based on studies concerning definitions of dyspareunia, genital sexual pain, different causes in pre/postmenopausal women, physical examination, management by age groups, and current/novel therapies. Evidence was drawn from systematic reviews of randomized controlled trials, clinical controlled studies, and case-control-studies, and from non-systematic reviews.

Summary All included studies showed a significant reduction of dyspareunia after specific treatment. Women who received hormonal or non-hormonal medication, or physical therapy, had a better quality of sexual life. Hormonal and physical therapies show faster efficacy than non-hormonal therapies. In addition, pharmacological, psychological, and sexological integrated therapies seem to be more effective than single treatments.

Keywords Dyspareunia · Endometriosis · Estrogen therapy · Female sexual disorders · Genital sexual pain · Genitourinary syndrome · Hormonal-non hormonal therapies · Ospemifene

Introduction

Sexuality is an essential component of human life with important effects on physical and psychological health as well as quality of life. Female sexual dysfunction, a general term including pain at intercourse and desire, arousal, or orgasm problems, is quite common. Female sexual dysfunction is influenced by numerous factors such as vaginal delivery, genital surgery, advanced age and hormonal changes, endocrine disorders, and psychiatric and psychological dysfunctions (depression, anxiety, distraction, negative body image, sexual abuse, and emotional neglect). Moreover, chronic diseases (vascular disease, diabetes mellitus, neurologic disease, and malignancy), common contextual or sociocultural factors (relationship discord, partner sexual dysfunction, life stage stressors, and cultural or religious messages that inhibit sexuality), and drug use could negatively influence sexuality [1•, 2].

The term "dyspareunia" (i.e., difficult or painful sexual intercourse) was coined by Barnes in 1874, who suggested that there were multiple physical pathologies that could cause such pain or interference with intercourse. Under the influence of the psychoanalytic movement during the twentieth century, dyspareunia returned to being considered a "hysterical" (that is, psychosomatic) symptom, but Barnes did not agree with only psychological interferences and may have paved the way for the DSM-III (American Psychiatric Association, 1980) to classify dyspareunia as a sexual problem. This classification was preserved by the DSM-III-R (American Psychiatric Association, 1987), which introduced the subcategory of "sexual pain disorder" and grouped dyspareunia with vaginismus in this subcategory. The conceptualization of dyspareunia

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as a sexual dysfunction with the attendant emphasis on interference with intercourse remains in the DSM-IV-TR (American Psychiatric Association, 2000) and exists in the ICD-10 (World Health Organization, 1992), where it is termed "nonorganic dyspareunia" including "pain and other conditions associated with female genital organs and menstrual cycle" [3]. Finally, the fifth edition of the DSM (DSM-V) fused dyspareunia with vaginismus into a single entry named genito-pelvic pain/penetration disorder [4].

Materials and Methods

We performed an international literature search of the principle electronic databases such as PubMed/MEDLINE, Scopus, and Cochrane Database of Systematic Reviews. Further systematic reviews were identified through searches in publications' reference lists and consultation with experts. We used terms including "Dyspareunia," "Genital pain in women," "Female sexual disorders," "Sexual dysfunction in women," "Treatment of dyspareunia." We considered articles published between 2010 and 2018 in English, finding 2300 items under "Dyspareunia," 1470 items under "Genital pain in women," 14,000 items under "Female sexual disorders," 3000 items under "Sexual dysfunction in women," and 1400 items under "Treatment of dyspareunia." We selected 64 articles, based on studies concerning definitions of dyspareunia, genital sexual pain, different causes in pre/postmenopausal women, physical examination, management by age groups, and current/novel therapies, through evidence from systematic reviews of randomized controlled trials, clinical controlled studies, and case-control-studies, and from non-systematic reviews.

Genito-Pelvic Pain/Penetration Disorder

"Genito-pelvic pain/penetration disorder (GPPD)" is a common distressing complaint in women of all ages that is under-recognized and under-treated [5, 6]. However, what does "pain" really mean? The International Association for the Study of Pain (IASP) defines pain as an uncomfortable feeling and emotional experience related to potential tissue damage. It is typically classified as either acute or chronic. Acute pain and its sudden onset is usually the result of a defined cause, and it resolves with the cure of this underlying cause. Chronic pain has gradually emerged as a distinct phenomenon that persists for a minimum of 6 months [7].

Current literature continues to refer to these problems as different conditions and with different terms; in the latest edition of the DSM, dyspareunia and vaginismus are identified as one entity, characterized by pain, anxiety, problems with penetration, or a combination of these, rather than as separate conditions and combines them in genito-pelvic pain/penetration disorder [3, 4].

Dyspareunia

Dyspareunia in women is defined as fear or anxiety, remarkable tensing of the abdominal and pelvic muscles, or pain caused by vaginal penetration, recurrent for at least 6 months. The prevalence of dyspareunia is approximately 10 to 20% in US women, with the leading causes varying by age group [8].

It may be classified as entry or deep. *Entry dyspareunia* is pain with initial or attempted penetration of the vaginal introitus (for low sexual arousal before penetration, genitourinary syndrome/vulvovaginal atrophy of menopause or provoked vestibulodynia), whereas *deep dyspareunia* is pain that occurs with deep vaginal penetration, caused by pelvic floor dysfunction, uterine position, endometriosis, genital infection, neurovascular diseases, and endocrine disorders.

Dyspareunia is also classified as *primary*, occurring with sexual debut and thereafter, or *secondary*, beginning after previous sexual activity that was not painful. Determining whether dyspareunia is entry or deep could point to specific causes, although the primary vs. secondary classification is less likely to narrow the differential diagnosis [8].

Dyspareunia may have a negative impact on a woman's mental and physical health, body image, relationships with partners, and efforts to conceive. It can lead to, or be associated with, other female sexual dysfunction disorders, including decreased libido, decreased arousal, and anorgasmia. Psychotherapy or sex therapy is useful for women who have relational or sociocultural factors contributing to their pain, and for those who experience anxiety in conjunction with their pain. Psychological, interpersonal, and sociocultural factors are most appropriately treated by a mental health subspecialist. Group cognitive behavior therapy and mindfulness-based interventions may be effective in treating several types of female sexual dysfunctions [8]. Significant risk factors and predictors for dyspareunia include younger age, education level below a college degree, urinary tract symptoms, poor to fair health, emotional problems or stress, and a decrease in household income greater than 20%.

Because dyspareunia can be distressing and emotional, the physician should first establish that the patient is ready to discuss the problem in depth. The history should be obtained in a nonjudgmental way, beginning with a general medical and surgical history before progressing to a gynecologic and obstetric history, followed by a comprehensive sexual history [9].

Causes of Superficial Dyspareunia in Premenopausal Women

Low Lubrication *Low lubrication* of the vagina, caused by a sexual arousal disorder (i.e., inability to maintain a lubrication during sexual excitement, due to dissatisfaction with current sexual relationships, negative body image, fear of pain during sex, history of sexual abuse, or religious restrictions about

sexuality) or chronic vaginal dryness, causes microtraumas and rubbing of vulvar and vaginal epithelium, and could provoke dyspareunia [10].

Chronic vaginal dryness can be due to hormonal (i.e., hypothalamic-pituitary dysfunction, premature ovarian failure), vascular (e.g., peripheral atherosclerosis, anemia), neurologic (e.g., diabetic neuropathy, spinal cord injury or surgery), or iatrogenic (e.g., hormonal contraceptive use, chemotherapy, radiation) disorders [9].

Puerperal Dyspareunia *Puerperal dyspareunia* is a common but overlooked disorder: Operative vaginal delivery, lacerations, perineal stretching, and episiotomy can result in fibrous scarring; moreover, during puerperium, a decreasing estrogen blood level occurs, which can lead to vaginal dryness and dyspareunia [9–11].

Causes of Deep Dyspareunia in Premenopausal Women

Endometriosis *Deep dyspareunia*, defined as painful intercourse with deep vaginal penetration, often conceals a very serious premenopausal chronic disease: *endometriosis*. It affects between 60 and 80% of patients undergoing surgery and between 50 and 90% of those using medical therapies. In women with endometriosis, deep dyspareunia is most severe before menstruation; it is usually positional, decreasing with changing coital position. Dyspareunia has been associated with the presence of deep endometriotic lesions of the uterosacral ligaments and the traction of scarred inelastic uterosacral ligaments during sexual intercourse or the pressure on endometriotic nodules imbedded in fibrotic tissue. More than 50% of women with endometriosis have suffered deep dyspareunia during their entire sex lives (primary deep dyspareunia) [9, 12, 13].

Pelvic Congestion Syndrome Pelvic venous syndromes, such as *pelvic congestion syndrome* (PCS), are poorly understood and frequently misdiagnosed disorders of the pelvic venous circulation.

PCS has been recognized as a potential cause of chronic pelvic pain (CPP), typically affecting young multiparous women. The cause is likely found in pelvic venous insufficiency (PVI), defined as incompetence of the ovarian vein or internal iliac vein and characterized by abnormal dilation in the interconnecting venous territories of these veins. Valvular insufficiency, venous obstruction, and hormones may all play a role in the development of this congestion [14, 15].

Interstitial Cystitis *Interstitial cystitis* is a severely debilitating disease of the urinary bladder, which is characterized by excessive urgency and frequency of urination, suprapubic pain, and CPP. Patients with interstitial cystitis can also suffer either deep dyspareunia, symptomatic flares, or both after sexual intercourse, which are caused by a direct irritation of the bladder during coitus [9, 13].

Uterine Myomas Despite the high prevalence of uterine myomas, few studies have investigated their impact on patients' quality of life and, in particular, on sexual function. The relationship between deep dyspareunia and uterine myomas was originally speculated in many case reports and reviews, suggesting that the enlarging uterus and myomas exert pressure on the surrounding adnexal structures and the cervix can become painful during intercourse [9, 13, 16].

Causes of Dyspareunia in Postmenopausal Women

Vaginal Atrophy/Genitourinary Syndrome of Menopause *Genitourinary syndrome of menopause* (GSM), previously known as atrophic vaginitis or vulvovaginal atrophy, affects more than half of postmenopausal women. In 2014, the International Society for the Study of Women's Sexual Health and the North American Menopause Society agreed that GSM is a more inclusive and accurate term to describe the conglomeration of external genital, urological, and sexual sequelae caused by hypoestrogenism during menopause. This clinical, common, chronic, under recognized, and undertreated condition is caused by low estrogen levels and occurs gradually during natural menopause but may be sudden if menopause occurs because of surgery, radiation, or chemotherapy [10, 17].

Manifestations of GSM are primarily divided into external genital and urological signs and symptoms. Common signs and symptoms, in order of prevalence, include vaginal dryness (in 75% postmenopausal women), dyspareunia (38%) and vaginal itching, discharge, and pain (15%). When the vulvovaginal epithelium has low lubrication, ulceration and fissures can develop during intercourse, causing dyspareunia. Vaginismus, or painful spasms of vaginal muscles, can also occur as a physiological response when there is anxiety towards expected sexual pain. Sexual manifestations are an extension of those of the external genitalia. The loss of estrogen is responsible for changes in vaginal microbial populations, including the reduction of Lactobacillus, changing the vaginal fluid to an alkaline pH of 5.0 or greater. The higher pH impairs the viability of healthy vaginal flora and promotes overgrowth of Gram-negative rod fecal flora including group B Streptococci, Staphylococci, and Diphtheroids, inducing vaginal and urinary tract infections and inflammation. Decreased levels of circulating estrogen and substantial vascularization are lost in the urogenital tract making the tissue atrophic. Estrogen deficiency causes loss in dermal collagen in the dense connective tissue of the vagina, bladder, and urethra and then causes the vaginal wall to become thinner and less elastic. Consequently, the vagina becomes shortened and narrowed that may lead to dyspareunia. The bladder and

urethra also become atrophic, causing urinary incontinence and frequency [18••, 19].

Although some women with mild GSM remain asymptomatic, many women report symptoms such as vaginal dryness, burning, irritation, decreased lubrication with sexual activity, and dyspareunia with resultant sexual dysfunction. For some women, symptoms can be severe enough to preclude penetrative sexual activity and to cause discomfort in non-sexual situations such as sitting or wiping [20, 21].

Examination

Physical Examination

Any physical examination should be gentle, methodical, and progressive to allow a precise etiological diagnosis; it should begin with a visual inspection of the external and internal structures. The mucosal surfaces should be inspected for areas of erythema or discoloration, which may indicate infection or dermatologic disease, such as lichen sclerosus or lichen planus; abrasions or other trauma indicate inadequate lubrication or forceful entry. Then, abdominal palpation searches for masses and scars and continues with the exploration of inguinal areas. Examination of the vulva should be a gentle but complete exploration of the labia majora, vestibule, vaginal opening, hymen, and low vagina. The swab test, touching the vestibular mucous membrane, can help with painful mapping. A lubricated speculum provides a complete examination of the vagina and cervix. Internal examination should be performed with a single finger to maximize the patient's comfort, to allow for palpation of the vagina, cervix, and urethral sidewalls searching for any painful areas. Palpation of the pelvic walls searches for trigger areas. Moreover, the clinical examination can evaluate the psychological experience of this symptom. In some women, fear or true phobia of penetration can be such that even the mere imagination of it is intolerable. Support therapy will also have to take this into account.

A physical examination in postmenopausal women can show scant pubic hair, loss of the labial fat pad, thinning and resorption of the labia minora, narrowing of the introitus, and increased vaginal pH. Internal examination findings include reduced vaginal caliber; smooth, shiny, pale mucosa with loss of folds, and a cervix flush with the vaginal vault. With inflammation, the vagina may appear erythematous, develop petechiae, and bleed easily. A pelvic examination can be helpful to exclude other vulvar and vaginal conditions that may present with symptoms similar to those of GSM, including irritant, infectious, or inflammatory vaginitis, dermatoses, and neoplasia.

Psychological Examination

The investigator must be patient and thorough and pay attention to characterize any site of pain (superficial, vulvar, vaginal, or deep), primary or secondary, intensity, repercussion on the reports, possibility of orgasm or not, evolutionary mode, possible psycho-sexual consequences and inadequate quality of sexual life, possible triggers (precise time report, sexual position, cycle period, stress), and associated urinary or digestive symptoms. The investigation must also focus on the antecedent sex life of the patient and on any experiences of sexual abuse. Dyspareunia can have a negative impact on a woman's mental and physical health, body image, relationships with partners, and efforts to conceive. Using a visual analogue pain scale and standardized questionnaires of sexuality addressing painful sexual symptoms and areas of quality of life can be a great help in investigation and in follow-up of the evolution of symptoms and effectiveness of a possible treatment, over time by objective quantitative data.

Additional Tests

Complementary examinations, such as an endovaginal/pelvic ultrasound or looking for pelvic, adnexal or uterine lesions, vaginal or urinary bacteriological, and cytological tests, can supplement clinical examination data. Pelvic MRI is indicated to search for endometriosis. Diagnostic laparoscopy is indicated for the search of deep endometriosis lesions when first- and second-line medical treatments failed [9, 10, 13, 16].

Moreover, electromyography (EMG) can be useful to provide insights into the mechanisms underlying pelvic floor muscle dysfunction (PFM) in women with dyspareunia. EMG is relatively simple to apply, and many commercial systems are available to clinicians and researchers; thus, EMG can be a useful clinical tool to evaluate PFM tone and function and could help to identify the specific mechanisms and the functional anatomy of the female pelvic floor associated with dyspareunia [22].

Treatments

Tables 1, 2, and 3 show, respectively, studies evaluating satisfaction with currently available vaginal, oral, and intrauterine therapies for treatment of dyspareunia.

Pharmacological Treatment

Estrogen Therapy Vaginal estrogen therapy (ET) is the standard treatment for many symptoms of GSM. It has proven to be successful in rapidly restoring vaginal epithelium and associated vasculature, improving vaginal secretions, lowering vaginal pH to restore healthy vaginal flora, and alleviating overall vulvovaginal symptoms. Though side effects are

Table 1 Studies evaluating satisfaction with currently available vaginal therapies for treatment of dyspareunia (literature data: 2008–2018)

Author, year	Study design	Study aims	Time	Sample	Sexual functioning measures
Caruso et al. [23•]	Case-control study	To evaluate sexual function and quality of life with an ultra-low concentration estriol vaginal gel (0.005%) in postmenopausal women	12 weeks	"68 postmenopausal women with GSM (53.4 ± 8.4 year) and 42 healthy controls (55.4 ± 8.3 year)"	Improvement of FSFI score and QoL; decreasement of FSDS score and VAS
Caruso et al. [24]	Randomized controlled trial	To evaluate the efficacy of low concentrations of vaginal estriol gel in postmenopausal women	12 weeks	"38 postmenopausal women with pelvic static disorders (60.3 ± 3.7 year) and 37 controls (59.5 ± 4.3 year)"	Improvement of FSFI score and QoL; decreasement of FSDS score and VAS
Archer et al. [25]	Randomized multicenter study	To examine the efficacy and safety of low-dose estradiol vaginal cream (0.003%) in postmenopausal women	12 weeks	"286 postmenopausal women with dyspareunia (59.5 ± 6.7 year) and 287 placebo controls (59.8 ± 6.1 year)"	Improvement of FSFI score, of QoL, of vaginal dryness; Decreasement of FSDS score, of VAS, of dyspareunia
Kroll et al. [26]	Randomized multicenter study	To evaluate efficacy and safety of a lower dose estradiol vaginal cream (0.003%) in postmenopausal women	12 weeks	277 postmenopausal women with dyspareunia (58.7 ± 6.4 year) and 273 placebo controls (58.6 ± 6.1 year)	Improvement of FSFI score, of QoL, of vaginal dryness; decreasement of FSDS score, of VAS, of dyspareunia
Labrie et al. [27]	Prospective, randomized, double-blind clinical study	To investigate the influence on moderate/severe pain at sexual activity of intravaginal prasterone (DHEA) in postmenopausal women	12 weeks	159 postmenopausal women with dyspareunia and 56 controls	Improvement of FSFI score, of QoL, of vaginal dryness, of desire arousal; decreasement of FSDS score, of VAS, of dyspareunia
Archer et al. [28]	Multicenter, randomized, double-blind clinical study	To confirm the local effects of intravaginal prasterone (3.25 mg, 6.5 mg) on moderate/severe dyspareunia in postmenopause	12 weeks	87 postmenopausal women (0.25% DHEA), 87 postmenopausal women (0.50% DHEA) and 81 placebo controls	Improvement of FSFI score, of QoL, of vaginal secretion and epithelial surface; decreasement of FSDS score, of VAS, of dyspareunia
Nappi et al. [29]	Multicenter, randomized, open-label study	To evaluate Monurelle Biogel® against vaginal dryness	8 weeks	48 women (55.8 ± 4.6 year) and 47 control group (56.5 ± 5.9 year)	Improvement of FSFI score, of QoL, of vaginal dryness; decreasement of FSDS score, of VAS, of dyspareunia

Table 2 Studies evaluating satisfaction with currently available *oral* therapies for treatment of dyspareunia (literature data: 2008–2018)

Author, year	Study design	Study aims	Time	Sample	Sexual functioning measures
Leonardo-Pinto et al. [30]	Prospective cohort study	To evaluate the effectiveness of dienogest 2 mg on endometriosis	12 months	30 women with diagnosis of deep infiltrating endometriosis	"Improvement of FSFI score, of QoL, of vaginal dryness; decreasement of FSDS score, of VAS, of dyspareunia, of dysmenorrhea and pelvic pain"
Maiorana et al. [31]	Observational, single-center, cohort study	To evaluate the effectiveness of dienogest 2 mg on endometriosis	1 month	132 women with diagnosis of endometriosis (33.6 ± 7.7 year)	Improvement of FSFI score, of QoL, of vaginal dryness; decreasement of FSDS score, of VAS, of dyspareunia, of dysmenorrhea and pelvic pain
Nappi et al. [32]	Multicenter study	To explore effects of ospemifene 60 mg on vaginal atrophy in postmenopausal women	12 weeks	1021 postmenopausal women and 724 placebo controls	Improvement of FSFI score, of QoL, of vaginal dryness; decreasement of FSDS score, of VAS, of dyspareunia
Goldstein et al. [33]	Prospective, open-label, pilot study	To examine changes to the vulva and vaginal region in menopausal women treated with ospemifene 60 mg	20 weeks	8 menopausal women (59 ± 4.7 year)	Improvement of FSFI score, of QoL, of vaginal dryness; decreasement of FSDS score, of VAS, of dyspareunia
Caruso et al. [34]	Prospective, observational study	To evaluate the effects of nutraceuticals containing equol (one table) on quality of life and sexual functions in perimenopausal women	6 months	72 perimenopausal women (52.4 ± 3.1 year)	Improvement of FSFI score and QoL; decreasement of FSDS score and VAS
Villa et al. [35]	Pilot, randomized study	To assess the efficacy of a nutraceutical supplement on symptoms in menopause	6 months	48 women (49.3 ± 3.9 year) and 27 controls (49.2 ± 2.3 year)	Improvement of FSFI score and QoL; decreasement of FSDS score and VAS
Caruso et al. [36]	Non-randomized trial	To evaluate the effects of nutraceuticals containing equol (one table) on vaginal health in postmenopausal women	8 months	72 postmenopausal women and 54 controls (51.3 ± 3.1 year)	Improvement of FSFI score, of QoL, of vaginal dryness, of desire arousal; decreasement of FSDS score, of VAS, of dyspareunia
Roghaei et al. [37]	Randomized, clinical trial	To compare the effects of danazolo with letrozole on endometriosis symptom relief	6 months	"38 women (letrozolo group), 37 women (danazolo group), 31 placebo controls"	Letrozolo more effective than danazolo in decreasement of FSDS score, of VAS, of dyspareunia, of dysmenorrhea and pelvic pain

Table 3 Studies evaluating satisfaction with currently available intrauterine therapies for treatment of dyspareunia (literature data: 2008–2018)

Author, year	Study design	Study aims	Time	Sample	Sexual functioning measures
Neri et al. [38]	Observational study	To evaluate improvement on QoL and sexuality during treatment with Jaydesse®	12 months	31 premenopausal women	Improvement of FSFI score and QoL; decreasement of FSDS score and VAS
Caruso et al. [39]	Prospective, controlled study	To investigate the impact of LNG-IUS (13.5 mg) on sexual function and QoL	12 months	62 women (26 ± 5 year) and 66 controls (25 ± 5 year)	Improvement of FSFI score and QoL; decreasement of FSDS score and VAS
Yucel et al. [40]	Prospective, cross-sectional, non-comparative study	To investigate the effectiveness of LNG-IUS in the relief of pain in women with endometriosis	12 months	45 women (36.77 ± 6.51 year)	Improvement of FSFI score, of QoL, of vaginal dryness; decreasement of FSDS score, of VAS, of dyspareunia, of dysmenorrhea, pelvic pain, size of endometriomas and CA-125

uncommon, systemic ET is associated with breast tenderness and/or enlargement, vaginal bleeding or spotting, nausea, and modest weight gain. When used concomitantly with progestin in women with a uterus, systemic estrogenic hormone therapies (HT) are associated with adverse effects such as endometrial bleeding, breast tenderness, increased risk of stroke, venous thromboembolism, and breast cancer in some subgroups of women [9, 41, 42].

Nowadays, low-dose vaginal/topic ET is the preferred pharmacological treatment. With low-dose topic estrogen therapy, systemic estrogen absorption is minimal and serum estradiol levels remain in the postmenopausal range. Multiple US Food and Drug Administration (FDA)-approved vaginal estrogen products with similar efficacy are available, and the choice is determined predominantly by patient preference [21, 23•, 24] (Table 1).

Estrogen creams or gels provide a soothing and moisturizing effect, but some patients find them messy and dislike the reusable applicators. A recent study demonstrated that a very low-dose estradiol vaginal cream (0.003%) [28, 29] or estriol vaginal gel (0.005%) [26, 27] met all three co-primary endpoints in postmenopausal women with GSM; it was efficacious in reducing the severity of vaginal dryness, decreasing vaginal pH, and improving the percentage of superficial cells while reducing parabasal cells on vaginal smears from baseline to final assessment when compared with placebo. The results also demonstrate that local low-dose delivery of estrogen directly to the vagina, even at 15 lg/dose, is a highly effective mode of treatment for postmenopausal women experiencing GSM-associated vaginal dryness. The advantage of this approach is the lack of appreciable increase in systemic estrogen exposure.

Vaginal estradiol tablets (10-mg dose) may be preferred in situations requiring more controlled dosing of vaginal ET. With creams and tablets, women may use daily dosing for the first 2 weeks followed by twice-weekly maintenance dosing. Ideally, women should be treated with the lowest dose and frequency of vaginal ET that effectively manages their symptoms [25, 26, 43, 44].

Sustained-release estradiol vaginal rings, which can be inserted and removed by patients, are effective for 90 days. The ring is especially useful for women who prefer not to use a vaginal estrogen product every few days.

Progestins Several pilot studies demonstrated that, after treatment with progestins, especially with *dienogest*, there was a significant decrease of genital sexual pain, dysmenorrhea, and premenstrual pelvic pain in women affected by deep dyspareunia due to endometriosis [12]. Precisely, *dienogest* 2 mg/daily inhibits the proliferation of the endometriotic stromal cells by reducing inflammatory cytokines. Including women with a diagnosis of deep endometriosis, treated with *dienogest*, these studies showed that this progestin is an

appropriate alternative to the clinical management of the main endometriotic symptoms, with pain, QoL, and sexual function score improvements, regardless of the change in volume of the lesions, thus avoiding surgical procedures of high complexity in all women studied.

Side effects associated with these drugs are frequent but seldom cause therapy abandonment. The main issue is erratic bleeding, which usually causes temporary pelvic pain relapse [30, 31, 45••] (Table 2).

Selective Estrogen Receptor Modulators Selective estrogen receptor modulators (SERMs) are synthetic nonsteroidal agents that exert variable mixed estrogen agonist and antagonist effects on target tissues. Of the currently available SERMs, the US Food and Drug Administration (FDA) approved in 2013 only *Ospemifene* for treatment of moderate to severe dyspareunia caused by GSM in menopausal women [46–48]. *Ospemifene*, when given orally at a dose of 60 mg daily, exerts estrogenic effects on vulvovaginal tissues and results in acidic vaginal pH and improvements in the vaginal maturation index and dyspareunia. Although ospemifene does not appear to stimulate breast tissue, its safety in women with or at high risk for breast cancer has yet to be established. Similar to estrogen therapy, *Ospemifene* increases the incidence of thromboembolism and should be avoided in patients with increased risk of venous thromboembolism. *Ospemifene* could be an option for the management of dyspareunia in postmenopausal women and may be particularly appealing for those who are unwilling or unable to use low-dose vaginal estrogen [21, 32, 49, 50, 51••, 52]. Moreover, a recent study showed improvement of the quality of the androgenic genitourinary tract tissues, mainly in the vulva, vestibule, urethral meatus, and vagina [33].

Vaginal Dehydroepiandrosterone *Dehydroepiandrosterone* (DHEA) is a steroid prohormone in the biosynthetic pathway of testosterone and estradiol. Short-term clinical trials with daily use of vaginal *DHEA* have found improvements in dyspareunia, vaginal pH, and the vaginal maturation index [19]. Vaginal *DHEA* is thought to exert its effect by local conversion to testosterone and estradiol; it has not been found to increase systemic steroid hormone levels, presumably because of local inactivation [27]. Therefore, it may be a safer alternative to vaginal ET in patients with contraindications to estrogen use (e.g., breast cancer survivors). Additionally, with the lack of the aromatase enzyme in the endometrium, vaginal *DHEA* is not converted to estradiol in the endometrium and does not exert any endometrial proliferative effects [28, 53].

Nutraceuticals Isoflavones can reduce menopausal symptoms in women. *Equol*, a nonhormonal estrogen receptor β-agonist, is a metabolite of the soy isoflavone daidzein with interindividual differences in its production by intestinal bacteria, such as lactic acid bacteria Lactococcus; in fact, only 30 to 50% of individuals can convert dietary daidzein to *Equol*. A recent study first evaluated the estrogenic activity of *Equol* on vaginal health in postmenopausal women. Women had an improvement of sexual coital pain after 8 months of nutraceutical intake, and this correlated positively with vaginal symptom improvement [34].

Nutraceuticals containing *Equol* could be effective in modulating postmenopausal symptoms, particularly vaginal symptoms, and could be well accepted by those women who usually do not wish to use hormone therapy or cannot use it for medical reasons [35, 36].

Progestogen Intrauterine Devices Levonorgestrel-releasing intrauterine devices reduce the intensity of deep dyspareunia with limited side effects [13].

A recent study investigated the effectiveness of a levonorgestrel-releasing intrauterine device (LNG-IUS) in the symptomatic relief of pain in women with endometriosis and additionally, to assess the changes in women's quality of life and serum cancer antigen (CA) 125 levels. All women who had an LNG-IUS inserted for the treatment of dysmenorrhea, CPP, or both for more than 6 months over a 2-year period were included in the study. Each woman was asked to complete questionnaires of the Short Form and visual analogue scales (VAS) at the first examination and the third, sixth, ninth, and twelfth months after LNG-IUS insertion. Several favorable outcomes were found following LNG-IUS insertion: (1) dyspareunia and dysmenorrhea were clearly reduced; (2) the size of endometriomas was decreased; (3) CA 125 levels significantly decreased; and (4) a few women experienced the typical systemic adverse effects of progestogens; however, LNG-IUS-related adverse events were generally tolerable and the discontinuation rate was low [38–40] (Table 3).

Aromatase Inhibitors More recently, aromatase inhibitors have been proposed for the treatment of endometriosis. In an open-label prospective study the efficacy of letrozole (2.5 mg/day) combined with norethisterone acetate (2.5 mg/day) was evaluated in the treatment of pain symptoms related to the presence of rectovaginal endometriosis. This combined treatment significantly reduced the severity of deep dyspareunia; however, pain recurred after the interruption of treatment. These findings were confirmed in another study combining letrozole with the desogestrel-only contraceptive pill [37, 54].

Non-hormonal Lubricants and Moisturizers Lubricants and moisturizers are used for sexual comfort and pleasure; they provide short-term relief of vaginal dryness and discomfort during sexual activity [29, 55]. They may be

water, silicone, or oil based. These therapy options do not reverse most vaginal atrophic effects and are effective for less than 24 h. Hence, they are more useful for women with mild to moderate vaginal dryness or should be used in conjunction with systemic or topical ET [5, 10].

Physical Treatments

Surgery Surgical laparoscopic excision of deep endometriotic nodules (including those in the rectovaginal septum and the bowel) has been shown to produce a significant improvement in deep dyspareunia in retrospective studies, in prospective studies, and in a randomized placebo-controlled trial.

Radical surgery (such as hysterectomy with or without bilateral oophorectomy) has been used in the past for treating pain symptoms due to venous congestion that failed to respond to medical treatment, but modern trans-catheter embolization has revolutionized the treatment of pelvic congestion syndrome [13, 14, 19].

Laser Therapy Recently, intravaginal laser therapy has been proposed for the treatment of GSM and/or urinary incontinence. In 2014, the Food and Drug Administration approved the use of two laser technologies, microablative fractional CO_2 laser (CO_2 laser), and non-ablative photothermal Erbium:YAG-laser (Er:YAG-laser) in postmenopausal women for genitourinary surgery. The International Continence Society refers to dyspareunia as one of several clinical sequelae of "high-tone pelvic floor dysfunction," in which symptoms can also manifest as muscle pain in the groin, lower back, or gluteal regions, urinary or bowel dysfunction, and/or elimination difficulties [56].

At specific diode parameters, laser therapy stimulates improved vascularity, improved glycogen storage, collagen and extracellular matrix production, and cellular proliferation to increase the thickness of the squamous epithelium with the formation of new papilla, thus enhancing the viability of the vaginal epithelium. Sexual function and overall sexual satisfaction of women, vaginal health, and maturation of vaginal epithelium increased significantly in all relevant studies. Specifically, there was increase of the vaginal epithelium thickness as well as improvement in vascularization and angiogenesis penetrating the new papillary formation. Fibroblast number and synthesis of fibrillar components of extracellular matrix were also increased. Additionally, the histopathological study evaluating the CO_2 laser effect reported elevated levels of glycogen, stored in large epithelial cells and augmented exfoliation of superficial epithelial cells. The vaginal microenvironment changed, with significant improvement of normal vaginal flora, increase of lactobacilli, and decrease of *E. coli* and Mobiluncus [57•, 58].

Psychological Treatment

Psychotherapy or sex therapy could be useful [9, 59]. A multimodal pain-driven management model is recommended, although treatment in the literature is still sparse. Treatment aims should be decided upon collaboratively and may extend beyond pain relief. Psychotherapy can be used to target specific cognitive, emotional, relational, and behavioral goals related to the experience of chronic pain. It is of benefit as it is noninvasive and does not cause unwanted side effects. Psychotherapy is recommended if patients report unwanted cognitions or behaviors, and have a difficult time emotionally and/or experience sexual and relationship difficulties. Therefore, when patients spontaneously report "unwanted cognitions," then the clinician must best adapt the treatment.

The practice of mindfulness-based cognitive therapy has also garnered attention in the treatment of dyspareunia. Techniques that help patients remain in the moment and find ways to tolerate and accept their pain have been growing in popularity. Such approaches also assist patients to become more attuned to the factors that increase or decrease their pain and encourage them to attend to positive events in their life and relationship [58, 59]. Finally, some patients would greatly benefit from sex or couples therapy. Ideally, the therapy would target the pain in a collaborative manner. Such a practice could involve improving communication, reducing feelings of guilt or shame and building positive sexual encounters while managing pain. Partners can be instructed in assisting with mindfulness or distraction to cope with the pain. Elements of a couple's therapy could be incorporated into individual therapy if the patient does not wish to have her partner present at every session. Addressing dyadic factors early in the management course of entry dyspareunia may improve the success of therapeutic interventions. In fact, in the case in which the partner of a woman with genital pain avoids sexual activity/intercourse for fear of provoking dyspareunia, he often does nothing but worsen the symptom; in fact, the woman could increase her expectations about future pain [60].

It is optimal to offer pharmacotherapy antidepressants and anticonvulsants in concert with psychotherapy. If a patient has a comorbid mood and/or anxiety disorder, the administration of appropriate medication may assist in reducing symptoms of those disorders, which might in turn improve a patient's pain experience [59, 61–64].

Conclusion

Dyspareunia is not a simple term to indicate a simple dysfunction. It may include several biological,

psychological, and dyadic disorders. Consequently, diagnostic procedures, as well as treatments, could be complex. Today, clinicians have the opportunity to adopt drugs to modulate the biological disorders in pre- and postmenopausal women. From a multifactorial point of view, either diagnostic or therapeutic integrated procedures for dyspareunia have to be used. In fact, the current and novel therapies for dyspareunia need to use not only a drug but at the same time a specific sexual therapy. Therefore, clinicians have to emphasize the concept that all women are different, and the concept of tailoring a treatment to a particular woman has to be adopted. Thus, the first step in prescribing a therapy to a woman with dyspareunia is to understand the needs of the patient.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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