

ภาวะความเจ็บปวดขณะร่วมเพศของสตรี

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Received: July 18, 2021

Revised: December 14, 2021

Accepted: June 27, 2022

บทคัดย่อ

ภาวะความเจ็บปวดขณะร่วมเพศของสตรี ตามนิยามของ Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) หมายถึง กลุ่มโรคที่มีความบกพร่องในการตอบสนองทางเพศหรือการมีความสุขทางเพศ นอกจากนี้ ตามนิยามของ International Classification of Diseases and Related Health Problem (ICD-10) ยังหมายถึง การที่บุคคลไม่สามารถมีความสัมพันธ์ทางเพศได้ตามที่ตนคาดหวังไว้ อันเป็นผลมาจากปัจจัยทางด้านจิตใจ สรีรวิทยา หรือทั้งสองปัจจัยร่วมกัน นอกจากนี้ ยังอาจเกี่ยวข้องกับปัจจัยอื่นๆ เช่น ปัญหาด้านความสัมพันธ์ระหว่างบุคคล ปัจจัยทางด้านสังคมวัฒนธรรม เป็นต้น ความผิดปกตินี้อาจเกิดต่อเนื่องตลอดชีวิต หรือเกิดขึ้นภายหลัง หรือเกิดขึ้นในทุกสถานการณ์ของกิจกรรมทางเพศ หรือจำเพาะเจาะจงกับบางสถานการณ์ก็ได้ ทั้งนี้การที่จะวินิจฉัยโรคในกลุ่ม sexual dysfunctions ได้นั้น อาการดังกล่าวต้องไม่ใช่อาการแสดงของโรคจิตเวชอื่นๆ เช่น โรคอารมณ์แปรปรวน โรควิตกกังวล โรคจิต เป็นต้น ต้องไม่เป็นผลโดยตรงจากยาหรือสารเสพติด ไม่ได้เป็นผลมาจากสาเหตุทางร่างกายอื่นๆ เช่น ปลายประสาทอักเสบ และไม่ได้เป็นผลจากปัญหาด้านความสัมพันธ์ที่รุนแรง ปัญหาความรุนแรงที่เกิดจากคู่นอน เช่น การทำร้ายร่างกาย หรือจากปัจจัยที่กระตุ้นให้เกิดความเครียดอย่างชัดเจน

คำสำคัญ: เพศหญิง ความเจ็บปวดขณะร่วมเพศ ความสัมพันธ์ทางเพศ

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Female sexual pain disorder

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Abstract

Female sexual pain disorder, as defined in the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a group of diseases characterized by impairments in sexual responsiveness or pleasure. In addition, according to the definition of the International Classification of Diseases and Related Health Problem (ICD-10) also refers to a person's inability to have a sexual relationship as expected, as a result of psychological and physiological factors, or a combination of both. It may also be related to other aspects, such as interpersonal issues, socio-cultural factors, etc. The disorder can be lifelong or acquired and may occur in all situations related to sexual activity (generalized) or specific to certain situations. In order to diagnose sexual dysfunctions, it must excluded the following events such as a symptom of other psychotic disorders, such as mood disorders, anxiety disorders, etc.; a direct consequence of drugs or other addictive substances; the result of other physical causes, such as peripheral neuropathy; and the result of a serious relationship problem, like sexual partner violence, physical abuse or other factors that clearly provoke stress.

Keywords: female, sexual pain, sexual relationship

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Introduction

Female sexual pain disorder, or genito-pelvic pain/penetration disorder (previously known as dyspareunia), is defined as persistent or recurrent symptoms with one or more of the following for at least 6 months: marked vulvovaginal or pelvic pain during penetrative intercourse or penetration attempts, marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during or as a result of penetration, and marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.¹

In the last 2 decades, there has been increased interest in the management of female sexual dysfunction, including sexual pain disorders, in the field of urology. Due to their complexity, sexual pain disorders are still largely misunderstood and often undertreated. The estimated prevalence in the United States varies between 3% and 25%, with causes differing by age group.^{2,3} Genito-pelvic pain/penetration disorder is frequently multifactorial and requires a multidisciplinary approach that includes biological, psychological, sociocultural and relational factors. Psychological factors that may contribute to dyspareunia include anxiety or guilt about intercourse, memories of distressing early sexual experiences, fear of penetration, unresolved anger, feelings of shame or guilt, and inadequate precoital stimulation.⁴

DSM-5 diagnostic criteria for Genito-pelvic pain/penetration disorder⁴¹ :

Criterion A: Persistent or recurrent difficulties with one or more of the following:

1. Difficulties in vaginal penetration during intercourse
2. Marked vulvovaginal or pelvic pain as a result of vaginal penetration
3. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during or as a result of vaginal penetration.
4. Marked tensing or tightening of the pelvic floor muscle during attempt vaginal penetration

Criterion B: the symptoms in criterion A have persisted for a minimum duration of approximately 6 months

Criterion C: the symptoms in criterion A cause clinically significant in the individual

Criterion D: the sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g. partner violence) or other significance stressors and is not attributable to the effects of a substance/medication or another medical condition

Common causes of Genito-pelvic pain/penetration disorder found in the urological setting include:

- Genitourinary syndrome of menopause (GSM)
- Vestibulodynia
- Urinary tract infections
- Interstitial cystitis
- Erosion of implantable mesh
- Tissue damage from radiation
- Pelvic organ prolapse
- Urethral abscesses/vaginal cysts
- Pelvic floor dysfunction
- Sexually transmitted diseases

Nonurological causes of GPPPD include:

- Irritable bowel syndrome
- Fibromyalgia
- Endometriosis
- Vaginitis/vulvovaginitis
- Vulvar dermatoses
- Childbirth

Anatomy

An understanding of female genital anatomy is essential in order to provide comprehensive evaluation and optimize treatment outcomes for women with sexual concerns. Female sexual organs include the clitoris (glans and crura), labia majora and minora, vulvar vestibule, vagina, cervix, vestibular bulbs and the pelvic floor muscles.

Vulva: The vulva is a complicated anatomical structure intricately involved in the female sexual response cycle. It is the

homologue of the male genital anatomy. It includes the mons pubis, labia majora, labia minora, vestibule and clitoris.

Vestibule: The vulvar vestibule is located between the labia minora and the hymen. This tissue is embryologically endoderm and mediated by testosterone. The medial border is the hymen and the lateral border, called Hart's line, is located inside the labia minora. The vestibule contains the external urethral meatus and the openings of the 2 greater vestibular Bartholin's and perivestibular/Skene's glands, which are analogous to the Cowper's glands and glands of Littre in the male.⁵ The vestibule is an area of significance in patients presenting with vulvar pain and GPPPD. The vulvar vestibule can become painful due to changes in hormones, inflammation or muscle hypertonicity (figure 1).

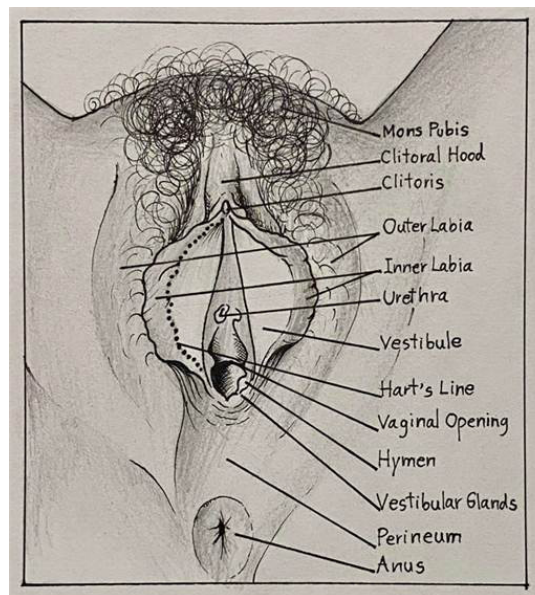


Figure 1 Vulva anatomy (photography by Krittin Naravejsakul).

Clitoris: The clitoris is composed of large dilated vascular spaces that engorge with blood during arousal. It is the female homologue of the male penis and includes a prepuce, glans, corona, bilateral corpora cavernosa and crura. The glans clitoris is the component of the clitoris that is visible but often covered by a “hood” of preputial skin, particularly in the unaroused state. This prepuce can develop phimosis and/or balanitis, which can contribute to clitoral pain (clitorodynia) and/or anorgasmia.⁶

Vagina: The vagina is an elastic, muscular canal that extends from the vulva to the cervix. It serves a multitude of functions in response to hormonal changes and plays a vital role in the female reproductive system and female sexual pleasure. The vaginal mucosa contains a high concentration of estrogen and androgen receptors.⁷ Estrogen modulates blood flow and lubrication by causing nitrous oxide release, which increases the capillary blood flow. This increased blood flow creates vasocongestion within the vaginal submucosa, increasing oncotic pressure, which leads to production of a fluid transudate (lubrication) that passes into the vaginal lumen via aquaporins located in the vaginal mucosa.^{8,9}

Pelvic floor: The female pelvic floor muscles support the bladder, uterus and colon and play a vital role in sexual function as well as bladder and bowel control. A clock face is used as a reference when describing the location of the pelvic structures. The 12 o'clock and 6 o'clock positions correspond to the anterior and posterior midline,

or pubic symphysis and anus, respectively.¹⁰ The obturator internus and externus can be palpated by sweeping from the pubic ramus downward along the muscle belly behind the pubic ramus at 1 and 11 o'clock. At 3 and 9 o'clock, the levator ani complex is present, and at 5 and 7 o'clock, the iliococcygeus muscle (distal) is palpable. Approximately a finger's length depth into the vagina, at around 4 and 8 o'clock, the ischial spines are palpated as bony prominences. The ischial spines serve as the anatomical marker for the pudendal nerve, which runs approximately 2 cm posteromedial to the ischial spine and innervates the clitoris, vulva and anus.¹¹

Autonomic nervous system: The female sexual response is dependent on the coordinated activity of parasympathetic, sympathetic and somatic innervation. The parasympathetic nervous system promotes vasodilation, leading to increased vaginal lubrication and clitoral engorgement. The sympathetic nervous system causes rhythmic smooth muscle contractions of the vagina during orgasm. The somatic nervous system, via the pudendal nerve, controls sensation and contractions of the somatic pelvic muscles that accompany orgasm.¹²

Hormonal: Estradiol is the primary “female” sex steroid and acts by binding to the estrogen receptor.^{13,14} Estrogens maintain female genital tissue integrity and thickness. Peak estradiol levels occur at the midpoint of the menstrual cycle and are associated with maximal vaginal mucosal thickness and glycogen content. Androgens (ie Dehydroepiandrosterone-DHEA,

androstenedione, testosterone) are necessary precursors for the biosynthesis of estrogens and have an important role in the physiology and homeostasis of the vagina.¹⁵ Androgen receptors are widespread throughout the genitourinary tract and independently regulate vaginal health such as vaginal and vestibular lubrication, smooth muscle activity and blood flow. Their production is significantly greater than that of estrogens in premenopausal women.¹⁶ Thus, decreased levels of androgens during menopause are also thought to be contributory to GSM.^{16,17}

Pathophysiology

Genitourinary syndrome of menopause. GSM, previously vulvovaginal atrophy/atrophic vaginitis, is characterized by genital symptoms (eg dryness, burning, irritation), sexual symptoms (eg lack of lubrication, discomfort or pain, decreased libido, difficulty with arousal and orgasm) and urinary symptoms (eg urgency, dysuria, recurrent urinary tract infections). GSM can also occur in hormone-depleted states, including breastfeeding, oral contraceptive use, adjuvant hormonal deprivation therapy for breast cancer treatment, gender-confirming hormone therapy, thyroid disorders and pituitary tumors.¹⁸⁻²⁰ As estrogen and androgens decline, blood flow to the vagina and vulva also decreases, which leads to impaired vaginal lubrication, vaginal burning, dryness, irritation and an increased pH.²¹ Impaired lubrication can affect sexual function and cause pain with intercourse (figure 2).

Vestibulodynia (VD), previously known as vulvar vestibulitis syndrome: It is defined as vestibule pain lasting more than 3 months, unrelated to infection, skin disorders or other identifiable factors. It is characterized by burning, stinging, itching or rawness. The most common factors associated with VD are hormonal changes (hormonally mediated), hypertonic pelvic floor dysfunction and an increased number of nerve endings in the mucosa of the vestibule (neuroproliferative VD).²²

Clitorodynia: It is a form of vulvodynia localized to the clitoris. It is characterized by frequent and intense pain episodes that can be provoked or unprovoked and can cause significant impairment in both daily and sexual function. It may be associated with other chronic pain disorders, lichen sclerosus, multiple sclerosis, pelvic surgery and vaginal delivery.²³ Physical examination may show clitoral adhesions, phimosis, balanitis or skin changes associated with lichen sclerosus.

Pelvic floor dysfunction: It refers to the constellation of symptoms secondary to the non-relaxing pelvic floor musculature. Pelvic floor dysfunction presentation depends on the particular muscles in spasm. Manifestations include dyspareunia, voiding dysfunction, incontinence, urinary retention, constipation and dyschezia.



Figure 2 Patient with genitourinary syndrome of menopause. (A) Note 50% resorbed and thin labia minora. (B) Note protruding urethra, pallor and erythema of vestibule. Vaginal pH is 7.5, while goal should be 4.5.

History and physical examination

Due to the sensitive nature of the topic, providers must be able to discuss the subject matter assuredly while making patients feel comfortable and safe. The most important goal during the introductory discussion is to provide validation of the patient's pain, which will aid in establishing rapport and trust between the patient and provider. This is best done with the patient fully dressed and ideally not in an examination room. A comprehensive history should then be performed using openended questions, affirming statements and reflective listening.

Using generalizing statements is a helpful tool to engage the patient, such as, "Many women with (a specified condition) experience (a specific or generalized issue with sex). Do you experience this?". The use of validated self-reported questionnaires, such as the Female Sexual Function Index, McGill Pain Questionnaire and the Patient Reported Outcomes Measurement Information System

(PROMIS)[®] vulvar discomfort scale, can also provide objective information when quantifying pain and its impact on the patient's life.

A focused sexual history should review the following:

- 1) Pain characteristics (location, duration, exacerbating factors, alleviating factors)
- 2) Associated symptoms such as bowel, bladder or musculoskeletal symptoms
- 3) Sexual activity and behavior
- 4) Medical history
- 5) Surgical history
- 6) Medication history (use of hormonal birth control, selective serotonin reuptake inhibitors etc)
- 7) Mental health history
- 8) Obstetrical and gynecologic history, including onset of menstruation, characteristics of periods and onset of menopause
- 9) History of physical or sexual abuse
- 10) Previous interventions

Physical examination: Many objective findings on physical examination can be seen in a patient with sexual complaints, and a full vulvar and vaginal examination will aid in finding the proper treatment for the patient. Important anatomy to assess includes:

- Labia majora and minora
- Clitoris, including glans and hood
- Urethra and periurethral glands
- Vestibule
- Vaginal vault
- Cervix
- Pelvic floor levator ani muscles

Important factors to evaluate in the focused genital examination include:

- Distribution of hair
- Symmetry and size of genital tissues
- Evidence of atrophy or stenosis
- Areas of provoked pain
- Color uniformity, erythema or other discoloration
- Visible lesions, excoriations or scars
- Pelvic organ prolapse
- Pelvic floor muscle tone and voluntary control
- Presence of vaginal discharge
- Presence or absence of vaginal rugae

It is advantageous for patients to visualize their anatomy with either a vulvoscope or a mirror as this empowers them to better understand and feel comfortable with their anatomy. Begin the physical examination by describing and explaining the specific actions during each step and discussing the examination findings with the patient. The examination

should include an external and internal musculoskeletal evaluation, external visual and sensory examination, and a bimanual examination if tolerated by the patient. The external musculoskeletal examination should include evaluation of posture/gait, taking note of any asymmetry and/or pain, palpation of abdominal, gluteal, back and lower extremity muscles, identifying areas of tension and/or pain, and an assessment of muscle strength, range of motion, sensation and reflexes.

Next, a systematic examination of the vulva is performed by inspecting the external genitalia, perineum, perianal areas and the mons pubis. The clinician should evaluate signs of infection, trauma, atrophy, fissures and dermatological changes. A cotton swab can be used to assess for vulvar allodynia and/or hyperalgesia by light palpation, which is suggestive of neuropathy. Next the vestibule should be examined. Physical findings to note include hyperemia or erythema, and periurethral and perivaginal glands. A cotton swab test should be performed by palpating the vestibule in 7 anatomical sites (12 o'clock, 1 o'clock, 3 o'clock, 5 o'clock, 7 o'clock, 9 o'clock and 11 o'clock).

The internal muscle examination should start with light palpation for general tone, then deeper pressure to assess for trigger points, which are hallmark diagnostic indicators of pelvic floor dysfunction. Using the index finger, the examiner can palpate the lateral, anterior and posterior walls of the vagina, the urethra and pelvic floor muscles, assessing for tone, tenderness or involuntary contractions.

Clinical criteria that indicate presence of a trigger point include

- 1) a palpable taut band
- 2) an extremely tender nodule in the taut band
- 3) the ability to reproduce the pain with palpation of the tender nodule and
- 4) painful limit to stretch or full range of motion.²⁴

If pain or hypertonic muscles are noted, consider pelvic floor physical therapy referral. If the patient can tolerate the single digit examination, a bimanual examination should be performed to evaluate the uterus and adnexa for any masses or tenderness. Next, the provider should proceed to an internal examination using a warmed, small-sized Graves or Pederson speculum. Slow insertion of the speculum while avoiding the urethra or vestibule is important to ensure patient comfort as this can elicit pain. This portion of the examination should be performed by providers who are trained and skilled in performing an internal vaginal examination. During the speculum examination, the internal vaginal tissue, cervix and vaginal secretions are evaluated. Cultures or biopsies can be collected at this time to rule out infections, dermatoses or abnormal cellular dysplasia that can cause dyspareunia or vulvodynia.

Treatment

Female sexual pain disorders are classified as genito-pelvic pain/penetration disorder (GPPPD) in the Diagnostic and

Statistical Manual of Mental Disorders 5th edition⁴¹. By definition, GPPPD consists of persistent or recurring difficulties within one or more of four of the following often interrelated symptom dimensions:

1. Difficulty having vaginal intercourse or penetration
2. Genito-pelvic pain
3. Fear of pain or vaginal penetration
4. Tension of pelvic floor muscles

Symptoms must not be explained by another “non-sexual” mental disorder or serious relationship dysfunction and should cause significant distress for a minimum of 6 months⁴¹. Difficult vaginal penetration ranges from situations involving sexual contact (intercourse or other vaginal penetration) to difficulty placing tampons or undergoing a gynecologic examination. Genito-pelvic pain is characterized by pain during vaginal penetration. The location of the pain can be superficial (vulvovaginal) and/or deep (vaginal canal or pelvic); provoked (by genital contact) and/or spontaneous. Marked fear or anxiety about vulvovaginal or pelvic pain either in anticipation of, during, or as a result of vaginal penetration can result from myriad physical, psychosocial, cultural, and religious factors⁴². Pronounced tensing or involuntary tightening of the pelvic floor muscles during attempted vaginal penetration can follow experiences of pain, fear, or anxiety or develop without obvious reason.

This article reviews evidence based therapeutic interventions and expert opinion for the management of female sexual pain

disorders. Treatment of Genitourinary syndrome of menopause, vulvodynia, vaginismus, and other specific disorders causing superficial vulvovaginal pain or deep/pelvic pain with sexual activity is addressed.

Treatment of vulvodynia

State-of-the-art research is attempting to define clinically relevant subgroups or phenotypes that can predict the success of specific treatments for vulvodynia. However in practice, a multidisciplinary approach is recommended, with therapy based on presenting symptoms, side effect profile of recommended treatments, cost, and patient preference (Figure 3). Predisposing or associated factors that contribute to, magnify or maintaining pain (mood, relationship or sexual concerns, hormonal deficiency, etc.) must be addressed.

Treatment approaches can be divided into distinct categories: surgical, pharmacological (oral, topical, injection), psychological (cognitive-behavioral, psychotherapy, mindfulness based relaxation therapy), physical (manipulative, myofascial physical therapy (PT), EMG biofeedback, dilators, and complementary/alternative such as acupuncture or hypnotherapy⁴⁴⁻⁴⁹). The majority of studies are small, single site, and retrospective, uncontrolled or case series. Some methodologically stronger randomized trials (active control or placebo control) have emerged. There are few trials of multimodal therapy⁵⁰⁻⁵². Treatment should begin with vulvar care, i.e., eliminating pads allergens

fabric softeners, soaps and other potentially irritating chemicals. Initial management will depend on findings but usually includes physical therapy, relaxation therapy, and topical medications outlined below. Oral medication and injections may follow and surgery may be considered if other approaches fail.

Pharmacological treatment

Medical options include topical application or injections of local anesthetics or injections of botulinum toxin A, oral neuropathic pain medications such as anticonvulsants or antidepressants (tricyclic antidepressants—TCAs and serotonin norepinephrine re-uptake inhibitors—SNRIs). In controlled trials, the placebo response rate is as high as 50%. Finally, up to 20% of women experience spontaneous improvement⁵⁴.

Tricyclic antidepressants modulate pain in the central nervous system at the level of the dorsal horn of the spinal cord and brain⁵⁵. TCAs are an excellent medication for generalized vulvodynia and may be effective for localized provoked although the only RCT failed to find differences compared with placebo. Uncontrolled and active control trials support use of TCAs. A randomized, prospective trial utilizing multimodal therapy by compared CBT, physical, and sex therapy to low-dose oral amitriptyline (10-20 mg daily) with or without topical triamcinolone⁵⁶. Women (n = 43) with localized and generalized pain, provoked or unprovoked, were included. There was significant improvement in pain and functioning

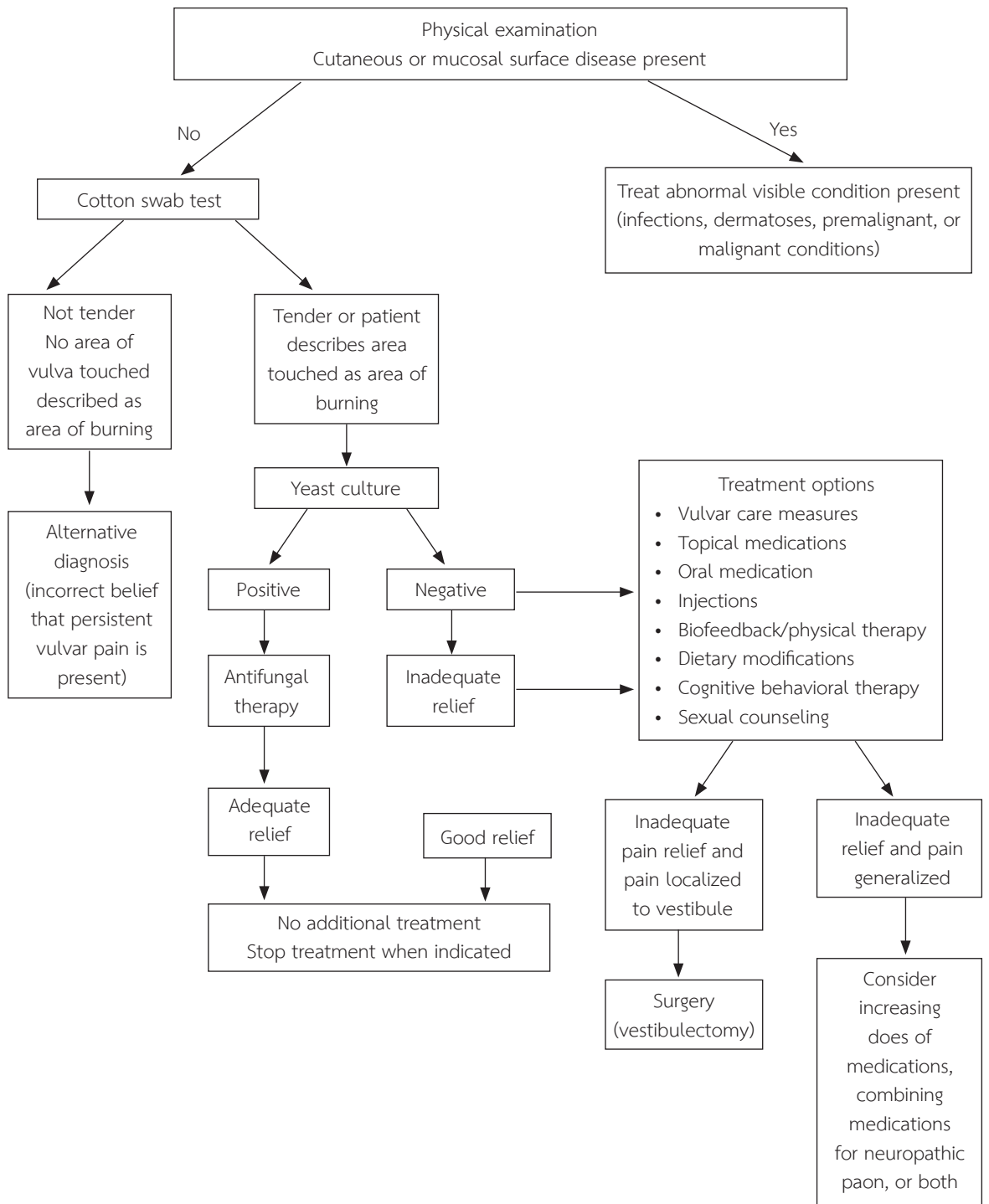


Figure 3 Persistent vulvar pain treatment algorithm [Adapted from Haefner HK, et al. 2005 with permission from Wolters Kluwer Health].

in both groups but no significant differences between the treatment groups were demonstrated. The one randomized, double blind, controlled trial of TCAs evaluated desipramine and topical lidocaine, as monotherapy or in combination compared with placebo. All groups had with similar response rates (defined as at least 50% pain reduction) ranging from 24% to 43%. Topical lidocaine alone produced the least improvement but the desipramine treatment arms had the highest dropout rates due to anticholinergic and noradrenergic side effects of dry mouth, tachycardia, hot flashes, and dizziness⁵⁵. Uncontrolled studies have shown more than 50% reduction in pain with tricyclic antidepressants, in particular amitriptyline⁵⁷.

Topical medications are frequently used for vestibulodynia. Topical amitriptyline avoids systemic side effects such as drowsiness. In a non-controlled prospective study of women with vestibulodynia, topical amitriptyline 2% cream yielded a 56% response rate with 10% pain free and 30% reporting a moderate degree of improvement⁵⁸. Overall, there is insufficient evidence to support the benefits of TCAs in the treatment of vulvodynia⁵⁹, but only one RCT has been performed and in clinical practice many women seem to benefit. Clearly further trials are warranted.

Gabapentin inhibits excitatory neurotransmitter glutamate and potentiates inhibitory GABAergic transmission. Oral gabapentin has proven effective in post-herpetic neuralgia, diabetic neuropathy, and

fibromyalgia. A multisite study of oral gabapentin for vulvodynia is in progress but in clinical practice anticonvulsants are useful for generalized vulvodynia and for spontaneous pain in women with localized vulvar pain. Topical gabapentin largely avoids systemic side effects such as sedation, dizziness, constipation⁶⁰. A retrospective study of 51 patients with both localized and generalized vulvodynia who received low dose (2%) and high dose (6%) topical gabapentin found 80% of women were responders (at least 50% improvement in pain scores). The treatment was well tolerated with 14% discontinuing for local irritation and urinary complaints⁶⁰.

Lidocaine a sodium channel blocker, inhibits transmission of C-fibers and continuous exposure is suggested to impede irritable nociceptors, and thus its role substantial role in neuropathic pain management. Topical lidocaine 5% is the most commonly prescribed medication for vestibulodynia, used twice per day to the vestibule and before any sexual activity⁶¹. In a randomized non-blinded trial, lidocaine 5% ointment was compared with pelvic floor EMG. No differences were found between these two active interventions⁶². An uncontrolled study also showed promise with aver 50% reduction pain in 61 women with dyspareunia who applied topical 5% lidocaine ointment nightly to the vestibule. At 6 months follow-up, 77% reported ongoing use⁶³. 5% lidocaine ointment for treatment of is a reasonable initial treatment alone or as adjunctive therapy with CBT and/or PT in women with vulvodynia.

Injections with lidocaine and methyl prednisone aim to decrease the local inflammatory reaction and take advantage of the sodium channel blocking effects of lidocaine. After one case study demonstrated complete relief of persistent vulvar vestibular pain with submucosal infiltration of betamethasone and lidocaine in the vestibular area⁶⁴, a prospective, non-randomized study of 22 patients utilized the same treatment. 32% experienced complete response and 36% experienced significant improvement, but 32% failed to respond despite multiple injections⁶⁵. It should be noted that topical corticosteroid creams are not effective. In another non-controlled trial, multilevel local anesthetic nerve blockade (caudal block, pudendal block, vulvar infiltration) using ropivacaine and bupivacaine in 26 patients with generalized vulvodynia showed 57% average improvement⁶⁶. The same protocol was used in patients with vestibulodynia with similar improvement in both pain and sexual functioning⁶⁷.

Botulinum toxin A reduces muscle hypertonicity and has antinociceptive effects in studies of neuropathic pain. Two small RCTS found significant improvement in both dyspareunia, but response was similar in the Botulinum toxin A and the saline injection groups⁶⁸. Another small study noted the placebo group reported a significantly larger reduction in sexual distress than the Botulinum toxin group⁶⁹. Reported side effects are rare but include hematoma and bleeding, toxin reactions and loss of pelvic sphincter control. Botulinum toxin should be considered as a

second-line treatment for vestibulodynia. It is also recommended for pelvic floor hypertonus and in women with vulvodynia if physical therapy and CBT are unsuccessful⁷⁰.

Cromolyn sodium blocks mast cell degranulation and inhibits the release of inflammatory mediators. It has been reported to prevent hypersensitivity to seminal fluid when applied topically⁷¹. The effectiveness of topical cromolyn cream did not exceed that of placebo in a double-blinded RCT for vestibulodynia, although symptoms of burning and dyspareunia improved in both groups⁷².

Capsaicin is an agonist of vanilloid receptors, located on the peripheral terminals of sensitive nociceptors. It has been recommended for treatment of post-herpetic neuralgia or peripheral neuropathy and was therefore investigated for vestibulodynia. Application of capsaicin to the skin causes irritation and pain, but used long term results in degeneration of C (pain) nerve fibers and desensitization⁷³. In a prospective uncontrolled trial, 33 women were treated with topical capsaicin 0.05%, with 19 patients reporting improvement in dyspareunia⁷⁴. The second study evaluating capsaicin in dyspareunia was a chart review of 42 women with vulvodynia. Post treatment, 95% of the patients was having vaginal inter-course compared with 62% prior to treatment. Given the retrospective nature of the study, the researchers could not evaluate which participants used additional therapies⁷⁴. Currently topical capsaicin is not currently recommended due to the burning sensation after application; however, other

substance P antagonists lacking this side effect are under evaluation.

Hormonal treatment

Some but not all studies have associated oral contraceptives (OCPs), particularly long term intake prior to the age of 18 with increased risk for vestibulodynia⁷⁵⁻⁷⁷. OCPs inhibit luteinizing hormone and therefore decrease ovarian estradiol and testosterone production. Oral intake of estrogens and progestins also increases hepatic production of sex hormone binding globulin which further lowers circulating free testosterone. Lack of testosterone has been shown to impact vestibular morphology, lubrication as well as libido⁷⁸. Vestibular glands which produce protective mucin are also rich in androgen receptors. The lower endogenous estrogen and bioavailable testosterone have been suggested to thin the vestibule, predisposing to inflammation and development of neuropathic pain⁷⁹.

Application of topical estradiol 0.03% and testosterone 0.1% twice per day may be effective in patients who suffer from vestibulodynia while taking oral contraceptives (OCPs). However it is preferable to discontinue hormonal contraceptives that suppress ovarian steroids. Levonorgestrel or copper IUD can be used. In a retrospective study, participants who had developed vestibular pain while using OCPs were asked to discontinue all oral hormones and to apply the above compounded estradiol-testosterone cream twice daily. After 6 months, significant

improvement in vestibular pain scores were noted⁷⁸. Topical estrogen ($\pm$ testosterone) is the first choice when vestibular pain is associated with hypoestrogenic disorders such as the climacteric, menopause, puerperium, lactation, hypothalamic amenorrhea, or systemic hormonal contraceptives⁸⁰.

Physical therapy (PT) and biofeedback pelvic floor dysfunction

Pelvic floor rehabilitation is the foundation of management of pelvic floor dysfunction. It requires a multimodal treatment plan that is developed with a licensed pelvic floor physical therapist. The mainstay of pelvic floor rehabilitation is pelvic floor physical therapy, which includes manual techniques of massage, myofascial and trigger point release, and joint mobilization. Adjunct therapies include trigger point injections with steroids or onabotulinumtoxinA for pelvic floor tightness or spasticity, intravaginal diazepam suppositories, transcutaneous electrical nerve stimulation and neuromodulation.^{39,40}

Women with vestibulodynia demonstrate increased pelvic floor muscle hypertonus, muscular instability, poor muscle control, decreased strength, and restriction of the vaginal opening^{81,82}. Chronic vulvar pain can also trigger chronic pelvic floor tightening as part of the normal pain response⁸³. Pelvic floor hypertonic dysfunction can activate viscerosomatic reflexes and visceral afferent neurons causing muscle over activity and a vaginismus type response⁴⁸. Muscle trigger points can cause referred, localized or

radiating pain and can present as sensations of vulvar burning, itching, and tingling⁸⁴. Physical therapy techniques for management include internal and external tissue mobilization and myofascial trigger point release, joint manipulation, biofeedback, electrical stimulation, use of dilators⁸⁵. PT improves pain threshold and dyspareunia, as well as overall sexual pain, pain catastrophizing, and pain related anxiety⁸⁶⁻⁸⁸. In a retrospective study, physical therapy yielded a 52% success rate with a significantly decreased pain, increased intercourse frequency, levels of sexual desire and arousal⁸⁹. Biofeedback with surface electromyography (EMG) to treat pelvic floor hypertonicity was also found to be an effective tool for pelvic floor myalgia and dysfunction in patients with vestibulodynia. 52% of participant were pain free at 6 months follow-up⁹⁰ with treatment gains maintained 3-5 years post treatment⁹¹. In another uncontrolled study, EMG biofeedback alleviated introital tenderness by up to 50% and allowed up to 90% of study participants to have intercourse without discomfort⁹².

Transcutaneous electrical nerve stimulation (TENS)

Beneficial effects of TENS were demonstrated in a randomized placebo-controlled trial of 40 women with vestibulodynia. After 20 sessions, the TENS treatment arm showed significant improvement of pain and sexual function compared with placebo⁹³.

Psychological interventions

Psychological factors play a significant role in development, maintenance and management of vulvodynia. Pain is both a physical and emotional experience. These factors should be addressed prior to and during treatment⁹⁴. Psychological interventions target emotions, cognitions, and dysfunctional couple interactions that impact sexual functioning and genital pain. Vulvar pain can have a tremendous impact on the patient's body image, sexual self-esteem, and sexual function- ing in their intimate relationship⁹⁵. Women with vulvodynia often report a sense of shame, isolation and blame themselves for their disease. There is a sense of loss and unfairness associated with anger, powerlessness, or depression. Anxiety, fear, and lower levels of pain self-efficacy are associated with more sexual impairment in women with vestibulodynia^{94,96}. Women with history of depression or anxiety are four times more likely to be diagnosed with vulvodynia⁴³. Vulvodynia sufferers are almost three times more likely to report severe physical or sexual abuse and continued fear of abuse⁴³.

Hypnotherapy

In addition to personal history of mood disorders or sexual, physical, and emotional trauma, the quality of patient's relationship with their partner plays an important role. Women with vulvodynia report more problematic relationships^{48,97}. Vestibulodynia is also associated with psychological and sexual consequences for

sexual partners. In couples with provoked vestibulodynia, the partner's perceptions and behaviors influence both the partner's and the patient's coping mechanisms and sexual outcomes. A perception of injustice can negatively impact the intimate relationship^{98,99}. Relationship factors such as partner catastrophizing and solicitousness also influence pain and sexual outcomes¹⁰⁰.

Cognitive behavioral therapy (CBT)

CBT is the most studied psychological intervention for vulvodynia. Individual and group CBT are validated, noninvasive options for treatment. CBT stresses self-management, relaxation, coping mechanisms¹⁰¹. The goal of CBT is to help women understand how thoughts and emotions impact behaviors and to modify these factors by redirecting negative thought pathways leading to behavioral changes. CBT reduces anxiety by giving patients more control over their pain sexual interactions⁵³. CBT has been shown to significantly decrease catastrophizing scores and improve sexual functioning¹⁰². Compared with supportive psychotherapy, CBT showed a greater improvement in pain severity on exam, overall sexual functioning, and greater global treatment satisfaction. Participants in both psychological treatment groups reported significant improvements in pain severity with sex, sexual and emotional functioning, and decreased anxiety and depression.

Acceptance-based psychological treatment approaches are of great value for couples where one partner suffers from genito-pelvic pain and who report perceived injustice⁹⁸. Couples who underwent CBT together experienced better sexual function, and less anxiety and depression for both partners after 12 sessions [73].

A comprehensive treatment approach for provoked vestibulodynia combined pelvic floor exercises, desensitization techniques (vaginal acupressure, masturbation, tampon use) and CBT. The 10 week therapy period included education about genital anatomy, relationship problems, sexual disorders, and practical exercises. Patients were instructed to perform daily self-examination with touch and massage using a hand mirror. Tampon use was encouraged. Once the home work was successfully executed, exercises with the partner were included. Sexual interest, sexual pleasure and frequency of masturbation were all increased and sexual pain was decreased at 6 month follow-up¹⁰⁴.

Two studies showed equivalent outcomes between CBT and vestibulectomy for patients with vestibulodynia^{61,105}. Surgical and psychosocial modalities can be complementary; addressing factors such as fear of sex and poor body image can improve surgical outcome⁵¹. The literature highlights the impact of psychosocial factors and role for psychosocial interventions in women with chronic vulvar pain¹⁰¹.

Mindfulness based stress reduction (MBSR) therapy

Mindfulness is the practice of relaxed wakefulness, defined as nonjudgmental moment awareness, and is an ancient eastern practice with roots in Buddhist meditation¹⁰⁶. Many pain programs now blend CBT and mindfulness treatments¹⁰⁷. In a recent study, 85 patients with vulvodynia who were treated with MBSR demonstrated significant improvements in pain, sexual distress, and depressive symptoms¹⁰⁸.

Hypnotherapy has shown promising results in the treatment of vulvar vestibulitis in a small pilot study of eight women with vestibulodynia who underwent six hypnotherapy sessions. Dyspareunia, pain associated with gynecologic exams, sexual satisfaction, and overall sexual function were improved¹⁰⁹.

Surgical treatment

Vestibulodynia: The treatment of GPPPD associated with VD requires a multidisciplinary approach as a majority of cases are multifactorial. Due to feedback loop of pain and anxiety associated with GPPPD, cognitive behavioral therapy and sex therapy have a role in treatment. Pelvic floor physical therapy, biofeedback, onabotulinumtoxin A injection, pudendal nerve blocks and neuromodulation are other adjuvant therapies that have been shown to be beneficial in the treatment of VD. In terms of medical management, discontinuation of hormonal

contraception should be considered, and patients should be counseled on alternative options for nonhormonal contraception. Hormone therapy of both estrogen and testosterone is the mainstay of medical management for hormonally mediated VD, including DHEA vaginal inserts and compounded estrogen/testosterone.^{37,38} Other considerations include the addition of topical steroids if VD is associated with dermatological conditions (eg lichen sclerosus), onabotulinumtoxin A injection and vaginal valium. In refractory cases or those with persistent pain despite correction with hormone therapy, surgical intervention consisting of vulvar vestibulectomy with vaginal flap advancement should be offered. Studies have shown a high success rate of cure when performed by an experienced surgeon (figure 4).

Vestibulectomy: Surgical removal of the painful vulvar vestibular tissue is the most widely investigated approach for dyspareunia in women with vestibulodynia, though controlled trials are lacking. The overall success rates are high (85–90%) but success refers to improvement of at least 50% and need not include painless intercourse. Surgery has risks, side effects, and some less than optimal outcomes⁵³.

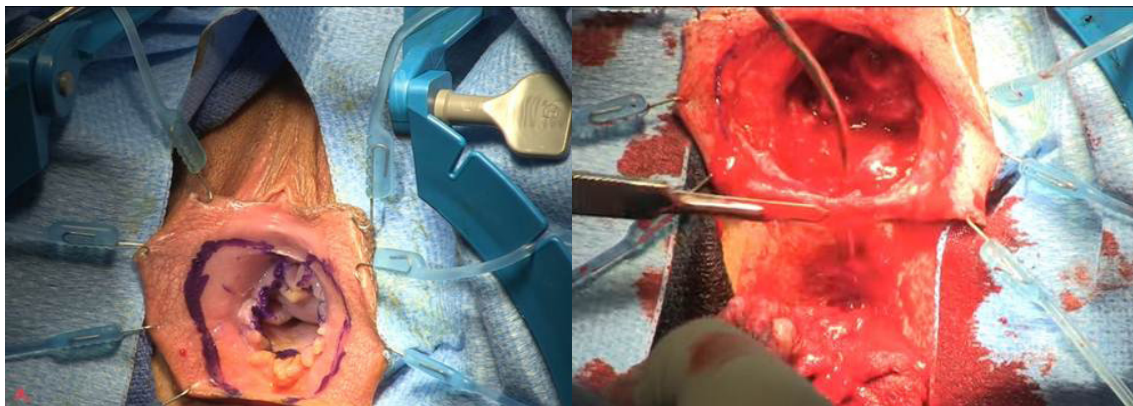


Figure 4 Complete vestibulectomy with left and right anterior vestibulectomy, and posterior vestibulectomy (A and B).

Clitorodysplasia: Treatment for clitorodysplasia is dependent on the underlying cause. Topical treatment with potent steroids is used for management of phimosis and treatment/management of lichen sclerosus. If pain is associated with correctable physical examination findings (clitoral pearl, adhesions refractory to medication), surgical treatments should be considered, including office-based lysis of adhesions or surgical dorsal slit (figure 5). Symptoms of GSM when used on its own. The

American College of Obstetricians and Gynecologists recommends use of nonhormonal options as the first choice for treatment of vaginal atrophy in women with current or a history of estrogen dependent breast cancer. However, they also consider vaginal estrogen therapy appropriate for patients with a history of estrogen dependent breast cancer who are unresponsive to non-hormonal remedies, but only after a thorough discussion of risks and benefits with their oncologist.²⁷



Figure 5 (A) Phimosis of clitoris. (B) Clitoral lysis of adhesions.

Treatment of genitourinary syndrome of menopause

Genitourinary syndrome of menopause. The primary goal for treating GSM is alleviation of symptoms, restoring vaginal pH and preventing recurrent urinary tract infections. For women with vulvovaginal symptoms related to sexual activity, multimodal treatment may be helpful. Lifelong low-dose vaginal hormone therapy is the mainstay of treatment (eg vaginal creams, intravaginal tablets, intravaginal rings). These have been shown to maintain tissue integrity, elasticity and pliability. Additional available treatment options include nonhormonal vaginal lubricants to be used during intercourse, long-acting vaginal moisturizers for symptom control, laser therapy and pelvic floor physical therapy with possible use of vaginal dilators.

Topical lubricants and moisturizers:

Various over-the-counter vaginal lubricants (water, silicone or oil-based) and moisturizers are commonly used for the treatment of postmenopausal women with vulvovaginal symptoms. These serve as supplemental/symptomatic treatments but do not correct the hormonal imbalance. They are used as needed typically for sexual activity but can be used independently of sexual activity. It is recommended to choose a product that is physiologically most similar to natural vaginal secretions, and balanced in terms of both osmolality and pH.²⁵ Water-based lubricants are often preferred over oil-based lubricants as they are non-staining and associated with fewer genital symptoms. Caution should be

used with oil based lubricants as this can lead to condom breakage.²⁶

Low dose vaginal estrogen and testosterone: Topical, low dose vaginal estrogen restores hormone levels within the tissue without significant systemic absorption. This typically results in rapid improvement in vaginal symptoms within 2 to 3 weeks but may take 2 months for maximal benefit. Topical estrogen is recommended by the American Urological Association for the treatment of recurrent urinary tract infections in premenopausal and postmenopausal women as data show it prevents urinary tract infection by restoring vaginal flora and pH.

Systemic estrogen therapy can be considered in addition to topical estrogen if there are concomitant vasomotor symptoms. Systemic estrogen has not been shown to treat.

Vaginal DHEA suppositories are approved for the treatment of moderate to severe GPPPD. DHEA is converted by enzymes in the vulva, vestibule and vagina into estrogen and testosterone. This results in significant improvements in vaginal epithelial cells and integrity, vaginal pH, parabasal cells and increased vaginal secretions, all without affecting serum levels of estradiol and testosterone or endometrial tissues²⁸⁻³¹.

Table 1 Pharmacological treatments for Genitourinary syndrome of menopause

Treatment	Product Name	Dose
Vaginal cream:		
17-beta-estradiol	Estrace®, generic	cream 0.5–1 gm daily for 2 wks, then 0.5–1 gm 1–3 times weekly
Conjugated equine estrogens	Premarin®	0.5–1 gm daily for 2 wks, then 0.5–1 gm 1–3 times weekly
Vaginal insert:		
Estradiol vaginal tablets	Vagifem®, Yuvaferm®	10 µg inserts daily for 2 wks, then twice weekly
Estradiol soft gel capsules	Imvexxy®	Four 10 µg inserts daily for 2 wks, then twice weekly
DHEA (prasterone) vaginal insert	Intrarosa®	6.5 mg capsule daily
17-beta-estradiol vaginal ring	Estring®	1 ring inserted every 3 months
Ospemifene oral tablets (selective estrogen receptor modulator)	Osphena®	60 mg tablet daily

Oral selective estrogen receptor modulators: Selective estrogen receptor modulators are oral systemic nonhormonal therapy approved for the treatment of GPPPD due to GSM. Ospemifene is the only selective estrogen receptor modulator approved by the U.S. Food and Drug Administration for treatment of moderate to severe dyspareunia.³² Several studies have shown that it increases vaginal maturation index and vaginal pH, causing improved lubrication. Common side effects include hot flashes, vaginal discharge and muscle spasm. Contraindications include estrogen dependent neoplasms, history of venous thromboembolism, previous stroke or myocardial infarction, and active heart disease (see table 1).^{32,33}

Vaginal dilators and lasers: Dilators have been shown to increase vaginal elasticity, which decreases pain with penetration. Women with GSM may see benefit from gentle stretching of the vagina with the use of lubricated gradual dilators in combination with correction of vaginal lubrication. Pelvic floor muscle therapy may also be useful in patients with nonrelaxing or high tone pelvic floor muscle dysfunction triggered by painful sexual activity related to GSM.³⁴ Patients and providers can find pelvic floor physical therapists through various online resources, such as APTA Pelvic Health ([https:// aptapelvichealth.org/](https://aptapelvichealth.org/)).

Laser therapy with either a fractional CO2 laser or erbium: YAG laser, can be used as a nonhormonal treatment option for GSM.³⁵ Although data are limited, several small

studies have shown restoration of the vaginal epithelium, increase in premenopausal vaginal flora and subjective improvement in symptoms of GSM, including lower urinary tract symptoms.³⁶ At this time, laser therapy is not U.S. Food and Drug Administration approved and should be used in experimental treatment only.

Conclusion

Female sexual pain disorders are within the scope of sexual medicine practice such as urologist, gynecologist, clinical sexologist and comfort with their management should be encouraged. Sexual pain may be multifactorial, and treatments often require a multidisciplinary approach that can include medical, surgical, behavioral and musculoskeletal interventions.

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