Vulvodynia: An Evidence-Based Approach to Medical Management

Case Studies and Commentary, *Jeffrey Campbell Andrews, MD, FRCSC*

Abstract

- *Objective:* To present key concepts in the diagnosis and treatment of vulvodynia.
- *Methods:* Review of the literature with case presentations.
- *Results:* Vulvodynia is a condition of vulvar discomfort that affects millions of women each year. The etiology is unknown. Treatment goals are to reduce pain, improve quality of life, and recover sexual function if it has been affected. There is no single effective treatment for vulvodynia, and there is no high-quality evidence of beneficial effect for any intervention. Rapid resolution of symptomatic chronic vulvodynia is unusual and improvement of pain may take months.
- *Conclusion:* The quality of evidence for efficacy for pain relief and for sexual function ranges from none to fair. In the absence of good quality evidence, providers and patients must discuss available evidence and make choices that are not based on confident recommendations.

Vulvodynia is a condition of vulvar discomfort that affects millions of women each year [1,2]. Although vulvodynia is a symptom, the term is also used to describe a cluster of pain disorders. Vulvodynia is defined as vulvar discomfort in the absence of relevant visible findings or a specific clinically identifiable neurologic disorder [3,4]. The International Society for the Study of Vulvovaginal Diseases (ISSVD) classification of vulvodynia distinguishes between generalized and localized findings [3–5]. These 2 subgroups are further subdivided into provoked, unprovoked, or mixed (continuous pain, exacerbated by touch) [5]. The vast majority of clinical presentations are either generalized unprovoked vulvodynia or vestibulodynia (localized provoked vulvodynia).

The point prevalence of vulvodynia is estimated to be 3% to 7% [1,2,6–9]. The prevalence, defined as a history of vulvodynia, is estimated to be 10% to 30% [1,2,6,19–11]. Most women with vulvodynia report having had pain for many years, and remission appears to be uncommon, occurring in less than 25%. The societal burden of vulvodynia is largely hidden. Of patients reporting vulvodynia in a survey, almost 40% never sought medical care [7]. Sixty percent of women with vulvodynia who sought medical care reported visiting more than 3 providers to receive a diagnosis, and 40% remained undiagnosed after 3 medical consults [7].

Women with vulvodynia report a significant burden of illness. Sixty percent reported a compromised ability to enjoy life, and 75% felt "out of control" of their bodies. Half reported a moderate to severe impact on their sex lives, causing them to terminate attempts at sexual intercourse or avoid sexual relations altogether [6]. Many women do not discuss their condition with others, and many providers do not encourage discussion of pain and sexuality issues.

CASE STUDIES

Initial Presentation

Case 1

A 54-year-old woman presents seeking pain relief. She reports a 2-year history of a constant burning pain in the region of the vulva. She believes the onset was gradual. The pain is interfering with her quality of life. She ranks the pain as 4–5 on a 0–10 visual analog scale.

She has seen 3 clinicians and tried several interventions, including topical vulvovaginal estrogen, but they did not result in any relief of symptoms. She denies a history of nocturia, dysuria, or urinary frequency. She is postmenopausal. She thinks her last provider told her that the problem was "in her head." The patient is a married mother of 2 and works as a marketing consultant.

Case 2

A 27-year-old woman presents seeking relief of her condition. She reports a 2-year history of painful intercourse. The degree of pain is such that she and her husband no longer attempt touching or penetration. She cannot recall if the onset of the problem was gradual. She

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does recall being treated for what seemed to be recurrent yeast infections and ultimately finding that she had pain symptoms without signs of a yeast infection. She has seen 3 clinicians, tried several interventions, and stopped her oral contraceptive pill but has not experienced any relief. She was evaluated for mild symptoms of frequency and urgency, with negative cultures. A urologist performed a cystoscopy and advised that findings were normal.

The patient is a wife and teacher. Her medical history is significant for anxiety and depressive disorder and irritable bowel syndrome. There is no history of physical or sexual abuse. The pain has significantly altered her relationship with her husband and her overall happiness and quality of life. She rates the pain as 1 on a 0–10 visual analog scale at the time of the visit, and states the pain would be 8 with attempted tampon insertion and 9–10 with attempted intercourse.

- **What are the 2 most common clinical presentations of vulvodynia?**

Generalized Unprovoked Vulvodynia

The term generalized unprovoked vulvodynia replaces older terminology, such as dysesthetic vulvodynia, essential vulvodynia, and burning vulva syndrome [4]. The onset can be acute or gradual [12]. The quality of the pain is usually described as burning or sometimes as stinging, irritation, itching, or a feeling of rawness. Most often, the location of the pain is diffuse, without clear borders. The pain intensity is generally reported as moderate to severe [13]. Any stimulus that results in pressure on the vulva can exacerbate the pain, including intercourse, tampon insertion, speculum insertion, tight-fitting clothing, bicycling, horseback riding, and even sitting, walking, or exercising [14]. Absence of physical findings is common, although varying degrees of erythema have been reported [12]. Generalized unprovoked vulvodynia is not a single disease process but rather a symptomatic description of several disease states [15].

Vestibulodynia

Vestibulodynia describes a syndrome of provoked, localized allodynia of the vestibule of the vulva not explained by another condition, with a duration of more than 3 months. The pain is not present all of the time; rather, it is evoked by touch: attempted intercourse, physical examination, other direct contact. Most patients with vestibulodynia complain of dyspareunia—pain with intercourse or the inability to have intercourse due to pain. Often the vestibulodynia is associated with vaginismus, an involuntary contraction of the pelvic floor muscles affecting the vaginal entrance. It can make penetration painful or even impossible. When painful penetration has been experienced, there may be an anticipatory set of responses that exacerbates the condition. Vestibulodynia may be primary (began with sexual debut or first attempts to use a tampon) or secondary (began after a period of time, previously the same provocation did not evoke pain).

Like generalized unprovoked vulvodynia, vestibulodynia is not one disease process but is a symptomatic description of several disease states [15]. Current theories about the various disease states include hormonally-mediated vestibulodynia, hypertonic pelvic floor dysfunction, and neuroproliferative vestibulodynia [16].

Dyspareunia and vaginismus are sensitive issues, as this type of pain involves activities and behaviors (sexual intimacy and vaginal intercourse) that have emotional qualities and repercussions. Pain is a complex perceptive experience involving psychological and relational meanings, which may become increasingly important as the pain becomes chronic.

- **What are other nosologies for vulvar pain?**

There are several nosologies for vulvar pain disorders, of which the ISSVD provides one. The ISSVD approach is informed largely by a gynecology/dermatology/pathology perspective [3,4]. The psychiatric nosology [17] subdivides pain disorders of the vulva into organic (labeled by biomedical diagnosis), psychiatric, somatoform, factitious, and malingering. If no biomedical or relevant psychological aspects can be defined and the pain is not a voluntary symptom, then a diagnosis of somatoform disorder is considered [17,18]. The field of sexology utilizes another nosology for classification of women's sexual pain disorders [19].

The experience of nociception and pain involves the nervous system, and the science of neurology uses different descriptors and terms to describe similar conditions. Using a neurologic classification, once the known causes (such as nociception and inflammation) have been ruled out, chronic pain is subdivided into neuropathic or functional [1,18,20–23].

Neurologic Classification

Neuropathic Pain

Neuropathic pain is a complex type of pain initiated or caused by a primary lesion or dysfunction in the nervous system [23,24]. Neuropathic pain manifests as a constant, burning pain with spontaneous sharp exacerbations and worsening upon normal sensory triggers causing considerable impact on the quality of life; persons must have

experienced pain for at least 3 months, with a mean pain intensity greater than 3/10 on a pain scale [24]. Generalized unprovoked vulvodynia would appear to fit within this definition. A wide range of factors is known to precipitate neuropathic pain, including diabetes, peripheral trauma and traumatic nerve lesion, post-surgical nerve lesion, spinal cord trauma, central nervous system trauma, infections such as herpes zoster and HIV, and mechanical pressure such as compression and entrapment syndromes. Numerous treatment studies exist for patients with painful diabetic peripheral neuropathy and for postherpetic neuropathy due to the prevalence of these conditions. This has resulted in medications being registered in many countries with 1 or 2 indications for specific neuropathic pain syndromes (diabetic peripheral neuropathy, postherpetic neuropathy). Supported by positive clinical empiricism, drugs demonstrated to have efficacy in diabetic peripheral neuropathy and postherpetic neuropathy are prescribed by physicians for other painful peripheral and central neuropathic conditions, where there is absence of, or scarce scientific evidence for efficacy [25]. Vulvodynia does not fit into the classic definition of neuropathic pain, based on clinical evidence of underlying neurologic disease or site of the lesion in the somatosensory pathway [25–27]. Also, vulvodynia is usually bilateral, and well-described neuropathic pain syndromes are usually unilateral (eg, postherpetic neuropathy, diabetic peripheral neuropathy, trigeminal neuralgia). Even atypical facial pain syndrome usually begins as unilateral and less than one-third of patients develop bilateral symptoms [28]. Generalized unprovoked vulvodynia may represent an entity within the spectrum of neuropathic pain syndromes, if understood as maladaptive nociception, neurogenic dysfunction in the form of dysregulation of inhibitory control.

Table 1. Pain Definitions

Term	Definition
Adaptive pain	Nociceptive pain, inflammatory pain
Maladaptive pain	Neuropathic pain, functional pain
Nociceptive pain	Results from noxious peripheral stimuli (heat, cold, irritant, force) detection at nerve endings and transmission along afferent sensory neurons to the spinal cord and then to the brain "Nociceptive" when the pain experience is the alerting signal of impending or current tissue damage from which the body should withdraw
Inflammatory pain	Results from inflammatory agents causing tissue damage, which stimulates the nerve endings and transmission
Neuropathic pain	"Neuropathic" when pain becomes a disease (ie, it is generated within the nerves and nervous centers) rather than from nociception or inflammation In most recognized types of neuropathic pain disorders, the pain results from damage to the afferent sensory neurons
Functional pain	Occurs in the absence of nociceptive agents, the absence of infection, and the absence of sensory nerve damage—the peripheral tissue and peripheral nerves are normal There is abnormal central processing at the level of the spine and/or the brain
Allodynia	A usually nonpainful stimulus, like light touch, is painful
Hyperalgesia	An increase in the magnitude of pain induced by a stimulus that is normally painful
Dysesthesia	Characterized by unusual sensation (burning, pain, tingling) Sensation occurs without any stimulation

Functional Pain

Functional pain is a disorder in which a person experiences chronic pain for which there is no known cause or any visible physical injury or disease: the pain is attributable to a functional disorder rather than organic disease; of at least 3 months' duration; and the pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. Examples of functional pain include fibromyalgia and painful bladder syndrome (pelvic pain, urgency, and frequency), functional abdominal pain syndrome, and irritable bowel syndrome.

The functional pain symptom or deficit is not intentionally produced or feigned (as in factitious disorder or malingering). There is overlap between the category of functional pain and the category of pain disorder and somatoform disorders in the DSM-IV-TR [17,18,20]. The common feature of the somatoform disorders is the presence of physical symptoms that suggest a general medical condition and are not fully explained by a general medical condition [17]. These pain syndromes could be further characterized into somatic pain syndromes, such as fibromyalgia and vulvodynia; and visceral pain syndromes, such as interstitial cystitis, painful bladder syndrome, irritable bowel syndrome, and chronic pelvic pain.

Rather than using the terms functional and somatization, it may be preferable to use the single descriptor idiopathic pain disorder [29]. See **Table 1** for pain definitions.

Physical Examination and Laboratory Testing

Case 1

On physical examination, using a coordinated technique of cotton swab touch and communication with the patient, the patient's pain is mapped to a bilateral area corresponding to the labia minora, the vestibule, and the upper perineum. The clitoris and surrounding tissue are

Table 2. Symptoms and Signs of Vestibulodynia Versus Generalized Unprovoked Vulvodynia

	Vestibulodynia	Generalized Unprovoked Vulvodynia
Symptoms		
Location	Vulva, vaginal entrance	Vulva
Quality descriptors	Sharp, tearing	Burning
Severity	Varies	Varies
Timing	Evoked by contact, especially attempted intercourse penetration	Constant, may vary in intensity
Duration	> 6 months	> 6 months
Signs		
Allodynia	Yes, in the vestibule	Not required, may be present in mixed disorder
Hyperalgesia	Yes, in the vestibule	Not required, may be present in mixed disorder
Dysesthesia	Usually not identified	Yes, can map zone of dysesthesia
Redness	Not required, may be present	Not required, may be present

not dysesthetic areas. The actual border of dysesthesia is not well defined—it is difficult for the patient to be certain where the dysesthetic tissue zone ends and normal sensation starts. A vulvoscope is used and no dermatologic or inflammatory condition is visualized. There is no significant atrophy. A digital exam demonstrates no hypertonus or tension in the pelvic floor musculature. The patient does not find the examination painful, but at the conclusion of the exam she reports that her burning pain level has risen from 4–5 to 8–9 out of 10. Vaginal pH is 4.5. A saline immersion microscopic exam of a vaginal specimen showed normal findings. No other lab tests or imaging studies were performed.

Case 2

On physical examination, using a coordinated technique of cotton swab touch and communication with the patient, the patient has severe tenderness localized to a small bilateral area of the vulvar tissue that extends from Hart's line to the hymenal ring in the posterior vestibule. The area of allodynia is easily identified by the patient's retraction from touch and expression of pain. The line of differentiation between normal sensation and pain is clear and reproducible. A vulvoscopic examination is only significant for a finding of subtle erythema of the inner vulvar vestibule. A digital examination of pelvic floor muscles reveals significant hypertonus of the levator ani muscles and pain from digital pressure. The patient reports that the pain from the internal portion of exam was 7/10, and that she is having persistent pain following the exam. Based on past experience, she believes this exacerbated pain level will last an hour or more. Vaginal pH is 4.5. A saline immersion microscopic exam of a vaginal specimen showed normal findings. No other lab tests or imaging studies were performed.

- **What are the clinical features of vulvodynia?**

Symptoms

The history of the symptoms and discussion with the patient is critical for making the correct diagnosis. History should identify the location, quality descriptors, severity, timing, duration, context/causative factors, modifying/alleviating factors, associated symptoms/signs, previous treatments, and comorbid conditions (**Table 2**). In addition to allergies, medications, and past medical and surgical history, sexual history is particularly important. This history should be obtained when the patient is clothed and has spent some time interacting with the provider. Ask permission to discuss sensitive issues, even if permission seems implied.

Sample questions to obtain relevant information are:

- What do you feel, what is your experience?
- How intense is the pain you feel? Score the pain between 0–10, where 0 is no pain and 10 is the worst pain you can imagine.
- Where exactly does it hurt? At the opening of the vagina, in the mid-vagina, or deep in the vagina? Diagrams may be helpful; often patients are unfamiliar with terminology or anatomic locations.
- When do you feel pain: all the time? before, during, or after intercourse?

A bladder screening questionnaire for conditions such as interstitial cystitis and painful bladder syndrome is advised. As many patients have psychological comorbidities, a profile

and assessment are advocated as part of a biopsychosocial perspective.

Signs

A detailed physical examination is suggested. In addition to routine examination elements, a complete skin examination is usually advised. Prior to performing the standard elements of gynecologic exam, a special cotton swab test is performed. Cotton swab testing is used to localize painful areas (allodynia) and to classify the area as having mild, moderate, or severe pain. The same mapping technique is used to determine the area involved in dysesthesia, in patients who do not have allodynia. A diagram of the pain locations is helpful to assist in assessing the pain over time. The vagina is examined and a wet prep, vaginal pH, and fungal and Gram stains are performed as indicated. Fungal culture may identify resistant strains, but sensitivity testing is generally not required.

In the majority of clinical presentations with provoked vulvodynia and exam findings of allodynia, the examination identifies the vestibule as the location of allodynia. The groups of patients with localized, provoked vulvodynia are described as having vestibulodynia. In the past, patients with a similar condition were described as having vulvar vestibulitis [30]. Because inflammation is not necessary and often not found, the term vestibulitis was misleading and has been replaced. Vestibulodynia was first described as a syndrome in 1987 by Dr. Edward Friedrich [14]. Friedrich's criteria are (1) severe pain in the vulvar vestibule upon touch or attempted vaginal entry (dyspareunia), (2) tenderness to pressure localized within the vulvar vestibule during cotton swab test, and (3) vulvar erythema (inflammation) of various degrees. In the years since, the third criterion has been designated optional, as visible findings are often not present.

An illuminated magnified view of the skin of vulva is recommended; the colposcope can be used for this assessment, and the examination is called vulvoscopy. If skin lesions are visualized and there is any uncertainty about the pathology, then a biopsy is recommended [31].

There are no laboratory tests or imaging studies for the diagnosis of vulvodynia. In cases of suspected causalgia, neuralgia, and pudendal nerve entrapment, specialized neurologic tests may be arranged.

Complications

Vaginismus is frequently found in association with vestibulodynia. This is exhibited by patient withdrawal from the examining contact, hypertonus in the pelvic floor muscles (especially levator ani muscles), and trigger point pain in the myofascial elements. The vaginismus can be graded by the intensity of the phobic attitude (mild, moderate, severe) toward penetration, the intensity of the pelvic floor hypertonicity (in 4 degrees), and coexisting personal or relational psychosexual problems. Hypertonicity of the pelvic floor causes a reduction of the introital opening, literally squeezed by the contracted surrounding muscle. It is a predisposing factor, contributing to introital dyspareunia (when the erect penis "forces" the narrower introitus), increasing the vulnerability of the vaginal mucosa to the microabrasions caused by the mechanical trauma of thrusting in unlubricated conditions (pain is a strong reflex inhibitor of vaginal lubrication).

- **What is the differential diagnosis?**

Case 1

Generalized unprovoked vulvodynia, idiopathic pain disorder, neuropathic pain disorder, pudendal nerve entrapment.

Case 2

Localized provoked vulvodynia, vestibulodynia, idiopathic pain disorder.

- **How is the diagnosis made?**

Generalized unprovoked vulvodynia is a diagnosis of exclusion, as is vestibulodynia. Exclusions include vulvar pain that is related to a specific recognized disorder such as infection (eg, candidiasis, herpes), inflammation (eg, lichen planus, immunobullous disorders), neoplasia (eg, Paget's disease, squamous cell carcinoma), or a neurologic disorder (eg, herpes neuralgia, spinal nerve compression) (**Table 3**). The group of patients with vulvar pain in whom there is not a recognized disorder are diagnosed with vulvodynia. This description is "essential," meaning there is not an identified etiology and there are not specific findings.

Vulvodynia may be associated with comorbid conditions, including interstitial cystitis, painful bladder syndrome, fibromyalgia, irritable bowel syndrome, functional abdominal pain syndrome, orofascial pain disorders, chronic fatigue syndrome, depression, and posttraumatic stress disorder [6,20,32–34]. These are considered overlapping conditions [35]. Given the overlapping perspectives, diagnostic terminologies, and comorbidities, patients may be best served by a holistic approach to diagnosis that takes into consideration the medical, developmental, psychologic, spiritual, and social conditions and symptoms that are present, and how they interact to produce a particular patient's condition.

Table 3. Differential Diagnosis of Vulvar Pain

Category	Specific Diseases/Comment
Infections	Candidiasis, trichomoniasis, chancroid, herpes simplex, herpes zoster (shingles), Bartholin's abscess
Noninfectious inflammation	Crohn's disease, Behcet's disease, apthous ulcers, pemphigus, pemphigoid, Sjogren's disease, podophyllin adverse effect, 5-FU adverse effect, allergic reaction to a topical substance (contact dermatitis)
Neoplasia	Squamous cell hyperplasia, vulvar intraepithelial neoplasia, carcinoma
Other skin disorder	Atrophy, trauma, lichen sclerosus, lichen planus, psoriasis
Neurologic disease/trauma	Pudendal neuralgia, pudendal nerve injury from childbirth trauma, pudendal nerve entrapment syndrome, referred pain from sacral nerve roots, postherpetic neuralgia, multiple sclerosis
Neuropathic pain disorder	May overlap with vulvodynia
Idiopathic pain disorder	Includes functional pain disorder and somatization
Functional pain disorder	Overlaps with vulvodynia and somatoform disorder and myofascial pain
Somatoform pain disorder or somatization	Overlaps with vulvodynia and functional pain disorder
Vulvodynia, subclassified by generalized or localized, by provoked or unprovoked or mixed	Overlaps with idiopathic pain disorder, functional pain disorder, and somatoform disorder, and possibly neuropathic pain
Vaginismus	Overlaps with functional pain disorder and vulvodynia
Psychological disorder	Factitious pain, malingering, psychiatric disease

Diagnosis

Case 1

This patient has generalized, unprovoked vulvodynia by definition. Due to overlapping nosology, this patient also could be described as having functional pain disorder and somatoform disorder. There is no history of injury to the pudendal nerves or the peripheral branches of the pudendal nerves, and therefore neuropathic pain disorder is unlikely. There is no specific history suggestive of pudendal nerve entrapment syndrome.

Case 2

This patient has vestibulodynia by definition. She has the Friedich's criteria of vestibulodynia: insertional dyspareunia, vestibular tenderness, and erythema. Formerly she would have been diagnosed with vulvar vestibulitis. Due to overlapping nosology, this patient also could be described as having functional pain disorder and somatoform disorder.

- **What are the pathogenic mechanisms of vulvodynia?**

The etiology of vulvodynia is unknown. Certainly, there is likely to be more than 1 cause, and for a single patient there may be multiple contributing factors. For most chronic pain conditions, the symptoms are poorly explained by a defined biomedical condition, the association between medical findings and disability is low, and the cause remains unclear. As stated under diagnosis, a biopsychosocial approach to understanding vulvodynia is advocated, taking into consideration the medical, developmental, psychologic, spiritual, and social conditions and factors that are present. Cognitive, affective, and behavioral factors play a role in exacerbation and maintenance of the pain complaints.

Several causes have been proposed for generalized unprovoked vulvodynia, including embryologic abnormalities, increased urinary oxalates, genetic or immune factors, hormonal factors, inflammation, infection, and neuropathic changes. Several causes have been proposed for vestibulodynia, including post-*Candida* vestibulodynia (caused by immune response to *Candida* or the treatment agents), hormonally mediated vestibulodynia (caused by synthetic combined hormonal contraceptives), hypertonic pelvic floor dysfunction vestibulodynia, and neuroproliferative vestibulodynia [16]. Hypertonic pelvic floor dysfunction is an equivalent term for myofascial pain disorder of the pelvic floor; this is another functional pain disorder without a known etiology. When vestibulodynia and hypertonic pelvic floor dysfunction are found in the same patient, it is not clear if one of these conditions caused the other, or if they are both caused by the same unknown etiology. Neuroproliferative vestibulodynia arises because of studies that showed neuroproliferation within vestibule skin biopsies [36,37].

These theories involve the "upregulation" of 3 systems. The immunologic system, including introital mast cells, inflammatory molecules, and nerve growth factors, may be upregulated by recurrent *Candida* infections, mechanical trauma, or chemical or physical damage. The pain system may be upregulated by proliferation of local nerve fibers and endings, contributing to the hyperalgesia and allodynia. The neuromuscular system may be upregulated with hyperactivity of the levator ani, which can be antecedent to vestibulodynia and comorbid with mild vaginismus or secondary to the vestibulodynia.

- **What are the goals of therapy for patients with vulvodynia?**
- **What therapies are available and what is the evidence of benefit?**

The goals of therapeutic intervention for patients with vulvodynia are to reduce pain, improve quality of life, and recover sexual function if it has been affected. There is no single effective treatment for vulvodynia. In fact, there is no high-quality evidence of beneficial effect for any intervention. State-of-the-art vulvodynia management is described in "The Vulvodynia Guideline" [38] and includes topical applications, oral medications, local and regional injections, physical therapy, cognitive therapy, and surgery. In general, treatment of vestibulodynia proceeds on a trial-and-error basis [39].

Nonpharmacologic Therapy

Complementary/Integrative Medicine Methods

Several vulvar care measures have been suggested, without scientific evidence of benefit. Cotton underwear is recommended during the day, with no underwear worn at night. If the patient is sweating with exercise, wicking underwear has been used by some patients. Vulvar irritants and douching should be avoided. The patient should use mild soaps for bathing and not apply soaps to the vulva. If menstrual pads are irritating, 100% cotton pads may be helpful. Adequate lubrication for intercourse is recommended. Consideration of the varying ingredients within moisturizers and lubricants is beyond the scope of this article. Cool gel packs are suggested for some patients.

For generalized unprovoked vulvodynia, there is insufficient evidence for acupuncture [40], photodynamic therapy, magnetic field therapy [41,42], and spinal cord stimulation [43,44].

For vestibulodynia, there is insufficient evidence for electronic stimulation [45,46], and for acupuncture [47].

Physical Therapy

Physical therapy techniques, with or without biofeedback, are currently used as interventions for vulvodynia, and vestibulodynia in particular. These techniques may be particularly helpful if there is concomitant vaginismus or hypertonicity of the pelvic floor musculature. Biofeedback may aid in developing self-regulation strategies for confronting and reducing chronic pain.

For generalized unprovoked vulvodynia, there is insufficient evidence for use of EMG-assisted pelvic floor physiotherapy [48]. For vestibulodynia, there is insufficient evidence for use of dilators [49] and pelvic floor physiotherapy [50–53].

Cognitive Behavioral Therapy

For generalized unprovoked vulvodynia, there is no evidence regarding cognitive behavioral therapy. For vestibulodynia, there is insufficient evidence regarding cognitive behavioral therapy [54–57].

Surgical Interventions

For generalized unprovoked vulvodynia, there is no proposed surgical intervention. For the diagnosis of pudendal nerve entrapment, there is a surgical intervention. There is fair evidence that vestibulectomy surgery provides a net benefit for patients with vestibulodynia, but the size of this effect cannot be determined with confidence, and the number needed to treat (NNT) is not known [54–76]. Observational trials reported an effect of 31% to 100%, with a median of 79% for patients who reported at least some improvement to complete relief. For 12 studies reporting complete relief as an outcome, the median effect size was 67% [60,62–65,67–69,71–73,76]. The absolute effect was estimated to be 30% from 1 randomized controlled trial (RCT) [55]. The effect size from this single RCT could be consistent with the effect size seen with observational trials, on the basis that surgery has been reported to have a placebo effect of 35% [77–79] and the placebo effect seen with vestibulodynia in RCTs of nonsurgical interventions was 40% to 50% [80–83]. If the presumptive bias inherent in observational studies due to selection and placebo effect is deducted from the observed effect reported from the vestibulectomy observational studies, the absolute difference would approximate 30%. There is insufficient evidence to support that a specific vestibulectomy surgical technique is superior to another vestibulectomy surgical technique. There may be subsets of patients who are more likely to experience a benefit from vestibulectomy surgery; patients with secondary dyspareunia had greater odds of improvement than patients with primary dyspareunia [74].

Pharmacologic Therapy for Generalized Unprovoked Vulvodynia

All of the generalized unprovoked vulvodynia intervention studies reported a beneficial effect and most reported a statistical analysis of before and after treatment data. They all had methodological weaknesses, including lack of control or placebo group, lack of double-blind evaluation, lack of pretreatment pain and functional status evaluation, lack of validated outcome measures of pain and sexual functioning, lack of long-term outcomes, sparse data, and selective outcome bias [40–44,48,84–95]. There were no randomized trials. Due to the lack of high-quality studies, it is useful to

Table 4. Pharmacologic Agents Used in the Treatment of Generalized Unprovoked Vulvodynia

Therapy	Evidence of Efficacy for Pain Reduction by 50%	Cost Considerations
5% xylocaine	Fair	Generic
Pregabalin (oral)	Fair	No generic
Gabapentin (oral)	Fair	Generic
Duloxetine (oral)	Fair	No generic
SSRI	Fair	Some generics
Topical capsaicin, or gabapentin, or nitroglycerin	Poor	Compounded
Oral TCAs, or venlafaxine, pentosan polsulfate, opioids, tramadol, carbamazine, lamotrigine, oxcarbazepine, topiramate, valproic acid	Poor	Some generics

look at indirect evidence from studies of neuropathic pain disorders and functional pain disorders [96–107].

Topical Applications

There is fair evidence for efficacy of 5% xylocaine topical application [99,102] (**Table 4**). The NNT for 5% lidocaine was 4.4 (95% confidence interval [CI], 2.5–7) [102]. There is poor evidence for efficacy of topical capsaicin [102,103]. For every patient helped by capsaicin for neuropathic pain, 2 patients had to discontinue the treatment due to adverse effects. One could predict that adverse effect rates would be substantially higher if capsaicin were applied to the genital area. There is insufficient evidence regarding topical gabapentin [87] and topical nitroglycerin [94].

Oral Medications

There is fair evidence for efficacy of pregabalin across a variety of neuropathic conditions and fibromyalgia. The NNT for a 50% reduction in pain score ranged from 4 to 6, with a median of 5.3; the number needed to harm (NNH) for a withdrawal from the study due to adverse effects ranged from 4.8 to 14, with a median of 7.6 [96,98–100,102,106,107]. In 1 small double-blind cross-over RCT, pregabalin had a better net benefit profile than amitriptyline [107]. There is fair evidence for efficacy of gabapentin across a variety of neuropathic conditions [84–86,96,99,102].

There is fair evidence for a small effect size of duloxetine, based upon studies of neuropathic peripheral pain and polyneuropathy [99,102] and fibromyalgia [105]. The NNT for a 50% reduction in pain score was 5.5 (95% CI, 3.4–14) [102].

There is fair evidence for efficacy of selective serotonin reuptake inhibitors (SSRIs: bupropion, citalopram, paroxetine), based upon indirect evidence from studies of neuropathy and fibromyalgia. The reported effects were described as partial relief, small effect size, and the NNT from 1 systematic review was 6.8 [99,102,105].

There is poor evidence for efficacy of tricyclic antidepressants (TCAs) such as amitriptyline and desipramine [108]. Partial relief was found for postherpetic neuropathy and for diabetic peripheral neuropathy [99], but not for HIV neuropathy, spinal cord injury neuropathy, cisplatin-induced neuropathy, neuropathic cancer pain, and phantom limb pain [99]; findings were mixed for fibromyalgia [101,105], and no effect was found for painful bladder syndrome [104]. For neuropathic conditions for which TCA drugs have been found effective (postherpetic neuropathy, diabetic peripheral neuropathy), the NNT was 3.1 (95% CI, 2.7–3.7) [88–90,99,101,102,104,105,107]. The NNH was reported to be 14.7 (95% CI, 10–25) [102,107]. There was poor evidence for efficacy of venlafaxine. Partial relief was found for diabetic peripheral neuropathy but no effect for postherpetic neuropathy or postmastectomy pain, and mixed results for diverse peripheral neuropathy conditions [99].

There is poor evidence for monoamine oxidase inhibitors, based upon studies of fibromyalgia [105].

There is poor evidence for pentosan polsulfate, based upon studies of painful bladder syndrome [104].

There is poor evidence for net benefit of opioids [99,102]. The NNH was reported to be 17.1 (95% CI, 10–66) [102].

There is poor evidence for net benefit of tramadol [99,102]. The NNH was reported to be 9 (95% CI, 6–18) [102].

There is insufficient evidence regarding first- and second-generation antiepileptic medications: carbamazepine [109], lamotrigine, oxcarbazepine, topiramate, and valproic acid [99,102].

Injections

There is insufficient evidence regarding intralesional interferon [91], botulinum toxin injections [92,93], and trigger point injections [95].

Summary

In summary, there is insufficient evidence for any therapeutic intervention for vulvodynia. Based on evidence from treatment studies of neuropathic pain disorders and functional pain disorders, there is fair evidence for 5 interventions. The 5% xylocaine is relatively less expensive, has the lowest adverse effect profile, and would be a good first-line choice. Gabapentin and pregabalin have a similar pharmacologic basis of altering pain experience. Pregabalin has a more stable dose response and would be easier to manage. Gabapentin has generic alternatives and would be

less expensive than pregabalin in most settings. Duloxetine is the SNRI with the best evidence of efficacy. There is not enough evidence to favor 1 SSRI over the alternatives; the SSRIs that have been studied include bupropion, citalopram, and paroxetine. The SSRI may be a good choice if there is comorbid anxiety and or depression that is untreated or undertreated. A combined approach, using psychosexual interventions, pharmacologic interventions, and rehabilitative interventions may prove most effective.

Placebo effect of interventions for generalized unprovoked vulvodynia, neuropathic pain disorders, and functional pain disorders. In large double-blind randomized placebo-controlled trials, the total percentage of patients reporting a clinically significant effect from an intervention for neuropathic pain or functional pain syndromes was in the range of 45%, with the placebo benefit profile accounting for 22% of the total effect [96–101]. The high-quality evidence from large double-blind RCTs suggests that the reported high response rates of up to 100% in retrospective nonrandomized studies was likely due to bias. Placebo responses have also been large across a number of clinical trials for treatment of women's sexual dysfunction [110].

One could surmise that on average an intervention for a neuropathic or functional pain syndrome would result in a reported benefit of greater than 50% pain reduction in 45 patients out of every 100 treated: 22 from a placebo effect, and 23 from an effect of the intervention [111]. In all, 55 of the 100 patients will report either withdrawal from the medication, lack of effect, or a less than 50% reduction in pain score.

Pharmacologic Interventions for Vestibulodynia

Success rates in studies of pharmacologic interventions for vestibulodynia vary from no effect to 100%. Most of the studies have methodological weaknesses, including lack of control or placebo group, lack of double-blind evaluation, lack of pretreatment pain and functional status evaluation, lack of validated outcome measures of pain and sexual functioning, and lack of long-term outcomes. There have been 7 randomized trials; of these, 2 were not placebo-controlled and demonstrated no effect [112,113]. The 5 placebo-controlled randomized trials of medical interventions all showed no effect of the target intervention when compared with placebo [45,80–83]. The majority of the published studies were nonrandomized, and almost all reported an effect. Most of these studies reported a statistical analysis of before and after treatment data.

Injections

There is fair evidence of a lack of efficacy for botulinum toxin injections [83,114–117]. The body of evidence for other injections was poor; there was insufficient evidence regarding steroid and "caine"-drug mixed injections [118,119], multilevel nerve blocks [120], intramuscular interferon [121,122], and intralesional interferon [91,123] (**Table 5**).

Table 5. Pharmacologic Agents Used in the Treatment of Vestibulodynia

Insufficient evidence of efficacy for pain/insufficient evidence of efficacy for sexual function
Injections of steroid and -caine mixtures
Multilevel nerve blocks
Interferon intralesional or intramuscular
Capsaicin topical
Montelukast topical
Steroid topical
Gabapentin topical
Ketoconazole topical
Calcium citrate oral
Evidence of nonefficacy for pain/nonefficacy for sexual function
Botulinum toxin injection
5% xylocaine topical
Cromolyn topical
Nifedipine topical
Desipramine oral
Fluconazole oral

Topical Applications

There is fair evidence of a lack of efficacy for 5% xylocaine topical application [80,112,124], for topical cromolyn [81], and for topical nifedipine [82]. The body of evidence for other topical applications was poor; there was insufficient evidence regarding capsaicin [125,126], montelukast [127], steroid [128], gabapentin [87], and ketoconazole [129]. There is no evidence for benefit of topical estrogen or for topical testosterone.

Oral Medications

There is fair evidence of a lack of efficacy for oral desipramine [80] and for oral fluconazole [113]. There is insufficient evidence regarding oral calcium citrate [130]. There is no evidence for benefit of withdrawing combined hormonal contraceptive medications, and the risk of unintended pregnancy must be considered.

There is insufficient evidence to support that any of the nonsurgical therapies confers a net benefit for patients with vestibulodynia. Further, single randomized placebo-controlled trials have demonstrated moderate- to high-quality evidence for a lack of benefit of topical 5% xylocaine, oral desipramine, oral fluconazole, topical cromolyn, topical nifedipine, and botulinum injections. The evidence was insufficient to draw reliable conclusions about the efficacy of numerous other interventions.

Summary

In summary, there is insufficient evidence for any nonsurgical therapeutic intervention for vestibulodynia. There is fair evidence for efficacy of vestibulectomy surgery. This leaves the patient and provider in a quandary if they wish to try nonsurgical interventions to improve the pain and sexual dysfunction. Open discussion of the state of the science and alternatives is advised. If interventions are chosen and prescribed, it should be with understanding of the lack of evidence for efficacy. When appropriate, patients should be offered the opportunity to enter placebo-controlled randomized controlled trials of potential therapeutic interventions.

Placebo effect. It is useful to look at the placebo-controlled randomized trials that reported before and after data for the placebo group to gauge the size of the placebo effect. The placebo effect, described as an absolute effect of greater than 50% decline in the pain score(s), was 40% [80], 46% [81], 50% [82], and 50% [83]. The highest quality evidence of placebo effect in vestibulodynia is from the VVCT study by Foster et al [80] and the botulinum study by Petersen et al [83]. The VVCT placebo-controlled randomized trial of 133 patients found no difference in validated pain outcome measures between the intervention groups and the placebo group [80]. The Petersen study [83] had fewer patients and showed a similar placebo effect, with no difference in validated pain outcome measures between the intervention group and the placebo group. The Nyirjesy publication [81] is important because it was well designed, although the data from 26 patients was sparse. No difference was found in pain and dyspareunia measures between the intervention group and the placebo group; however, a placebo effect was found. Similarly, Bornstein's [82] placebo-controlled trial of 30 patients found a placebo effect, but no difference in outcomes between the intervention group and placebo group. Murina et al [45] designed a randomized placebo-controlled trial but focused their results and conclusions on the positive effect between the posttreatment outcome measures and pretreatment measures within the treatment group; the trial showed no effect when the electronic stimulation intervention was compared to the placebo.

This analysis highlights the challenge of making necessary informed clinical decisions in the absence of high quality evidence. As Bornstein observed [113], "It is astonishing that the currently available vestibulitis treatments have been introduced without first establishing their effectiveness in a prospective randomized study. Every new treatment is introduced as the state-of-the-art approach without subjecting it to thorough evaluation. This phenomenon results from our desire to provide our patients quick relief from the misery of vestibulitis, especially if the treatment seems noninvasive."

Clinical inferences can be drawn from the observation that there is a consistent 50% placebo response rate in placebo-controlled trials of patients with vestibulodynia. In the absence of an effective nonsurgical intervention and insufficient evidence about several interventions, the placebo effect may play a role as a therapeutic cofactor. Certain types of provider-patient interactions and statements may be more likely to confer a benefit. Further research may focus on which interventions are most likely to achieve a net placebo benefit without significant risks, adverse effects, or costs.

Treatment and Course

Case 1

This patient had already been treated with oral amitriptyline (reported no benefit and side effect of drowsiness caused her to discontinue), topical 5% xylocaine (reported no benefit), and venlafaxine (reported no benefit). There was a lengthy education and counseling session, and access provided to further resource materials. She was given a prescription for pregabalin. She returned after 3 weeks and reported a reduction in her pain score from 4–5 down to 2–3. She has decided to remain on this therapy and will return if her pain increases. She returned after a 6-month interval and reported that she had good days and bad days and that the pain, while present, was more tolerable than it had been several months earlier.

Case 2

After a lengthy education and counseling session, the patient opted to have vestibulectomy surgery. She was referred to a surgeon. After informed consent, she underwent vestibulectomy. Six weeks after surgery, she was initiated with a physiotherapist because of the preoperative hypertonus of the pelvic floor muscles and concomitant vaginismus, and used dilators and lubricant. At a 6-month postoperative visit, she reported that she was having no pain with intercourse and her sexual relationship was normal.

SUMMARY

Vulvar pain is a symptom of a set of complex disorders and is often a frustrating experience for patients and their providers. Vulvodynia can be difficult to treat. Many treatments for vulvodynia, both generalized and localized, have been discussed. No single treatment is successful in all women with vulvodynia. Rapid resolution of symptomatic chronic vulvodynia is unusual. Improvement of pain may take months. The expected level of improvement needs to be addressed realistically with patients.

Note: The author is solely responsible for the content of this article and the decision to submit for publication. No statement in this article should be construed as an official position of the Vanderbilt Evidence-Based Practice

Center, the International Society for the Study of Vulvovaginal Disease, or the GRADE Working Group.

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References

1. Bachmann GA, Rosen R, Pinn VW, et al. Vulvodynia: a state of the art consensus on definitions, diagnosis, and management. J Reprod Med 2006;51:447–56.
2. Masheb RM, Nash JM, Brondolo E, Kerns RD. Vulvodynia: an introduction and critical review of a chronic pain condition. Pain 2000;86:3–10.
3. Haefner, HK. Report of the International Society for the Study of Vulvovaginal Disease Terminology and Classification of Vulvodynia. J Low Gen Tract Dis 2007;11:48–9.
4. Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. J Reprod Med 2004;49:772–7.
5. Edwards L. Subsets of vulvodynia: overlapping characteristics. J Reprod Med 2004;49:883–6.
6. Arnold LD, Bachmann GA, Rosen R, Rhoads GG. Assessement of vulvodynia symptoms in a sample of U.S. women: a prevalence survey with a nested case control study. Am J Obstet Gynecol 2007;196:128.e1–6.
7. Harlow BL, Stewart EG. A population-based assessment of chronic unexplained vulvar pain: have we underestimated the prevalence of vulvodynia? J Am Med Womens Assoc 2003; 58:82–8.
8. Reed BD, Haefner HK, Harlow SD, et al. Reliability and validity of self-reported symptoms for predicting vulvodynia. Obstet Gynecol 2006;108:906–13.
9. Lavy RJ, Hynan LS, Haley RW. Prevalence of vulvar pain in an urban, minority population. J Reprod Med 2007;52:59–62.
10. Reed BD, Crawford S, Couper M, et al. Pain at the vulvar vestibule: a web-based survey. J Low Genit Tract Dis 2004;8:48–57.
11. Schultz WW, Basson R, Binik Y, et al. Women's sexual pain and its management. J Sex Med 2005;2:301–16.
12. McKay M. Burning vulva syndrome: report of ISSVD task force. J Reprod Med 1984;29:457.
13. Lynch PJ. Vulvodynia: a syndrome of unexplained vulvar pain, psychologic disability, and sexual dysfunction. The 1985 ISSVD presidential address. J Reprod Med 1986;31:773–80.
14. Friedrich EG. Vulvar vestibulitis syndrome. J Reprod Med 1987;32:110–4.
15. Edwards L. New concepts in vulvodynia. Am J Obstet Gynecol 2003;189(3 Suppl):S24–30.
16. Goldstein AT. Moving beyond the diagnosis of vestibulodynia —a holiday wish list [editorial]. J Sex Med 2009;6:3227–9.
17. Diagnostic and statistical manual of mental disorders, 4th ed, text revision. Washington DC: American Psychiatric Association; 2000.
18. Lynch PJ. Vulvodynia as a somatoform disorder. J Reprod Med 2008;53:390–6.
19. van Lankveld JJDM, Granot M, Weijmar Schultz WCM, et al. Women's sexual pain disorders. J Sex Med 2010;7:615–31.
20. Mayer E, Bushnell MC, editors. Functional pain syndromes: presentation and pathophysiology. Intl Assoc for the Study of Pain; 2009.
21. Hawthorn J, Redmond K. The physiology of pain. In: Hawthorn J, Redmond K, editors. Pain: causes and management. Oxford: Blackwell Science; 1998:7–28.
22. Mascherpa F, Bogliatto F, Lynch PJ, et al. Vulvodynia as a possible somatization disorder. More than just a notion. J Reprod Med 2007;52:107–10.
23. Dieleman JP, Kerklaan J, Huygen FJPM, et al. Incidence rates and treatment of neuropathic pain conditions in the general population. Pain 2008;137:681–8.
24. International Association for the Study of Pain (IASP): www.iasp-pain.org/terms-p.html Accessed 2 Jan 10.
25. Hansson PT, Dickenson AH. Pharmacological treatment of peripheral neuropathic conditions based on shared commonalities despite multiple etiologies. Pain 2005;113:251–4.
26. Cruccu G, Anand P, Attal N, et al. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2004;11:153–62.
27. Attal N, Cruccu G, Haanpaa M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153–69.
28. Forssell H, Tenovuo O, Silvoniemi P, Jakelainen SK. Differences and similarities between atypical facial pain and trigeminal neuropathic pain. Neurology 2007;69:1451–9.
29. Lipowski ZJ. Chronic idiopathic pain syndrome. Ann Med 1990;22:213–7.
30. Marinoff SC, Turner ML. Vulvar vestibulitis syndrome: an overview. Am J Obstet Gynaecol 1991;165:1228–33.
31. Diagnosis and management of vulvar skin disorders. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 May. 11 p. (ACOG practice bulletin; no. 93).
32. Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome, and similar diseases in women: a systematic review. J Urol 2007;177:450–6.
33. Peters KM, Carrico DJ, Ibrahim IA, Diokno AC. Characterization of a clinical cohort of 87 women with interstitial cystitis/painful bladder syndrome. Urology 2008;71:634–40.
34. Arnold LD, Bachmann GA, Rosen R, et al. Vulvodynia: characteristics and associations with comorbidities and quality of life. Obstet Gynecol 2006;107:617–24.
35. The Overlapping Conditions Alliance www.overlappingconditions.org.
36. Krantz KE. Innervation of the human vulva and vagina. Obstet Gynecol 1959;12:382–96.
37. Weström LV, Willén R. Vestibular nerve fiber proliferation in vulvar vestibulitis syndrome. Obstet Gynecol 1998;91:572–6.
38. Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. J Lower Genital Tract Dis 2005;9:40.
39. Landry T, Bergeron S, Dupuis MJ, Desrochers G. The treatment of provoked vestibulodynia: a critical review. Clin J Pain 2008;24:155–71.
40. Powell J, Wojnarowska F. Acupuncture for vulvodynia. J Royal Soc Med 1999;92:579–81.
41. Zawislak AA, McCarron PA, McCluggage WG, et al. Novel bioadhesive patch-type system for photodynamic vulvodynia

therapy after delivery of 5-aminolevulinic acid: preliminary evaluation. J Reprod Med 2007;52:645–53.
42. Holcomb RR, Worthington WB, McCullough BA, McLean MJ. Static magnetic field therapy for pain in the abdomen and genitals. Pediatric Neurol 2000;23:261–4.
43. Whiteside JL, Walters MD, Mekhail N. Spinal cord stimulation for intractable vulvar pain. A case report. J Reprod Med 2003;48:821–3.
44. Nair AR, Klapper A, Kushnerik V, et al. Spinal cord stimulator for the treatment of a woman with vulvovaginal burning and deep pelvic pain. Obstet Gynecol 2008;111(2 Pt 2):545–7.
45. Murina F, Bianco V, Radici G, et al. Transcutaneous electrical nerve stimulation to treat vestibulodynia: a randomised controlled trial. BJOG 2008;115:1165–70.
46. Nappi RE, Ferdeghini F, Abbiati I, et al. Electrical stimulation in the management of sexual pain disorders. J Sex Marital Ther 2003;29 Suppl 1:103–10.
47. Danielsson I, Sjoberg I, Ostman C. Acupuncture for the treatment of vulvar vestibulitis: a pilot study. Acta Obstetricia et Gynecologica Scandinavica 2001;80:437–41.
48. Glazer HI. Dysesthetic vulvodynia. Long-term follow-up after treatment with surface electromyography-assisted pelvic floor muscle rehabilitation. J Reprod Med 2000;45:798–802.
49. Murina F, Bernorio R, Palmiotto R. The use of amielle vaginal trainers as adjuvant in the treatment of vestibulodynia: an observational multicentric study. Medscape J Med 2008;10:23.
50. Goldfinger C, Pukall CF, Gentilcore-Saulnier E, et al. A prospective study of pelvic floor physical therapy: pain and psychosexual outcomes in provoked vestibulodynia. J Sex Med 2009;6:1955–68.
51. Forth HL, Cramp MC, Drechsler WI. Does physiotherapy treatment improve the self-reported pain levels and quality of life of women with vulvodynia? A pilot study. J Obstet Gynaecol 2009;29:423–9.
52. Bergeron S, Brown C, Lord MJ, et al. Physical therapy for vulvar vestibulitis syndrome: a retrospective study. J Sex Marital Ther 2002;28:183–92.
53. Fisher KA. Management of dyspareunia and associated levator ani muscle overactivity. Phys Therapy 2007;87:935–41.
54. Granot M, Zimmer EZ, Friedman M, et al. Association between quantitative sensory testing, treatment choice, and subsequent pain reduction in vulvar vestibulitis syndrome. J Pain 2004;5:226–32.
55. Bergeron S, Binik YM, Khalife S, et al. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain 2001;91:297–306.
56. Bergeron S, Khalife S, Glazer HI, Binik YM. Surgical and behavioral treatments for vestibulodynia: two-and-one-half year follow-up and predictors of outcome. Obstet Gynecol 2008; 111:159–66.
57. Landry T, Bergeron S, Dupuis MJ, Desrochers G. Surgical and behavioral treatments for vestibulodynia: two-and-one-half year follow-up and predictors of outcome. Obstet Gynecol 2008;111:159–66.
58. Chaim W, Meriwether C, Gonik B, et al. Vulvar vestibulitis subjects undergoing surgical intervention: a descriptive analysis and histopathological correlates. Eur J Obstet Gynecol Reprod Biol 1996;68:165–8.
59. Gaunt G, Good A, Stanhope CR. Vestibulectomy for vulvar vestibulitis. J Reprod Med 2003;48:591–5.
60. Bergeron S, Bouchard C, Fortier M, et al. The surgical treatment of vulvar vestibulitis syndrome: a follow-up study. J Sex Marital Ther 1997;23:317–25.
61. Traas MA, Bekkers RL, Dony JM, et al. Surgical treatment for the vulvar vestibulitis syndrome. Obstet Gynecol 2006;107: 256–62.
62. Goldstein AT, Klingman D, Christopher K, et al. Surgical treatment of vulvar vestibulitis syndrome: outcome assessment derived from a postoperative questionnaire. J Sex Med 2006; 3:923–31.
63. McCormack WM, Spence MR. Evaluation of the surgical treatment of vulvar vestibulitis. Eur J Obstet Gynecol Reprod Biol 1999;86:135–8.
64. Goetsch MF. Simplified surgical revision of the vulvar vestibule for vulvar vestibulitis. Am J Obstet Gynecol 1996;174:1701–5.
65. Schneider D, Yaron M, Bukovsky I, et al. Outcome of surgical treatment for superficial dyspareunia from vulvar vestibulitis. J Reprod Med 2001;46:227–31.
66. Kehoe S, Luesley D. Vulvar vestibulitis treated by modified vestibulectomy. Int J Gynaecol Obstet 1999;64:147–52.
67. Lavy Y, Lev-Sagie A, Hamani Y, et al. Modified vulvar vestibulectomy: simple and effective surgery for the treatment of vulvar vestibulitis. Eur J Obstet Gynecol Reprod Biol 2005; 120:91–5.
68. Bornstein J, Goldik Z, Stolar Z, et al. Predicting the outcome of surgical treatment of vulvar vestibulitis. Obstet Gynecol Surv 1997;52:618–9.
69. Bornstein J, Abramovici H. Combination of subtotal perineoplasty and interferon for the treatment of vulvar vestibulitis. Gynecol Obstet Invest 1997;44:53–6.
70. Eva LJ, Narain S, Orakwue CO, Luesley DM. Is modified vestibulectomy for localized provoked vulvodynia an effective long-term treatment? A follow-up study. J Reprod Med Jun 2008;53:435–40.
71. Rettenmaier MA, Brown JV, Micha JP. Modified vestibulectomy is inadequate treatment for secondary vulvar vestibulitis. J Gynecol Surg March 2003;19:13–7.
72. Goetsch MF. Surgery combined with muscle therapy for dyspareunia from vulvar vestibulitis: an observational study. J Reprod Med Jul 2007;52:597–603.
73. Goetsch MF. Patients' assessments of a superficial modified vestibulectomy for vestibulodynia. J Reprod Med Jun 2008; 53:407–12.
74. Bohm-Starke N, Rylander E. Surgery for localized, provoked vestibulodynia: a long-term follow-up study. J Reprod Med Feb 2008;53:83–9.
75. Leclair CM, Goetsch MF, Lee KK, Jensen JT. KTP-nd:YAG laser therapy for the treatment of vestibulodynia: a follow-up study. J Reprod Med Jan 2007;52:53–8.
76. Bornstein J, Zarfati D, Goldik Z, Abramovici H. Perineoplasty versus vestibuloplasty for severe vulvar vestibulitis: a randomized comparison. Br J Obstet Gynecol 1995;102:652–5.

77. Johnson AG. Surgery as a placebo. Lancet 1994;344:1140–2.
78. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81–8.
79. Daniels J, Gray R, Hills RK, et al; on behalf of the LUNA Trial Collaboration. Laparoscopic uterosacral nerve ablation for alleviating chronic pelvic pain. A randomized controlled trial. JAMA 2009;302:955–61.
80. Foster D. Vulvar Vestibulitis Clinical Trial (VVCT) outcomes following oral desipramine and topical lidocaine. Abstract and data presented at ISSVD, Edinburgh, UK 18 Sep 09, http://clinicaltrials.gov/ct2/show/NCT00276068.
81. Nyirjesy P, Sobel JD, Weitz MV, et al. Cromolyn cream for recalcitrant idiopathic vulvar vestibulitis: results of a placebo-controlled study. Sex Transm Inf 2001;77:53–7.
82. Bornstein J. Topical nifedipine for vestibulodynia—a placebo controlled study. Abstract and data presented at ISSVD Conference, Edinburgh, UK 18 Sep 09.
83. Petersen CD, Giraldi A, Lundvall L, Kristensen E. Botulinum toxin type A—a novel treatment for provoked vestibulodynia? Results from a randomized, placebo controlled, double blinded study. J Sex Med 2009;6:2523–37.
84. Ben-David B, Friedman M. Gabapentin therapy for vulvodynia. Anesth Anal 1999;89:1459–62.
85. Sasaki K, Smith CP, Chuang YC, et al. Oral gabapentin (neurontin) treatment of refractory genitourinary tract pain. Tech Urology 2001;7:47–9.
86. Harris G, Horowitz B, Borgida A. Evaluation of gabapentin in the treatment of generalized vulvodynia, unprovoked. J Reprod Med 2007;52:103–6.
87. Boardman LA, Cooper AS, Blais LR, Raker CA. Topical gabapentin in the treatment of localized and generalized vulvodynia. Obstet Gynecol 2008;112:579–85.
88. McKay M. Dysesthetic ("essential") vulvodynia. Treatment with amitriptyline. J Reprod Med 1993;38:9–13.
89. Munday PE. Response to treatment in dysaesthetic vulvodynia. J Obstet Gynaecol 2001;21:610–3.
90. Reed BD, Caron AM, Gorenflo DW, Haefner HK. Treatment of vulvodynia with tricyclic antidepressants: efficacy and associated factors. J Lower Genital Tract Dis 2006;10:245–51.
91. Kent HL, Wisniewski PM. Interferon for vulvar vestibulitis. J Reprod Med 1990;35:1138–40.
92. Gunter J, Brewer A, Tawfik O. Botulinum toxin a for vulvodynia: a case report. J Pain 2004;5:238–40.
93. Yoon H, Chung WS, Shim BS. Botulinum toxin A for the management of vulvodynia. Int J Impotence Res 2007;19:84–7.
94. Walsh KE, Berman JR, Berman LA, Vierregger K. Safety and efficacy of topical nitroglycerin for treatment of vulvar pain in women with vulvodynia: a pilot study. J Gender-Specific Med 2002;5:21–7.
95. Langford CF, Udvari NS, Ghoniem GM. Levator ani trigger point injections: an underutilized treatment for chronic pelvic pain. Neurourology Urodynam 2007;26:59–62.
96. Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrolment: definition, and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. Br J Clin Pharm 2008;66:266–75.
97. Quessy SN, Rowbotham MC. Placebo response in neuropathic pain trials. Pain 2008;138:479–83.
98. Freeman R, Decruz ED, Emir E. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy. Findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008;31:1448–54.
99. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237–51.
100. Freynhagena R, Strojekb K, Griesingc T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254–63.
101. Heymann RE, Helfenstein M, Feldman D. A double-blind, randomized, controlled study of amitriptyline, nortriptyline, and placebo in patients with fibromyalgia. An analysis of outcome measures. Clin Exp Rheumatol 2001;19:697–702.
102. Finnerup NB, Otto M, McQuay HJ, et al. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005;118:289–305.
103. Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2009;CD007393.
104. Dimitrakov J, Kroenke K, Steers WD, et al. Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. Arch Intern Med 2007;167:1922–9.
105. Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. JAMA 2009;301:198–209.
106. Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008;136:432–44.
107. Bansal D, Bhansali A, Hota D, et al. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. Diabetic Med 2009;26:1019–26.
108. Norpramin (desipramine hydrochloride)—Dear Healthcare Professional Letter. Extreme caution should be used when this drug is given to patients who have a family history of sudden death, cardiac dysrhythmias, and cardiac conduction disturbances; seizures precede cardiac dysrhythmias and death in some patients. Posted 2 Dec 09. Accessed 12 Jan 10 at: www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm192655.htm
109. Carbamazepine—Drug Information Page. Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis) that can be caused by carbamazepine therapy are significantly more common in patients with HLA-B*1502, which occurs almost exclusively in patients with ancestry in Asia, including South Asian Indians. Posted 12 Dec 07. Accessed 12 Jan 10 at: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm.
110. Bradford A, Meston C. Correlates of placebo response in the treatment of sexual dysfunction in women: a preliminary report. J Sex Med 2007;4:1345–51.

111. Cruccu G. Treatment of painful neuropathy. Curr Opin Neurol 2007;20:531–5.
112. Danielsson I, Torstensson T, Brodda-Jansen G, Bohm-Starke N. EMG biofeedback versus topical lidocaine gel: a randomized study for the treatment of women with vulvar vestibulitis. Acta Obstetricia et Gynecologica Scandinavica 2006;85:1360–7.
113. Bornstein J, Livnat G, Stolar Z, Abramovici H. Pure versus complicated vulvar vestibulitis: a randomized trial of fluconazole treatment. Gynecol Obstet Investigation 2000;50:194–7.
114. Bennani B, Raki S, Monnier G, et al. [Botulinum toxin for vulvar vestibulitis]. [French] Annales de Dermatologie et de Venereologie 2006;133:807–8.
115. Romito S, Bottanelli M, Pellegrini M, et al. Botulinum toxin for the treatment of genital pain syndromes. Gynecol Obstet Invest 2004;58:164–7.
116. Brown CS, Glazer HI, Vogt V, et al. Subjective and objective outcomes of botulinum toxin type A treatment in vestibulodynia: pilot data. J Reprod Med 2006;51:635–41.
117. Dykstra DD, Presthus J. Botulinum toxin type A for the treatment of provoked vestibulodynia: an open-label, pilot study. J Reprod Med 2006;51:467–70.
118. Murina F, Tassan P, Roberti P, Bianco V. Treatment of vulvar vestibulitis with submucous infiltrations of methylprednisolone and lidocaine. An alternative approach. J Reprod Med 2001;46:713–6.
119. Segal D, Tifheret H, Lazer S. Submucous infiltration of betamethasone and lidocaine in the treatment of vulvar vestibulitis. Eur J Obstet Gynecol Reprod Biol 2003;107:105–6.
120. Rapkin AJ, McDonald JS, Morgan M. Multilevel local anesthetic nerve blockade for the treatment of vulvar vestibulitis syndrome. J Obstet Gynecol 2008;198:41.e1–5.
121. Bornstein J, Pascal B, Abramovici H. Treatment of a patient with vulvar vestibulitis by intramuscular interferon beta; a case report. Eur J Obstet Gynec Repro Bio 1991;42:237–9.
122. Bornstein J, Pascal B, Abramovici H. Intramuscular beta-interferon treatment for severe vulvar vestibulitis. J Reprod Med 1993;38:117–20.
123. Marinoff SC, Turner ML, Hirsch RP, Richard G. Intralesional alpha interferon: cost effective therapy for vulvar vestibulitis syndrome. J Reprod Med 1993;38:19–24.
124. Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. Obstet Gynecol 2003;102:84–7.
125. Murina F, Radici G, Bianco V. Capsaicin and the treatment of vulvar vestibulitis syndrome: a valuable alternative? Medscape Gen Med 2004;6:48.
126. Steinberg AC, Oyama IA, Rejba AE, et al. Capsaicin for the treatment of vulvar vestibulitis. Am J Obstet Gynecol 2005; 192:1549–53.
127. Kamdar N, Fisher L, MacNeill C. Improvement in vulvar vestibulitis with montelukast. J Reprod Med 2007;52:912–6.
128. Munday PE. Treatment of vulval vestibulitis with a potent topical steroid. Sex Transm Infect 2004;80:154–5.
129. Morrison GD, Adams SJ, Curnow JS, et al. A preliminary study of topical ketoconazole in vulvar vestibulitis syndrome. J Dermatolog Treat 1996;7:219–21.
130. Solomons CC, Melmed MH, Heitler SM. Calcium citrate for vulvar vestibulitis: a case report. J Reprod Med 1991;36:879–82.