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% [1,2,6,9–11]. 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
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 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].

• 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 biologic 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 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.

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.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Adaptive pain</td>
<td>Nociceptive pain, inflammatory pain</td>
</tr>
<tr>
<td>Maladaptive pain</td>
<td>Neuropathic pain, functional pain</td>
</tr>
<tr>
<td>Nociceptive pain</td>
<td>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</td>
</tr>
<tr>
<td>Inflammatory pain</td>
<td>Results from inflammatory agents causing tissue damage, which stimulates the nerve endings and transmission</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>“Neuropathic” when pain becomes a disease (ie, it is generated within the nerves and nervous centers) rather than from nociception or inflammation</td>
</tr>
<tr>
<td>Functional pain</td>
<td>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</td>
</tr>
<tr>
<td>Alldynia</td>
<td>A usually nonpainful stimulus, like light touch, is painful</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>An increase in the magnitude of pain induced by a stimulus that is normally painful</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>Characterized by unusual sensation (burning, pain, tingling) Sensation occurs without any stimulation</td>
</tr>
</tbody>
</table>

Table 1. 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
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 vulvoscopy 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.

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

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

- **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/ameliorating 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 (alldynia) 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 alldynia. A diagram of the pain locations is helpful 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 alldynia, the examination identifies the vestibule as the location of alldynia. 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).

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**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.

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**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, orofacial 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.
VULVODYNIA

Table 3. Differential Diagnosis of Vulvar Pain

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

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 Friedrich’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.

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 alldynia. 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

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

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 of 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 monamine oxidase inhibitors, based upon studies of fibromyalgia [105].

There is poor evidence for pentosan polysulfate, 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 171 (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
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 intraligamental 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 intraligamental 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.

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

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