文章编号：1001-6325(2008)04-0315-16

专题综述

Vulvodynia: A review of pathophysiological factors and treatment options

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Abstract: Vulvodynia, or chronic vulvar pain, affects 16% of women in the general population and has negative effects on numerous aspects of a woman's life. The purpose of this paper is to review the literature on the etiology and treatment of vulvodynia. Since relatively little research has been carried out on unprovoked generalized vulvodynia (UGVD), this review focuses on provoked vestibulodynia (PVD), a subtype of vulvodynia characterized by a severe, burning/sharp pain that occurs in response to pressure localized to the vestibule. Research examining the pathophysiology of PVD provides evidence that both peripheral (e.g., vestibular tissue abnormalities, pelvic floor hypertonicity) and central (e.g., increased neural activation) factors are involved in the development and maintenance of PVD. Additionally, psychological reactions to the pain may vary and influence the expression and course of the pain. Despite the multitude of factors involved in PVD, most treatment studies to date are unimodal in nature, retrospective, and uncontrolled. A review of treatment studies targeting peripheral (e.g., topical applications, vestibulectomy) and central (e.g., antidepressants, pain management therapy) components of PVD is provided, and the need for multimodal treatment plans which target both levels of pain processing is discussed. Given the complexity of PVD, a biopsychosocial approach is recommended for future research endeavors and treatment plans.

Key words: Vulvodynia; provoked vestibulodynia; treatment; pathophysiological factors; etiology

外阴痛:病理生理因素和临床治疗新观点方面的综述

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摘要:慢性外阴疼痛,简称为外阴痛,在普通妇女人群中的发病率约为 16%。本文简要概述了外阴痛的病因学以及治疗现状。到目前为止,对自发性广泛性外阴痛(unprovoked generalized vulvodynia,UGVD)的研究较少,本文重点讨论了外阴痛的一个亚类,即诱发的阴道前庭痛(provoked vestibulodynia,PVD),其症状为压迫阴道前庭周围可产生严重的烧灼样痛或剧烈疼痛。以往的研究表明外周(如阴道前庭组织异常、骨盆肌张力增高)和中枢(如神经中枢冲动增多)因素都参与了 PVD 的发生和维持过程。此外,由于患者对疼痛的心理性反应各异,也影响了疼痛症状的表现和时程。尽管 PVD 的发生包含多种因素,但到目前为止,对其治疗的研究都是单一的,回顾性和不可控的。本综述着眼于对 PVD 的外周(如局部用药、外阴大腺切除术等)和中枢(如应用抗抑郁药、镇痛治疗等)治疗,同时还讨论了针对于痛觉传递过程中不同水平(外周和中枢)的多向治疗方案。鉴于 PVD 机制的复杂性, 今后对

收稿日期:2007 - 12 - 14

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PVD 的治疗推荐应用生物心理社会学疗法。

关键词：外阴痛；诱发的阴道前庭痛；治疗；病理生理因素；病因学
中图分类号：R 441.1 **文献标志码**：A

1 Introduction

Vulvodynia, or idiopathic chronic vulvar pain, is a common problem affecting women of all ages. A recently published population-based study estimated that the lifetime cumulative incidence of vulvodynia is 16%, indicating that approximately 14 million women in the United States alone may experience vulvodynia at some point during their lifetime[1]. Relatively unknown until recently, vulvodynia has gained increased attention from Western governments, scientists, and health care professionals. This increased awareness may be due, at least in part, to a greater willingness of women to discuss such an intimate problem and to a better recognition of the condition by health professionals. Changes in the conceptualization of vulvodynia may have also played a role.

Past conceptualizations of vulvodynia were unidimensional, focusing solely on physical or sexual explanations for the pain. These lines of investigation rarely yielded much useful information in terms of etiology or treatment[2]. Many current conceptualizations, therefore, view vulvodynia from a multidimensional viewpoint. For example, we apply a multidimensional pain approach to the understanding and treatment of chronic vulvar pain. This view is consistent with current biopsychosocial pain perspectives that evolved from the Gate Control Theory of Pain, which states that the experience of pain includes both sensory and affective components and that psychological factors can play a role in pain control[3]. According to this theory, although the study of underlying physiology is important, it is not sufficient to capture the entire pain experience. In line with this approach are findings indicating that vulvodynia disrupts sexual functioning, interferes with the reproductive process, and negatively impacts psychological well-being, relationship adjustment, and overall quality of life[4-5]. In addition, physical and psychological factors can maintain and exacerbate the pain, resulting in a vicious cycle of pain. This model has implications for multimodal treatment[6], as it implies that targeting several factors involved in the vicious cycle will likely be more effective than unimodal treatment options.

Unfortunately, little is known about the factors involved in the development and maintenance of chronic vulvar pain. As well, a myriad of treatment options has been suggested, all with varying degrees of success as assessed by mostly retrospective studies. Few randomized controlled trials have been conducted in the area of vulvodynia, and fewer treatments have withstood the test of such trials. Further, the bulk of the existing research in the area of vulvodynia has focused on a common vulvodynia subtype called provoked vestibulodynia (PVD); very little systematic work has been conducted on the relatively less common, but still prevalent, condition of unprovoked generalized vulvodynia (UGVD). This review paper will present the most recent definition of vulvodynia, describe PVD and UGVD, and focus on the pathophysiology and treatment of PVD.

2 Vulvodynia

Vulvodynia has recently been defined as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder"[7]. Vulvodynia is divided into two categories based on pain location: localized vulvodynia refers to pain in one particular area of the vulva, such as the vulvar vestibule (i.e., vaginal entrance) or clitoris, whereas generalized vulvodynia refers to pain affecting

the entire vulvar region (i.e., the mons pubis, clitoris, labia majora, labia minora, and vulvar vestibule). Each category is further divided according to the temporal pattern of the pain. Provoked pain occurs in response to external stimulation (e.g., pressure) to the affected area, unprovoked pain occurs in the absence of stimulation, and some types of vulvodynia have a mixed presentation of provoked and unprovoked pain. Provoked pain can result from sexual activities (e.g., vaginal penetration), non-sexual activities (e.g., gynecological examinations), or both types of activities.

The categorization of vulvodynia according to pain location and temporal pattern of pain allows for the subdivision of vulvodynia into two common subtypes: provoked vestibulodynia (PVD), formerly termed vulvar vestibulitis syndrome, and unprovoked generalized vulvodynia (UGVD). PVD is perhaps the most common type of vulvodynia in pre-menopausal women, affecting 12% of women in the general population[8]. PVD is characterized by a severe, burning/sharp pain that occurs in response to pressure localized to the vestibule[9]. UGVD affects 6% ~7% of women in the population[8]; it is characterized by spontaneously-occurring burning pain over the entire vulvar area. These two forms of vulvodynia are diagnoses of exclusion; other possible causes for the pain (e.g., infection, inflammation) must be ruled out[7].

Friedrich[10] proposed the following diagnostic criteria for PVD: severe pain upon vestibular touch or attempted vaginal entry, tenderness to pressure localized within the vulvar vestibule, and physical findings limited to vestibular erythema (i.e., redness). Although the latter criterion has not received support in terms of its reliability and validity, the first two have[9]. In relation to the first, dyspareunia (i.e., painful intercourse) is the defining symptom of PVD and is often the patient's presenting complaint. Dyspareunia can be present from the first intercourse attempt (i.e., primary PVD) or it may develop after a period of pain-free intercourse (i.e., secondary PVD). The cotton-swab test, the standard gynecological method for diagnosing PVD, is used to assess the second diagnostic criterion. It consists of the application of a cotton-swab to various areas of the vulva to assess pain; if the patient reports pain in response to vestibular palpation, the diagnosis of PVD is confirmed.

The diagnosis of UGVD is based on the description, location, and quality of the pain. It is a non-cyclic, chronic vulvar pain that often extends to the perineal and rectal areas[11]. Patients typically describe this pain as burning, although descriptors such as stinging, irritating, and raw are also often used[11]. The pain of UGVD often occurs independently of stimulation, however, light tough may exacerbate the pain, and some patients with UGVD may also have PVD. McKay[12] recommends the following evaluation for UGVD: examination of the skin for dermatoses and infectious agents, followed by an assessment of nerve function and the anatomical distribution of the affected area.

Given that the research concerning etiology and treatment of UGVD is in its infancy and that relatively more research has been conducted in the area of PVD, this paper will focus on PVD. Specifically, peripheral and central pathophysiological factors believed to be involved in the development and maintenance of PVD and treatments targeting local and non-local components of this condition will be reviewed.

3 Pathophysiological Factors Involved in PVD

3.1 Vestibular factors

The vulvar vestibule surrounds the vaginal introitus. Its medial boundary is the hymen and laterally, it is bounded by Hart's line. Hart's line is a distinct line of demarcation evident at the base of the inner aspect of each labium minus, separating the non-keratinized squamous epithelium of the vestibule from the keratinized epithelium of the labia minora. The vestibule, therefore, includes the vaginal introitus, the urethral opening, and the ducts of Bartholin's glands[13].

It is innervated by the pudendal nerve[14] and contains free nerve endings, the majority of which are believed to be C-fibers[15]. The vestibule is composed of visceral tissue but has a non-visceral innervation, and sensations of touch, temperature, and pain are similar to those evoked in the skin[16]. Under normal circumstances, the vestibule is a source of pleasure during vaginal penetration; its erotic potential in response to stimulation was documented in 1953[17]. However, in patients suffering from PVD, even light pressure can evoke intense pain. Although the cause of this heightened sensitivity is unknown, comparisons of vestibular tissue in women with PVD and non-affected women have revealed abnormalities that could potentially contribute to an increase in sensitivity.

Although early, uncontrolled studies concluded that inflammation plays a role in the etiology of PVD, recently published controlled studies suggest that inflammatory indices are common in the vestibules of both affected and non-affected women[18-19]. Other investigations suggest that altered vestibular tissue properties play a role in the development and/or maintenance of PVD. These studies have found evidence of an increased innervation of nerve fibers[15,20-22], increased vanilloid receptor VR1 expression[23], increased blood flow[24], and the presence of calcitonin gene-related peptide[25] in the vestibular tissue of women with PVD. These alterations could lead to an increase in sensitivity of the vulvar vestibule, and this pattern has indeed been found in women with PVD.

Controlled studies examining sensory functioning in the vestibules of women with PVD via Quantitative Sensory Testing (QST) have documented abnormal sensory functioning in response to a variety of stimuli (e.g., mechanical, thermal). Women with PVD have been shown to have significantly lower mechanical pain thresholds (i.e., higher sensitivity to pain) in the vestibule as compared with non-affected women[26-30]. Additionally, women with PVD have significantly lower vestibular thresholds for heat and cold pain than non-affected women[28-29]. Further, in conjunction with QST methods, Pukall *et al.*[26,27] assessed pain intensity and unpleasantness ratings on Likert scales of 0 (no pain at all, not at all unpleasant) to 10 (worst pain ever felt, most unpleasant ever) during painful stimulation in women with PVD and non-affected control participants. Results indicated that pain intensity ratings, which measure the sensory component of the pain, did not differ between the groups the first time they perceived pain. However, women with PVD reported significantly higher unpleasantness ratings in response to this equally intense pain, suggesting that women with PVD have a greater affective or emotional response to the pain. A similar pattern has been demonstrated in other chronic pain populations[31]. Thus, these studies indicate that women with PVD exhibit hyperalgesia (i.e., an increased response to painful stimuli) in response to painful stimulation. Interestingly, this heightened sensitivity is not restricted to pain.

Women with PVD are also more sensitive to non-painful mechanical and thermal stimulation in the vestibule than non-affected women[26,28-29]. Pukall *et al.*[26] found dramatic differences in tactile thresholds between women with PVD and control participants: women with PVD were able to perceive non-painful stimuli at levels that were imperceptible to control women. As well, vestibular pain thresholds of women with PVD were similar to the tactile thresholds of control women; that is, women with PVD experienced pain to stimuli that were just barely perceptible to non-affected women[26]. These results indicate that allodynia (i.e., pain in response to a non-painful stimulus) also exists in women with PVD. Taken together, the findings of hyperalgesia and allodynia in patients with PVD suggest a significant shift in perceptual response to painful and non-painful stimuli.

What causes the increase in sensitivity is unknown, but many theories have been proposed. Early injury to the vestibule has been suggested as a possible etiological pathway for PVD. Studies have found that earlier versus later age of menstrual tampon use and of first sexual intercourse are associated with an increased

risk of PVD later in life[8,32], possibly due to mechanical trauma. In addition, a history of repeated yeast infections and early oral contraceptive use has been associated with PVD[32-34]. It has been theorized that these factors could lead to damage of the vestibular tissue through changes in the bacterial and hormonal milieu (see Systemic factors). It is also possible that early alterations to the vestibular area from these and/or other factors can lead to hyperinnervation and concomitant hypersensitivity of the area, as has been demonstrated in the wounded hindpaw of young versus adult rats[35]. Although a promising etiological avenue to consider, early vestibular damage cannot fully explain the development of PVD; the pain of PVD may predate the patient's first attempt at vaginal insertion. For example, Harlow *et al.*[8] found that women who experienced pain upon first tampon use had a higher likelihood of developing vulvodynia later in life, suggesting that the heightened sensitivity may already have been present prior to the insertional event. As well, factors other than those possibly leading to vestibular tissue damage have been associated with PVD, suggesting that local vestibular tissue factors may not be the sole etiological avenue to consider. Indeed, abnormalities have been found in pelvic floor muscle function of women with PVD.

3.2 Pelvic floor muscle function

Controlled studies examining various indicators of pelvic floor muscle function in women with PVD have found abnormalities in affected women. For example, White *et al.*[36] compared pelvic floor electromyographic (EMG) responses in women with PVD and asymptomatic women. They found that women with PVD demonstrated elevated and unstable resting baseline EMG responses and poor contractile potential among other indices. In addition, a controlled study utilizing a pelvic floor muscle assessment protocol conducted by pelvic floor physical therapists revealed similar results. Reissing *et al.*[37] found that women with PVD had significantly more restriction of the vaginal opening, higher levels of vaginal hypertonicity (i.e., increase in muscle tension), and lower vaginal muscle strength in comparison to control women.

In fact, ninety percent of the affected women demonstrated pelvic floor pathology, leading the authors to conclude that such pathology should be considered a core characteristic of women with PVD, and confirming the findings from a previously published uncontrolled study[38].

In the past, it was unknown whether the hypertonicity in women with PVD was a cause or result of the pain[2]; however, the findings of Reissing *et al.*'s study suggest that the increase in muscle tension initially acts as a protective guarding response from the pain. This conclusion is based on the findings of significant hypertonicity at the superficial muscle layer, less consistent findings at the deep muscle layers, and the lack of generalized pelvic floor hypertonicity. Moreover, it supports a cyclic explanation for the pain: the tension begins as a protective guarding response to vestibular pain, and over time, this response leads to an increase in resting tone. The protective response and increase in tone result in an increase in vaginal opening pressure during insertional activities, which further increases the pain, and results in an increase in the protective guarding response. This cycle may be perpetuated over time[37]. These results indicate that pelvic floor hypertonicity can play an important role in the maintenance and exacerbation of pain in women with PVD. Additional research has shown that factors outside the genital and pelvic floor areas may also contribute to the experience of PVD.

3.3 Systemic factors

Several factors outside the genital and pelvic areas have been proposed to play a role in the increase of vestibular sensitivity in women with PVD, including hormonal and genetic factors. Hormonal factors have been found to be associated with PVD in controlled studies. For example, it has been reported that women who use oral contraceptives have an increased risk of developing PVD later in life[32,34], with those starting at an earlier age (i.e., before the age of 16) at espe-

cially high risk. Consistent with these results is the finding that oral contraceptive use may render the vestibular mucosa more sensitive to mechanical pain stimuli in non-affected women, perhaps due to the prolonged exposure to progestins[39]. In addition, early menarche (i.e., before the age of 11) and dysmenorrhea are also associated with an increased risk of PVD[8,32]. These findings support the potential role of hormones in PVD; however, the hormonal mechanisms through which the heightened sensitivity occurs are unknown. It is likely that a combination of many different factors, including those that have local and systemic effects, are involved in the development and maintenance of PVD. Some researchers have also proposed that genetic factors play a role in PVD.

Gerber *et al.*[40] conducted a series of studies examining genetic factors in women with PVD. They demonstrated that affected women were more frequently homozygous at allele 2 of both the interleukin-1 receptor antagonist gene and the interleukin-1 beta gene than non-affected women. These alleles are associated with severe and prolonged pro-inflammatory immune responses[41]. Consistent with this finding, they demonstrated that the immune systems of women with PVD are not as effective in terminating the inflammatory process as the immune systems of non-affected women. Based on these results, they proposed that some women with PVD have a genetic susceptibility to develop a chronic localized vestibular inflammation after an initial inflammatory response has been triggered. The prolonged and intensified inflammation could then trigger other events that may result in increased pain sensitivity due to chronic inflammatory processes in both genital and non-genital areas of the body. Supporting this conclusion is recent evidence indicating a generalized increase in sensitivity in women with PVD.

Controlled studies have demonstrated that, in addition to heightened vestibular sensitivity, women with PVD also have a generalized, non-vulvar sensitivity to pain. They have been shown to report significantly more non-vulvar pain-related complaints (e.g., migraine, dysmenorrhea) than non-affected women; as well, women with PVD rate these non-vulvar pain complaints as more severe and interfering than control participants[26,42-43]. In addition to these self-report results are QST studies indicating higher sensitivity to various forms of stimulation outside the vestibular region. Women with PVD have been found to exhibit higher sensitivity to touch, pressure, pain, and heat pain at locations such as the deltoid muscle and forearm[26,30,44]. The changes appear to be widespread: a recent study examining tender point sensitivity over nine bilateral areas ranging from the back of the neck to the knees indicated that women with PVD had significantly more painful tender points than non-affected women[42]. These results are consistent with several studies documenting increased sensitivity outside the primary area of pain complaint in patients with chronic pain disorders (e.g., migraine)[45]; they imply that central, in addition to peripheral, factors play a role in the development and maintenance of PVD.

3.4 Central factors

Consistent with the idea that central factors play a role in PVD are findings from recent studies examining brain function and structure. Pukall *et al.*[46] used functional magnetic resonance imaging (fMRI) to investigate neural activity patterns in women with PVD and non-affected women during non-painful and painful vestibular stimulation. Results indicated that PVD was associated with changes in the central nervous system processing of sensory information from the vestibule. This study documented that the increases in vulvar sensitivity to tactile and painful stimuli are paralleled by increases in cerebral neural activation, a pattern typical of patients with other syndromes causing hypersensitivity (e.g., irritable bowel syndrome)[47]. Consistent with the multidimensional experience of pain, increases in neural activation were found in areas representing the sensory and affective dimensions of pain, for example, the insular and somatosensory cortices, and the anterior cingulate cortex (ACC), respectively. In fact, the ACC was only activated in women with

PVD in response to pain; this activation could be due to the heightened unpleasantness ratings of affected women during painful vestibular stimulation. As well, it could partially represent their increase in affective responding to many pain-related measures (e.g., pain catastrophizing)[26].

In addition, Kuchinad, Pukall, and Bushnell[48] examined grey matter density in women with PVD and control women. They demonstrated that women with PVD exhibit morphological differences in grey matter density. Increases were found in the hippocampus and in a large area encompassing several regions of the basal ganglia, and a decrease was found in the frontal cortex (i.e., Brodmann's area 9/10). Increases in overall and regional grey matter have been demonstrated in chronic back pain patients[49] and in patients with other disorders (e.g., post-traumatic stress disorder)[50]. The decrease in the frontal region is consistent with fMRI findings that pain activates this area in control participants[51], but not in women with PVD[46]. Taken together, these functional and structural neural changes suggest that the symptoms of PVD may be mediated by abnormalities in the central nervous system; however, further research is necessary in order to fully examine this avenue.

3.5 Possible subsets of PVD

The question of localized versus generalized pain in women with PVD is an intriguing one that has led some researchers to suggest that subsets of women with PVD exhibit different pain patterns. Indeed, it is possible that subsets of women with PVD exist, with some having a more localized etiology and symptom expression than others whose vulvar pain may be related to or maintained by a generalized disorder of sensory modulation. Although it is impossible to determine which pain the localized, generalized, or even a combination of both initiates the process of PVD given the present lack of prospective studies, there is some suggestion that women with the primary and secondary forms of PVD differ in critical ways. Studies investigating medical histories in women with primary and secondary PVD indicate that women with primary PVD are less likely to have confirmed physical findings of infections (e.g., group B streptococcus, human papillomavirus) or to report having undergone aggravating local treatments before pain onset (e.g., high dose fluoroucil)[52] than women with secondary PVD. As well, they are more likely to recount histories of childhood nocturnal enuresis[53] and dysmenorrhea[54] than women with secondary PVD. Further, women with primary PVD have lower resting and pain-provoked systolic and diastolic blood pressure than women with secondary PVD[54], a pattern that has been demonstrated in patients with low back pain[55].

Regarding pain characteristics in women with primary and secondary PVD, although there are no significant differences in current vulvar pain ratings, women with primary PVD report a history of more severe pain[52] and rate the intensity of heat pain applied to their forearms as significantly higher than women with secondary PVD[54]. Combined with the finding of a higher incidence of dysmenorrhea in women with primary PVD[54], these studies suggest that women with primary PVD may suffer from a more generalized alteration in pain modulation than women with secondary PVD, perhaps due to different underlying etiological pathways. A discrepancy in genetic profiles has been proposed as the main differentiating factor between women with primary and secondary PVD. In 1991, Goetsch[52] reported that women with primary PVD had strong family histories of dyspareunia or tampon intolerance, suggesting a genetic component in its development. Recently, it has been shown that women with primary PVD are more frequently homozygous for allele 2 of the interleukin-1 receptor antagonist gene than women with secondary PVD[56]. These results indicate that the primary and secondary forms of PVD may result from different etiological pathways and lead to different outcomes; however, more research is needed to further characterize the differences between these groups.

3.6 Summary

Numerous factors have been found to play a role in PVD, ranging from local vestibular abnormalities, to pelvic floor dysfunction, to genetics, and to central changes in pain modulatory systems. As well, PVD may actually encompass subsets of patients who express similar symptoms but differ in terms of etiological and maintaining factors. It is likely that many different factors play a role in PVD, and that these factors differ according to subsets of PVD. In addition, psychological reactions to the pain may vary and influence the expression and course of the pain. Given the complexity of PVD, it would be logical to assume that treatment options would target multiple aspects of this condition simultaneously; however, treatment options for PVD have typically been unimodal and consecutive. Therefore, the treatment literature is characterized by a wide variety of medical/surgical, psychological, and alternative approaches directed at proposed mechanisms and symptoms.

4 Treatment

Treatment interventions for PVD are generally delivered in a linear fashion beginning with purportedly less invasive, safer options followed by more risk-laden modalities such as surgery. This stepwise approach is based on clinical observations and assumptions since there are currently no standardized, evidence-based treatment guidelines for vulvodynia[57]. Despite the publication of recent studies indicating the involvement of central pain mechanisms[46], interventions aimed at such factors, in particular psychological pain management, do not figure prominently in the recommended treatment algorithm[58]. The present section will focus on treatments targeting both peripheral and central mechanisms.

4.1 Treatments targeting peripheral factors

Medical interventions targeting local factors include topical applications, injections, and surgery. Among the many proposed local medications, daily intravaginal applications of an estrogen cream have been recommended but there are no published studies concerning the outcome of this regimen[58]. Topical corticosteroids and antifungals have been widely used but without any demonstrated effectiveness to date[59], although they have been the object of few studies. One randomized controlled trial examined the use of an oral antifungal medication for PVD with and without recurrent candidiasis. In a group of women with PVD adhering to a low oxalate diet with calcium citrate supplementation, Bornstein *et al.*[60] assigned half to a weekly dose of 150 mg of fluconazole over a six-month period. They found that the addition of the systemic antifungal did not improve the outcome attained by following the low oxalate diet: 15% of participants in the antifungal group had a satisfactory response, compared to 30% in the diet-only group.

In recent years, the most frequently prescribed topical medication has been lidocaine, a local anesthetic gel or ointment[58]. Two studies to date have examined its effectiveness in women with PVD. Using a prospective design, Zolnoun *et al.*[61] showed that nightly applications of 5% lidocaine ointment for seven weeks resulted in a significant pre- to post-treatment decrease in pain and an increase in the ability to engage in intercourse. Danielsson *et al.*[62] conducted a randomized trial comparing topical lidocaine and electromyographic (EMG) biofeedback. Forty-six participants either applied 2% lidocaine gel daily for two months, followed by a 5% ointment for another two months, or engaged in daily biofeedback home training exercises. At a one-year follow-up, both treatments yielded significant decreases in vestibular pain pressure thresholds as well as improved quality of life and sexual functioning, with no significant differences between groups. However, the lack of placebo control conditions in these studies does not allow us to conclude that lidocaine is efficacious, although it appears to be a safe and promising first-line intervention.

The use of cromolyn cream has also been attempted since it blocks mast cell degranulation, yet studies examining the presence of mast cells in women with

vulvodynia have yielded contradictory results[22,63]. Interestingly, findings from a randomized double-blind placebo trial of cromolyn cream revealed that participants in both the therapy and placebo groups showed statistically significant improvements in symptoms, but they did not differ significantly from one another[64].

The effects of topical nitroglycerin were studied prospectively in a group of women with four different types of vulvovaginal conditions: cyclic vulvovaginitis, PVD, UGVD, and vulvar dermatosis[65]. Although a significant pre- to post-treatment decrease in pain was noticed, 76% of patients reported headache with each use, which limits the interest of using this medication.

Capsaicin, which is used to treat neuropathic pain, was recently evaluated retrospectively in women with PVD[66]. In order to prevent the strong burning sensation which accompanies the application of capsaicin, participants were instructed first to apply a 2% lidocaine gel. Participants showed a significant decrease in pain and an increased ability to engage in intercourse post-treatment. It is unclear whether the observed positive results of capsaicin outweigh its painful side effects due to the uncontrolled, retrospective design of this study. In summary, there are no efficacious topical applications for PVD to date, although among those that were studied, lidocaine and cromolyn cream appear to have the least negative side effects. Other local medical treatments include interferon, lidocaine, and botulinum toxin A injections.

In the 1990s, intralesional interferon injections for PVD were commonly performed, with success rates from retrospective reports ranging from 38% to 88%[67]. However, they are less often used today, perhaps due in part to the fact that human papillomavirus infections are no longer thought to play a role in the pathophysiology of PVD. Other types of injections have recently been attempted, with mixed results. Namely, steroid-lidocaine submucous infiltrations in the vulvar vestibule were carried out in two studies. Murina *et al.*[68] reported that 68% of 22 participants responded favorably to this treatment, although outcome measures were not specified, and Segal *et al.*[69] reported complete pain relief in a case study of one patient. Three case reports focusing on the management of PVD with botulinum toxin A injections were published, with two indicating successful outcomes[70-71] and one, a modest outcome[72]. Another pilot study involving 12 patients showed significant pain reduction from baseline to one month post-treatment, with effects lasting from eight to 14 weeks, depending on the dose[73]. In addition, no negative side effects were reported. Considering these promising results, randomized controlled studies should be conducted to examine the efficacy and safety of botulinum toxin A injections as a treatment for PVD. Within the context of current treatment algorithms[58], a surgical approach is often the next step when other local medical treatments fail to alleviate the pain.

Vestibulectomy has been the most studied treatment for PVD, although the majority of reports are retrospective. Nevertheless, recent publications continue to support the positive outcome of this surgical excision[74-77], with success rates of 65% ~70% or higher[67,78]. Other uncontrolled studies have yielded similar results using modified vestibulectomy a slightly less invasive procedure[79-80]. Only two predictors of surgical outcome have been identified to date: women with UGVD and women with primary PVD respond less favorably to a surgical approach than women with secondary PVD[81]. Since research concerning vestibulectomy is plagued by methodological flaws two being the variations in patient selection and surgical techniques some clinicians still hold reservations about this procedure and warn that it should only be recommended after failure of more conservative treatments[82]. Others claim that there are little data to justify this cautionary statement[76].

Bergeron *et al.*[83] conducted a randomized treatment outcome study of PVD comparing vestibulectomy, group cognitive-behavioral therapy (CBT) and EMG biofeedback. Findings of this study support the efficacy of vestibulectomy. Although all three treatments yiel-

ded significant improvements at post-treatment and at six-month follow-up on self-reported pain during intercourse, pain during the cotton-swab test, and psychosexual functioning, vestibulectomy resulted in approximately twice the pain reduction (47% ~ 70% depending on pain measure) of the two other treatments (19% ~ 38%). However, seven of the initial 29 women who had been randomized to surgery refused to go ahead with the procedure, and 2 of the 22 women who underwent the surgery did not benefit from it in terms of pain reduction. At a 2.5-year follow-up, participants in the three treatment conditions had not only maintained their gains but significantly reduced their pain since the 6-month follow-up[84]. Vestibulectomy remained superior to the other two conditions in its impact on pain during the cotton-swab test but was equal to group CBT for self-reported pain during intercourse. Moreover, no woman in the vestibulectomy condition had a recurrence of her pain. Overall, these results suggest that vestibulectomy is a safe and efficacious treatment for PVD, but not one that is unanimously embraced by all patients. Indeed, some women prefer to opt for non-medical interventions, such as those targeting the pelvic floor.

Non-medical, local interventions consist primarily of biofeedback and pelvic floor physical therapy. Glazer *et al.*[38] were the first to apply EMG biofeedback training to the treatment of vulvodynia. In their initial retrospective study, they found that after an average of 16 weeks of practice, approximately half of 33 patients with mixed vulvar pain complaints reported pain-free intercourse. A subsequent prospective study yielded similar findings: 51.7% of 29 women with PVD reported negligible pain with intercourse following four to six months of daily biofeedback exercises[85]. Biofeedback was also evaluated in two randomized treatment outcome studies. First, Bergeron *et al.*[83] compared vestibulectomy, cognitive-behavioral therapy and biofeedback and showed significant pre- to post-treatment changes in pain in women assigned to the biofeedback condition, although their pain reduction was about half that of women assigned to vestibulectomy. Gains were maintained at 6-month and 2.5-year follow-ups[86]. More recently, Danielsson *et al.*[62] also demonstrated that biofeedback training resulted in significant improvements in pain and psychosexual functioning at a 12-month follow-up, but did not differ from topical lidocaine. Randomized studies comparing biofeedback to a wait-list control are needed to confirm its efficacy.

Electrical stimulation of the pelvic floor, which is often a component of physical therapy, was also assessed prospectively in a group of 29 women with PVD[87]. After 10 weeks of treatment, participants reported significantly improved pain and sexual function as per standardized measures.

Some have argued that pelvic floor physical therapy might be a more optimal modality since it includes but is not limited to EMG biofeedback or electrical stimulation. Indeed, physical therapy also involves education about the role of the pelvic floor musculature in the maintenance of vulvar pain, manual techniques (e.g. stretching) and insertion techniques (accommodators)[86,88]. Bergeron *et al.*[89] carried out a retrospective telephone interview study of 35 women with PVD who had taken part in pelvic floor physical therapy. Approximately half of the women deemed this treatment successful. Overall, self-reported pain during intercourse and during gynecologic examinations was significantly reduced pre- to post-treatment, and significant increases in frequency of intercourse, sexual desire, and sexual arousal were noted.

Overall, studies to date suggest that pelvic floor physical therapy/biofeedback represents a non-invasive, low risk treatment option for PVD, although randomized controlled trials are necessary to confirm the efficacy of this intervention. Moreover, there is an emerging trend toward combining pelvic floor physical therapy and cognitive-behavioral sex therapy within the context of a multimodal approach to the treatment of vulvodynia[86,88].

4.2 Treatments targeting central factors

Medical interventions targeting central factors in-

clude oral medications such as antidepressants and anticonvulsants. The latter are reserved for UGVD and thus will not be reviewed here. Initially, tricyclic antidepressants were thought to help alleviate pain associated with UGVD, but not PVD[90]. However, two recent studies have examined their effectiveness in mixed groups of women suffering from both localized and generalized vulvodynia. Munday[91] retrospectively assessed 32 women who were treated with amitriptyline but who were also offered supportive psychotherapy. Forty-seven percent reported a complete response to treatment, but it is impossible to attribute this improvement solely to the effect of the medication. Reed[92] conducted a quasi-experimental, prospective three-month follow-up study of 83 women who were prescribed amitriptyline, desipramine, or another tricyclic drug. Fifty-nine percent improved by more than 50%, compared to 38% of the women who were not taking a tricyclic antidepressant. This response was not influenced by the diagnosis (UGVD or PVD), providing preliminary evidence in support of the use of tricyclics to treat PVD. However, it should be noted that these drugs harbor negative sexual side effects[93]. It is not clear at this point whether the apparent pain-related benefits outweigh the negative impact on sexual functioning, since sexual dysfunction such as lack of arousal may contribute to increased pain. In fact, certain treatments such as sex therapy focus on reducing PVD-associated sexual dysfunction partly in an effort to diminish its negative effect on pain.

Cognitive-behavioral sex therapy and pain management, or their combination, are the main non-medical interventions targeting central factors in women with PVD. Despite their widespread use in the multidisciplinary treatment of other chronic pain syndromes[94] and their similar or superior success rates as compared to other non-medical interventions (e.g., biofeedback)[83], they are largely absent from current treatment recommendations. This is surprising in light of the robust findings indicating that women with PVD consistently report dramatic impairments in sexual desire, arousal, and orgasm in comparison to no-pain controls[5].

Initial studies reported success rates ranging from 43 to 68% with a combination of sex therapy and behavioral pain management, although treatment protocols were either unstandardized or multidisciplinary[95-96]. Bergeron *et al.*[83,97] investigated the efficacy of a combination of group cognitive-behavioral sex therapy and pain management (CBT) in two different randomized studies of women with PVD. In the first study, described above (see Treatments targeting peripheral factors), participants who received CBT reported significant improvements in pain at a six-month follow-up, although pain decreases were significantly below those of women who underwent a vestibulectomy. However, at a 2.5-year follow-up, the two groups did not differ with respect to pain experienced during intercourse, suggesting that the long-term results of CBT may be similar to those of vestibulectomy. In another ongoing study[97], participants were randomly assigned to either a corticosteroid cream condition or to group CBT for a 13-week treatment period. At post-treatment, women in both groups showed significant decreases in pain and increases in sexual functioning, but those in the CBT condition were significantly more satisfied with their treatment, displayed significantly less catastrophizing about pain, and reported significantly better global improvements in sexual functioning than women in the corticosteroid cream condition. These preliminary results suggest that CBT may yield a positive impact on more dimensions of PVD than does a corticosteroid cream. In a similar fashion, Ter Kuile and Weijenborg[98] conducted a prospective study evaluating the effects of group CBT delivered over a period of six months. Post-treatment findings revealed that participants reported significantly less coital pain, less sexual dissatisfaction, less vestibular pain, less vaginal muscle tension, and more pain control than at pre-treatment. In summary, studies focusing on CBT show that it is a promising, non-invasive therapeutic option which should be included in the multimodal manage-

ment of vulvodynia.

In an effort to find further sources of pain relief, some alternative treatments have been explored. One case study showed that hypnosis brought on a complete relief of pain in a woman with PVD, and that gains were maintained at a one-year follow-up[99]. Building on this promising result, Pukall *et al.*[100] conducted a prospective pilot study in which eight women each took part in six hypnotherapy sessions. They found significant post-treatment decreases in pain experienced during intercourse and during a gynecological examination (cotton-swab test), as well as a significant improvement in sexual satisfaction. Acupuncture was also assessed prospectively in 13 women with PVD[101]. Results indicated that at a three-month follow-up, 11 women experienced the treatment as positive. Unfortunately, the measurement of pain was not reported due to a problem encountered during the experimentation. Considering that hypnosis and acupuncture are devoid of adverse effects and are used in the treatment of other pain conditions, more rigorous studies evaluating their efficacy are warranted.

4.3 Summary

In conclusion, despite the high number of interventions targeting peripheral mechanisms, only vestibulectomy has demonstrated efficacy. Interventions focusing on central mechanisms, whether medical or psychological, are less frequently recommended but show promising results. With regards to the methodological characteristics of the studies focusing on the treatment of vulvodynia, many suffer from several limitations including lack of control groups, poor or absent specification of outcome, non-standardized treatment protocols, non-blind evaluation of outcome, rudimentary or absent pain and sexual function measurement, and short follow-ups. However, whereas most studies published before the new millennium were retrospective, the quality of designs is improving and more prospective work is being conducted. Nonetheless, there is still an urgent need for randomized controlled trials investigating the efficacy of proposed interventions. Moreover, in line with a biopsychosocial model of vulvodynia, it is unlikely that any single treatment modality will impact positively on all aspects of the condition, which emphasizes the importance of adopting a multidisciplinary, multimodal treatment approach. Future studies should examine combined interventions and evaluate their presumed superiority over a unimodal, sequential treatment delivery.

5 Discussion and Conclusions

Since the turn of the millennium, research into the etiology and treatment of vulvodynia has grown considerably across disciplines such as gynecology and psychology, and among pain specialists. Research to date has provided evidence for the roles of both peripheral and central/psychological mechanisms in the pathophysiology of PVD, supporting a biopsychosocial model of chronic vulvar pain. Despite this support, most treatment studies focus on treating only one aspect of the condition either the vestibular pain or the psychological correlates of the pain, but rarely both. In addition, this unimodal treatment algorithm implies that there exists a single etiological factor for each woman. However, research indicates the possibility of multiple etiological pathways, as exemplified by the less than 100% success rate of vestibulectomy; perhaps treating a single etiological pathway does not lead to complete success. These findings indicate that multiple factors should be addressed simultaneously in treatment. For example, the conclusion that pelvic floor hypertonicity exacerbates and maintains vulvar pain in PVD provides strong support for the use of pelvic floor physical therapy in combination with other interventions. Moreover, treatment plans should focus on sexual functioning and mental health in women with PVD in addition to pain reduction.

The disparities in treatment success and potential pathophysiological factors involved in primary and secondary PVD indicate possible subtypes of PVD. Further research is necessary to examine the unique factors which contribute to the development and maintenance

of these two forms of PVD and to determine whether they are distinct conditions. Similarly, as can be evidenced by the focus on PVD in this review, little information about UGVD exists. Research investigating peripheral and central mechanisms of pain processing in women with UGVD is needed to determine which treatment options will likely be successful for women suffering from this condition.

The next stride in research should be to increase the number of prospective studies and randomized controlled trials to rigorously examine the efficacy of not only the current treatment options already available, but also the combination of these, and other novel, therapeutic options. These multimodal treatment plans should be consistent with the biopsychosocial model and thus should examine outcome measures including, but not limited to, pain reduction. A second line of much-needed research is to focus on determining factors that predict successful treatment outcomes. These predictions will help health professionals individually tailor treatment options to patients in an attempt to relieve the suffering of women affected by vulvodynia, a highly prevalent but under-investigated gynecological pain problem.

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