Treatment of Vulvodynia: Pharmacological and Non-Pharmacological Approaches

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Abstract

Vulvodynia is a common, recurrent, vulvar pain condition with debilitating consequences for affected women's health and quality of life. The heterogeneity of women suffering from vulvodynia as well as its uncertain and likely multifactorial etiology pose a significant challenge to identifying any kind of "gold standard" treatment. Thus, treatment providers must be well versed in the various options and the evidence for each. In this review, we begin with pharmacological treatments, followed by non-pharmacological treatments, surgery, and finally multimodal treatments. For each approach, we briefly discuss the method, mechanism of action, and empirical support for the treatment. In sum, pharmacological treatments that *may be beneficial* but require further research include antinociceptive agents (lidocaine, capsaicin), anti-inflammatory agents (corticosteroids, interferon), neuromodulating medications (anticonvulsants and antidepressants), hormonal agents, and muscle relaxants (e.g., botulinum toxin). There is strong evidence to support and *recommend* non-pharmacological interventions including psychological therapy, pelvic floor physical therapy, as well as surgery (i.e., vestibulectomy for provoked vestibulodynia) for the treatment of vulvodynia. We conclude this review with a discussion of issues that may have hindered progress of treatment efficacy and effectiveness, and recommendations for moving the field forward.

Key points:

- Psychological interventions, pelvic floor physical therapy, and vestibulectomy (for provoked vestibulodynia) are *recommended* empirically-supported treatments for vulvodynia.
- Pharmacological treatments that *may be beneficial* include antinociceptive agents (lidocaine, capsaicin), anti-inflammatory agents (corticosteroids, interferon), neuromodulating medications (anticonvulsants and antidepressants), hormonal agents, and muscle relaxants (e.g., botulinum toxin). These treatments all require further placebo-controlled study.
- More rigorous randomized-controlled studies focusing on a multimodal approach are needed given its ability to target multiple etiologies simultaneously.

1. Introduction

Vulvodynia is a diagnosis pertaining to vulvar pain lasting at least three months and without a clear identifiable cause [1]. Population-based studies estimate its prevalence to be 8% [2, 3], and new onset of vulvodynia occurs in approximately 4.3 cases per 100 woman-years [4]. Vulvodynia adversely affects women and their romantic partners' sexual function and satisfaction, as well as their psychological and relationship health and well-being [5, 6]. The debilitating consequences of vulvodynia together with its high prevalence translate into countless women searching for an effective treatment. Yet only 50% of treatment-seekers ever receive an accurate diagnosis, and they see an average of five health care providers before receiving a diagnosis [7, 8].

The *2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia* [1] included the following pain descriptors: localized (i.e., a portion of the vulva) or generalized (i.e., the entire vulva), provoked or spontaneous, primary or secondary onset, and temporal pattern (e.g., intermittent). It remains unclear whether these descriptors characterize distinct etiological pathways or predict women's pain trajectories. Women with vulvodynia may have comorbid pain syndromes (e.g., fibromyalgia, painful bladder syndrome). Associated factors include genetics, hormones (e.g., pharmacologically induced), inflammation, musculoskeletal (hypertonic pelvic floor muscles, myofascial, biomechanical), neurologic mechanisms (central and peripheral), psychosocial factors (e.g., mood, interpersonal, sexual function), and structural defects (perineal descent) [1]. Given that multiple factors are frequently associated with the development and maintenance of this condition, vulvodynia is widely considered the result of a multifactorial process [1]. Identification of the relevant associated

factors in individual women has important treatment implications and underscores that there is no one-size-fits-all approach to treatment.

Historically, treatment recommendations have proceeded from non-pharmacological to pharmacological treatments, followed by surgical intervention in some cases. This approach has largely been based on clinical experience and the small number of randomized-controlled trials (RCTs) for individual treatments. The heterogeneity of women suffering from vulvodynia poses a significant challenge to identifying any kind of "gold standard" treatment. This review will begin with an overview of pharmacological treatments, followed by non-pharmacological treatments, surgery, and finally multimodal treatments. For each treatment, the method, mechanism of action, and empirical support will be discussed. *Recommended* treatments are those with favorable results following adequately powered RCTs, whereas *not recommended* treatments include those that demonstrated no benefit or did not outperform placebo conditions in adequately powered RCTs. Treatments deemed as *potentially beneficial* include those that have demonstrated mixed findings in a small number of studies or have shown promise in uncontrolled or underpowered RCTs, but that require additional study before recommendations regarding efficacy can be made. The review will conclude with a discussion of issues that may have impeded progress of treatment efficacy and effectiveness, and thoughts for future directions. It should be noted that much of the review will discuss research that focuses on a subtype of localized vulvodynia, provoked vestibulodynia (PVD; pain localized to the vulvar vestibule on contact) given that it is most common, especially among premenopausal women [8], and hence has received more research attention.

2. Pharmacological options

Researchers have devoted a great deal of attention to pharmacological treatments of vulvodynia relative to non-pharmacological treatments. The use of various antinociceptive, anti-inflammatory, and neuromodulating agents comes from evidence that women with vulvodynia have increased innervation and/or sensitivity of nocioceptors in the vulvar mucosa [9-11], as well as greater inflammation and increased nerve density in the vestibular tissue [12].

2.1 Antinociceptive Agents

Topical lidocaine was previously recommended as a first-line treatment for vulvodynia [13] based on promising results in uncontrolled trials [14, 15]. However, in the only double-blind placebo-controlled RCT ($N = 133$), Foster et al. [16] compared four treatment arms: desipramine with placebo cream, placebo tablets with topical lidocaine, combination desipramine and lidocaine, and placebo tablets and placebo cream. No group differences for pain reduction via the tampon test (i.e., pain experienced when inserting and removing a tampon) were observed. Although secondary outcomes (i.e., intercourse pain, vulvar algesiometry, and cotton swab test) demonstrated improvement post-treatment, there was no difference between the lidocaine and placebo groups. Based on this evidence, lidocaine is no longer recommended as a first-line treatment for vulvodynia [17]. However, given that this was only a single relatively small trial, further placebo-controlled studies should be conducted, with potential investigation into subgroup responders, before firmly recommending against lidocaine.

Two small uncontrolled pilot studies ($Ns = 26$ and 27) examined the use of multilevel nerve blockade (i.e., caudal epidural blockade, a transvaginal pudendal block, and local infiltration of the vestibule with bupivacaine) in women with generalized and provoked vulvodynia [18, 19]. The researchers observed improvements in pain ratings post-treatment [18, 19], but mixed findings for improvements in sexual functioning. RCTs are needed.

Capsaicin is a vanilloid receptor agonist that leads to desensitization of the receptors with systematic exposure [20]. Compared to controls, women with vulvodynia have increased density of vanilloid receptors in their vestibular tissue [21]. Uncontrolled studies using capsaicin reported improvements in pain and sexual frequency [22, 23]; however, these studies combined capsaicin with topical lidocaine to minimize the side effect of burning pain making it difficult to isolate the effects. A small RCT (n = 23; 9 treatment, 14 controls), published only in abstract form, demonstrated a 77% reduction in pain for those in the treatment group, compared to no change in pain for those in the control group [24]. Larger placebo-controlled studies are needed to determine if capsaicin is effective and the appropriate dosing.

2.2 Anti-inflammatory Agents

Case reports and case series have found symptomatic improvement following treatment with interferon when women with vulvodynia also show signs of human papillomavirus (HPV) infection [25-30]. Interferon decreases production of inflammatory cytokines, which are higher in the hymenal tissue of women with vulvodynia [17]. In the only placebo-controlled cross-over trial, women with vulvodynia and koilocytosis on biopsy (N =17) were treated with a serial intradermal vulvar injection of interferon alpha 2-b or serial injection of saline [31]. No improvement in vulvodynia symptoms were observed with the saline treatment. Following interferon treatment, 15 of 17 women reported complete resolution of their pain. Within this study, a second control group without HPV showed no improvements with interferon treatment. Interferon treatment may be considered for women with vulvodynia and histologic findings suggestive of HPV infection, if other treatments have failed.

Corticosteroids have strong anti-inflammatory effects by reducing the production of interleukin-β, which researchers have found to be elevated in the hymeneal tissue of women

with vulvodynia [32]. Smaller and likely underpowered RCTs using high potency topical steroids have shown negligible effects [33, 34]. Case reports and series using combined local subcutaneous infiltration of lidocaine and a steroid (methylprednisolone or betamethasone) to the vestibule have shown some success [35-37]. In the largest RCT ($N = 97$) Bergeron et al. [38] randomly assigned women to topical hydrocortisone 1% (twice daily) or group CBT (12 sessions). Both groups showed a significant improvement in pain and sexual functioning post-treatment, but effects were larger among those in the CBT group. At this time, more controlled studies are needed before corticosteroids (either topical or injections) are recommended for treatment of vulvodynia [17].

Recent studies have provided more evidence for the role of inflammation in the pathophysiology of vulvodynia, supporting further investigation into anti-inflammatory treatments. Other potential anti-inflammatory agents include cromolyn (a mast cell stabilizer), enoxaparin (a low molecular weight heparin with anti-heparinase activity), cutaneous fibroblast lysate (containing anti-inflammatory cytokines), and meloxicam (Cox- 2 inhibitor) [39-42]. Evidence from small RCTs, suggest no benefit to cromolyn relative to placebo [39], and modest improvements in vulvar pain following enoxaparin, fibroblast derived lysate [40, 41], and topical meloxicam with lidocaine [42]. Although potentially beneficial, further research including larger samples is needed before these treatments can be recommended.

2.3 Neuromodulating Agents

There is a long history of the use of anticonvulsants and antidepressants as treatment for vulvodynia. Gabapentin is thought to attenuate depolarization of nociceptors resulting in decreased pain [43]. In their critical review, Spoelstra et al. [44] concluded that while results seem promising for both oral and topical gabapentin [45-52], RCTs are needed. A recent

placebo-controlled crossover RCT ($N = 89$) found no difference between women treated with long acting oral gabapentin as a solitary treatment versus placebo for pain outcomes [53], but did observe improvements in sexual function in the gabapentin group among those with pelvic floor muscle pain [53]. Uncontrolled studies have also shown the potential benefits of topical gabapentin [47, 50], but placebo-controlled studies are needed before it can be recommended. Other studies have examined the use of pregabalin [51, 54], lamotrigine [55], and carbamazepine [56], but more rigorous RCTs are needed before any treatment recommendations can be made.

Antidepressant medications are thought to exert their pain mediating effects by increasing the release of inhibitory neurotransmitters (noradrenalin and serotonin), which play a role in modulating signalling from peripheral nociceptors [43]. Large retrospective and prospective uncontrolled studies have shown favourable results for amitryptyline [51, 52, 57-62]; however, two small controlled trials did not show any benefit [33, 63]. In the RCT described earlier, Foster et al. [16] did not observe any benefit of desipramine over placebo for pain during the tampon test. Smaller uncontrolled studies and case reports of other antidepressants (e.g., escitalpram, nortriptyline, venlafaxine, milnacipran) alone or in combination with other medications [45, 53, 61, 64], as well as the use of topical amitriptyline alone or with baclofen [57, 65] have observed favourable effects. The mixed findings suggest that more and larger RCTs are necessary before recommending the use of antidepressant medications for vulvodynia.

2.4 Muscle relaxants

Botulinum toxins (BoNT) are a group of neurotoxins produced by Clostridium bacteria, with most research focused on the BoNT type A (BoNT-A). BoNT blocks the release of acetylcholine as well as other neurotransmitters and neuropeptides at the neural synapse, which causes a localized and temporary muscular paralysis and analgesic effects [66, 67]. Case reports

and small, prospective, uncontrolled studies have shown that women with vulvodynia report significant improvement in pain and sexual functioning with the injection of 10 to 100 units of BoNT-A [68-73], with effects maintained two years post-treatment [69]. In an RCT ($N = 64$) women with vulvodynia were randomized to receive 20 units of BoNT-A or saline in the bulbospongiosus muscles [74]. Both groups reported a significant reduction in pain and improved sexual functioning post-treatment; however, there was no difference between BoNT-A and saline treatment. Of note, the BoNT-A dose was lower than in previous uncontrolled studies, which may account for the lack of differences observed in this small RCT. Additional placebo-controlled trials are warranted given the promising findings from early prospective studies.

Uncontrolled studies have shown potential improvement in vulvodynia patients with the use of vaginal diazepam—a benzodiazepine with muscle relaxing properties [75]. Murina et al. [76] conducted an RCT ($N = 42$) randomizing patients with vulvodynia and moderate to severe pelvic floor hypertonic dysfunction to transcutaneous electrical nerve stimulation (TENS) alone or TENS with vaginal diazepam. Greater improvement in pain and pelvic floor function was observed in the TENS plus vaginal diazepam group than the TENS alone group.

2.5 Hormonal Agents

There is some evidence suggesting increased incidence of vulvodynia among women using combined hormonal contraception (CHC), leading to speculation that relative estrogen or testosterone deficiency may contribute to the development of vulvar pain [77]. Two RCTs sampling women with secondary vulvodynia that developed while using CHC have tested the effect of local estrogen replacement with conjugated equine estrogen (CEE) [78, 79]. Langlais et al. [79] ($N = 20$) reported significant improvements in superficial dyspareunia relative to placebo using topical CEE, whereas Bazin et al. [78, 79] ($N = 61$) did not observe any improvement in

dyspareunia relative to placebo using intravaginal application of CEE. A case series study (*N* = 50) reported that topical estradiol and testosterone compound cream applied to the vestibule twice daily for an average of 20 weeks was associated with reduced pain during the cotton swab test [38, 80]. The cessation of CHC and addition of topical estrogen alone or in combination with testosterone may be a reasonable first-line treatment in women who develop vulvodynia while on CHCs, especially if the patient history and physical exam reveal evidence of vulvar dryness and atrophy. However, prospective RCTs are still needed.

3. Non-pharmacological options

Current evidence and international consensus guidelines support non-pharmacological treatments including psychological interventions and pelvic floor physical therapy as first-line interventions for the management of vulvodynia [17]. Alternative approaches including acupuncture, hypnosis, and laser therapy will also be discussed.

3.1 Psychological interventions

Psychological interventions for vulvodynia have primarily been cognitive-behavioral therapy (CBT) and delivered in individual, group, and couple formats. The treatment aims to reduce pain and its associated distress, improve sexual function and satisfaction for both partners, and strengthen the couple relationship. These aims are achieved through psychoeducation and by introducing strategies that (1) target the maladaptive thoughts, emotions, behaviors and couple interactions that are associated with vulvodynia (e.g., avoidance, catastrophizing, excessive anxiety), and (2) increase adaptive coping (e.g., communication skills, expanding the sexual repertoire away from painful intercourse)[81].

In one of the first RCTs, women with PVD (*N* = 78) were randomized to surgical vestibulectomy, biofeedback, or group CBT. At 6-month post intervention follow-up, those who

received CBT reported significant improvements in their pain during intercourse, but those who underwent vestibulectomy reported the greatest pain reduction [82]. At 2.5-years follow-up, there were no longer any differences in pain during intercourse between women in the vestibulectomy and CBT groups, and improvements in pain, sexual function, and psychological adjustment were maintained for all treatment groups. Importantly, women who received CBT had a lower attrition rate than those who underwent vestibulectomy, and were more satisfied with their treatment than women who received biofeedback [82].

Another RCT ($N = 97$) randomized women with PVD to a 13-week treatment of corticosteroid cream or group CBT [38]. Women in both groups reported significant improvements in pain and sexual function from baseline to post-treatment and 6-months later, although the CBT group reported significantly greater improvements at the 6-months. Again, the women in the CBT group reported higher treatment satisfaction than those in the corticosteroid group. A final RCT ($N = 50$) examined the efficacy of individual CBT in comparison to supportive psychotherapy. Those randomized to the CBT group reported greater improvements in pain and sexual function from pre- to post-treatment compared to the supportive therapy, with gains maintained one year later [83]. These results suggest that CBT entails targeted components, beyond the supportive elements of therapy.

Given the large body of evidence indicating that romantic partners both impact and are impacted by vulvodynia, Bergeron and colleagues developed a 12-session couple-format treatment for PVD, based on acceptance-based CBT approaches [84, 85]. A prospective pilot study found that women reported significant pre- to post-treatment improvements in pain during intercourse and sexual functioning, and both partners' reported improvements in sexual satisfaction and other psychological and relational outcomes [85]. While limited by a small

sample size ($N = 8$ couples), a couples-based approach may be beneficial and its efficacy is currently being evaluated in a large-scale RCT [84].

Brotto and colleagues have incorporated mindfulness into a 4-session group CBT program [86-88], which is consistent with evidence of the effectiveness of mindfulness in the treatment of other chronic pain conditions [89]. In a quasi-experimental design using a wait-list control comparison group ($N = 85$), women in the mindfulness group reported significant improvements from pre- to post-treatment, and from post-treatment to 6-month follow-up in pain catastrophizing and hypervigilance, cotton-swab provoked allodynia, and sexual distress, but not in pain during intercourse [86]. Taken together, there is strong evidence supporting the efficacy of psychological treatments for vulvodynia; it is therefore a recommended first-line treatment.

3.2 Pelvic floor physical therapy

There is considerable evidence linking vulvodynia to pelvic floor muscle (PFM) dysfunction (e.g., [17, 90, 91]). Women with vulvodynia display hypertonicity in the PFM and poorer PFM strength and control [17]. The goal of pelvic floor physical therapy (PFPT) is to restore proper function to the PFM and tissues, decrease neural tension and vulvovaginal pain and in some cases, improve sexual function [92].

Manual PFPT includes a variety of techniques (e.g., stretching, massage, and myofascial trigger points) to facilitate muscle relaxation, improve circulation, and increase mobility. Although limited by small samples, three prospective studies show promising results for decreasing self-reported pain during intercourse following use of vaginal dilators alone [93-95]. To date, no RCTs have examined the effect of other forms of manual therapy alone in vulvodynia; however, a randomized feasibility study provided preliminary support for the use of myofascial trigger point release for pelvic pain disorders [96].

Retrospective and prospective studies examining the effectiveness of assisted therapies have observed significant improvements in self-reported pain, dyspareunia, and sexual functioning following peripheral neuromodulation with TENS, with some evidence that these effects are maintained over time [97-99]. Two RCTs, one involving TENS and the other including TENS with vaginal diazepam showed modest improvements in pain and pelvic floor instability compared to placebo-controlled conditions [76, 94] whereas the addition of palmitolethanolamide and transpolydatin was not supported [100]. Morin et al. [101] conducted a triple-blind, parallel-group, RCT to examine the efficacy of central neuromodulation (transcranial direct-current stimulation; TDCS) for PVD. There was no evidence to support the use of TDCS for pain reduction or improved sexual function.

Initial uncontrolled, non-randomized studies using biofeedback via electromyographic (EMG) observed moderate reductions in reported vestibular pain [102, 103]. In their prospective randomized study Danielsson et al. [15] compared 4-months of EMG biofeedback to topical lidocaine. No group differences were observed; however, positive outcomes (e.g., reported vestibular pain, sexual function, and quality of life) were maintained 12 months later for both groups. In the RCT [104] comparing CBT, EMG biofeedback, and vestibulectomy described earlier, women receiving EMG biofeedback reported on average a 35% reduction in pain and this was maintained at the 2.5 year follow-up; however, both the CBT and vestibulectomy conditions produced greater improvements in reported pain.

Most of the existing research has examined a comprehensive multimodal approach to PFPT, which includes the manual and assisted therapies described above with other approaches including education and at home exercises. Retrospective and prospective studies show that the majority of women (71% to 76%) report significant improvements in their intercourse pain, pain

during gynecological examinations, and sexual functioning following 6 to 10 sessions of multimodal PFPT [97, 105-111]. A pilot RCT ($N = 20$) comparing CBT and multimodal PFPT showed that both interventions produced significant decreases in self-reported pain [112]. In sum, a systematic review ($K = 43$ studies) found that PFPT is effective for decreasing pain during intercourse and improving sexual function [92]. It is therefore currently recommended as a first-line treatment for vulvodynia [113].

3.3 Alternative approaches

Acupuncture, hypnosis, and laser therapy are alternative approaches with few adverse effects; however, these approaches require more thorough investigation regarding their efficacy. The western view of acupuncture is that the placement of needles at specific pain points releases endorphins and opioids, the body's natural analgesics, resulting in pain reduction [114]. To date, three small uncontrolled and non-randomized studies have demonstrated mixed support for the treatment of vulvodynia with acupuncture [115-117]. In a wait-list controlled RCT ($N = 36$), Schlaeger et al., [118] found that vulvar pain and intercourse pain were significantly reduced, and overall sexual functioning significantly improved, following acupuncture. Hypnotherapy has been shown to alleviate the subjective experience of pain in other populations [119]. Evidence from a case study [120] and an uncontrolled, non-randomized pilot study ($N = 8$) [119], observed that hypnotherapy (6 to 12 sessions) was associated with reported improvements in pain (e.g., gynecologic examination, intercourse, and non-coital), and psychosexual functioning (e.g., sexual satisfaction) from pre- to post-intervention.

Evidence for treatment with energy devices such as fractional CO_2 laser therapy and low-level laser therapy (LLLT) is mixed, and currently there is an FDA warning against the use of energy devices to perform "vaginal rejuvenation," and for procedures to treat symptoms related

to sexual function, because of concerns regarding adverse events [121, 122]. In a case series, women with either vestibulodynia ($N = 37$) or genitourinary syndrome of menopause ($N = 33$) underwent three sessions of fractional ablative CO_2 laser treatment. No group differences were observed; however, 67.4% of women reported significant improvements in pain during intercourse, and improvements were maintained at four-month follow-up [121]. In a small ($N = 34$) double-blind, placebo-controlled RCT [122], 12 sessions of LLLT resulted in a greater proportion of women (i.e., 78%) reporting some improvement (using a 100-point pain scale) in their intercourse pain following treatment relative to their intercourse pain at the time of recruitment compared to those (i.e., 44%) in the placebo sham LLLT condition. No group differences were observed for any other outcomes (e.g., pain during Q-tip examination, daily and intercourse pain using the visual analog scale, tampon test). Although sham controlled multicenter trials are underway, there is currently insufficient evidence for fractitional CO_2 laser or LLLT as a treatment for vulvodynia.

4. Surgery

In comparison to other treatment approaches, vulvar vestibulectomy surgery has been studied extensively [123]. Vestibulectomy can include partial or complete excision of the vestibular mucosa with, or without, a vaginal advancement flap [124]. In general, the literature is difficult to compare because of variability in surgical procedures, lack of control conditions, poorly defined outcomes and definitions of “success”, and lack of follow-up [17]. Of note, the evidence only supports vestibulectomy as an effective treatment for localized PVD. It is contraindicated for generalized vulvar pain disorders and non-provoked vestibulodynia [124].

In a systematic review ($K = 33$ studies), Tommola et al. [124] found that vestibulectomy resulted in significant self-reported relief of dyspareunia in 79% of patients, some relief in 89%

of patients, and no relief in 12% of patients. In studies ($K = 6$) that examined pain and tenderness of the vestibular mucosa following surgery via the cotton-swab test, lack of tenderness was reported for 70% to 85% of women following surgery [104, 125]. In addition, Tommola et al. [124] observed significant improvements in sexual functioning following vestibulectomy and that these effects were maintained 12 to 30 months following surgery [126-130]. Moreover, women are generally highly satisfied with the procedure [131, 132]. Complications are infrequent and can include bleeding, infection, increased pain, scar tissue, wounds, and cyst formation [5, 17].

Some experts have questioned why vulvar vestibulectomy is typically recommended only after less invasive interventions are unsuccessful [17, 111]. In their observational case-controlled study, Tommola et al. [111] observed similar long term outcomes for pain and sexual function when comparing women with severe PVD who were treated with conservative interventions and those who received vestibulectomy surgery. Such findings highlight that conservative treatment might be preferable as a first-line intervention**.**

5. Multimodal approaches

Consistent with recommendations of the *Fourth International Consultation on Sexual Medicine for women's sexual pain disorders* [17], and the evidence for multiple etiological pathways in vulvodynia, a multidisciplinary model of care that can targets pain pathways simultaneously is considered optimal. Multimodal treatment that combines interventions (e.g., PFPT, CBT, oral gabapentin) rather than preceding sequentially may support a more expedient treatment process and promote greater engagement from both patients and clinicians, possibly leading to less resistance to any single modality [133]. There are a small number of published uncontrolled quantitative [44, 134-136] and qualitative studies [88, 137-139] evaluating a

multimodal treatment, typically combining psychotherapy, physical therapy, and prescriptive therapy. Results indicate that women experienced improvements in their pain as well as their ability to manage the pain, and psychological and sexual well-being, and that the benefits may also extend to partners of the women. The lack of RCTs makes it unclear whether a multimodal approach is superior to any single modality, but findings are promising.

6. Conclusions

Our updated review of the literature supports the conclusions from the *Fourth International Consultation on Sexual Medicine* [17] that, currently, the best treatment options for vulvodynia are psychological interventions, pelvic floor physical therapy, and vestibulectomy (for provoked vestibulodynia). More rigorous studies are needed focusing on a multimodal approach given its ability to target multiple etiologies simultaneously. Pharmacological treatments that *may be beneficial* and considered as second-line avenues include antinociceptive agents (lidocaine, capsaicin), anti-inflammatory agents (corticosteroids, interferon), neuromodulating medications (anticonvulsants and antidepressants), hormonal agents, and muscle relaxants. These treatments all require further placebo-controlled study. An important consideration is that the definition of "successful" treatment varies considerably across health care providers and affected women and couples. Symptoms may be reduced following treatment but still persist to some degree, or symptoms may reoccur even following more invasive treatment such as surgery [127, 140]. Thus complete resolution of pain is often an unrealistic goal. For some, pain reduction or enhanced pain management skills may be sufficient for increasing women's quality of life, and can be an important end-point of treatment in and of itself.

There are some methodological, theoretical, and clinical issues that may have hindered advances in the treatment of vulvodynia. First, a major limitation is the lack of placebo-controls, with the few placebo-controlled trials clearly demonstrating strong placebo effects [141]. Some treatments (e.g., vestibulectomy, physical therapies) have not been subjected to a placebo-controlled trial, likely due to the logistics of performing a sham version of these treatments. Although these treatments have demonstrated strong efficacy in other study designs—including in RCTs, which compared against other supported treatments—whether they lead to improvements beyond placebo cannot be fully determined. A second challenge has been the neglect of the romantic partner in treatment, despite painful intercourse being an inherently interpersonal problem [6]. Partners can be included in any treatment by inviting them to participate in appointments and providing them with education and/or involving them in the treatment itself. Partner support or resistance to treatment can play a major role in compliance with a treatment protocol and subsequent outcomes [142].

Third, the heterogeneity of women suffering from vulvodynia poses significant challenges for treatment trials. There is evidence that they differ in several characteristics including age of onset, location and quality of the pain, and presence of comorbidities [4, 143, 144] but see also [145]. Such differences may imply various underlying pathophysiology, experienced consequences (i.e., sexual, psychological), and treatment responsiveness, although evidence of empirically-derived subgroups is sparse. Unfortunately, although there are a limited number of well-designed RCTs studies of vulvodynia, very few differentiated among potential subtypes. When women with different characteristics or etiologies are examined together as a single group, it is possible that treatment efficacy for a subgroup of women will be masked by those for whom the treatment is ineffective, rendering the overall findings non-significant [146]. As researchers

uncover the underlying mechanisms and etiology of different forms of vulvodynia, they can develop corresponding treatment algorithms to guide decision-making in a more evidence-based manner. King, Rubin, and Goldstein [147] published such an algorithm to differentiate between vulvar pain subtypes based on the associated factors outlined earlier. Some experts have suggested that classifying vulvodynia subtypes based on pain descriptors—including potential combinations of these characteristics—may be more useful than subgroups based on hypothesized etiology [1, 133].

Corsini-Munt et al. [148] outline a number of additional barriers and gaps in treatment knowledge and research of vulvodynia, as well as possible solutions to mitigate their effects. These include: 1) assessment of multiple domains of impairment beyond pain; 2) examining treatment predictors and moderators including the presence of co-morbid conditions; 3) inclusion of more diverse and representative samples; 4) explicitly testing the purported mechanisms of action; and 5) more effective and wider dissemination of empirically-supported treatment protocols. Collaboration across research teams and health disciplines may be the key to improving the size and representativeness of research participants, and enhancing efficacy by ensuring that treatments reflect the biopsychosocial complexity of vulvodynia.

Compliance with Ethical Standards

Conflict of Interest: Natalie O. Rosen, Samantha J. Dawson, Melissa Brooks, and Susan Kellogg-Spadt have no conflicts of interests.

Funding: In the preparation of this article, N. O. Rosen was supported by a New Investigator Salary Award from the Canadian Institutes of Health Research (CIHR).

References

1. Bornstein J, Goldstein A, Stockdale CK, Bergeron S, Pukall CF, Zoloun D et al. 2015 ISSVD, ISSWSH, and IPPS consensus terminology and classification of persistent vulvar pain and vulvodynia. Obstetrics & Gynecology. 2016;127:745-51.

2. Harlow BL, Stewart EG. A population-based assessment of chronic unexplained vulvar pain: Have we underestimated the prevalence of vulvodynia? Journal of the American Medical Women's Association. 2003;58:82-8.

3. Reed BD, Harlow SD, Sen A, Legocki LJ, Edwards RM, Arato N et al. Prevalence and demographic characteristics of vulvodynia in a population-based sample. American Journal of Obstetrics and Gynecology. 2012;206:170.e1-9.

4. Reed BD, Legocki LJ, Plegue MA, Sen A, Haefner HK, Harlow SD. Factors associated with vulvodynia incidence. Obstetrics & Gynecology. 2014;123:225-31.

5. Bergeron S, Corsini-Munt S, Aerts L, Rancourt K, Rosen NO. Female sexual pain disorders: A review of the literature on etiology and treatment. Current Sexual Health Reports. 2015;7:159-69.

6. Rosen NO, Bergeron S. Genito-pelvic pain through a dyadic lens: Moving toward an Interpersonal Emotion Regulation Model of women’s sexual dysfunction. The Journal of Sex Research (Annual Review of Sex Research). 2018.

7. Harlow BL, Wise LA, Stewart EG. Prevalence and predictors of chronic lower genital tract discomfort. American Journal of Obstetrics and Gynecology. 2001;185:545-50.

8. Harlow BL, Kunitz CG, Nguyen RH, Rydell SA, Turner RM, Maclehose RF. Prevalence of symptoms consistent with a diagnosis of vulvodynia: population based estimates from 2 geographical regions. American Journal of Obstetrics and Gynecology. 2014;210:e1-8.

9. Bohm-Starke N, Hilliges M, Brodda-Jansen G, Rylander E, Torebjork E. Psychophysical evidence of nociceptor sensitization in vulvar vestibulitis syndrome. Pain. 2001;94:177-83.

10. Tympanidis P, Terenghi G, Dowd P. Increased innervation of the vulval vestibule in patients with vulvodynia. British Journal of Dermatology. 2003;148:1021-7.

11. Halperin R, Zehavi S, Vaknin Z, Ben-Ami I, Pansky M, Schneider D. The major histopathologic characteristics in the vulvar vestibulitis syndrome. Gynecologic and Obstetric Investigation. 2005;59:75-9.

12. Westrom LV, Willen R. Vestibular nerver fibre proliferation in vulvar vestibulitis syndrome. Obstetrics & Gynecology. 1998;91:572-6.

13. Haefner HK, Collins ME, Davis GD, Edwards L, Foster DC, Hartmann KE et al. The vulvodynia guideline. Journal of Lower Genital Tract Disease. 2005;9:40-51.

14. Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. Obstetrics & Gynecology. 2003;102:84-7.

15. Danielsson I, Torstensson T, Brodda-Jansen G, Bohm-Starke N. EMG biofeedback versus topical lidocaine gel: A randomized study for the treatment of women with vulvar vestibulitis. Acta Obstetricia et Gynecologica Scandinavica. 2006;85:1360-7.

16. Foster DC, Kotok MB, Huang LS, Watts A, Oakes D, Howard FM et al. Oral desipramine and topical lidocaine for vulvodynia: A randomized controlled trial. Obstetrics & Gynecology. 2010;116:583-93.

17. Goldstein A, Pukall CF, Brown C, Bergeron S, Stein A, Kellogg-Spadt S. Vulvodynia: Assessment and treatment. The Journal of Sexual Medicine. 2016;13:572-90.

18. McDonald JS, Rapkin AJ. Multilevel local anesthetic nerve blockade for the treatment of generalized vulvodynia: A pilot study. The Journal of Sexual Medicine. 2012;9:2919-26.

19. Rapkin AJ, McDonald JS, Morgan M. Multilevel local anesthetic nerve blockade for the treatment of vulvar vestibulitis syndrome. American Journal of Obstetrics and Gynecology. 2008;198:e1-5.

20. Baron R. Capsaicin and nociception: From basic mechanism to novel drug. The Lancet. 2000;356:785-6.

21. Tympanidis P, Casula MA, Yiangou Y, Terenghi G, Dowd P, Anand P. Increased vanilloid receptor VR1 innervation in vulvodynia. European Journal of Pain. 2004;8:129-33.

22. Murina F, Radici G, Bianco V. Capsaicin and the treatment of vulvar vestibulitis syndrome: A valuable alternative? Medscape General Medicine. 2004;6:48.

23. Steinberg AC, Oyama IZ, Rejba AE, Kellogg-Spadt S, Whitmore KE. Capsaicin for the treatment of vulvar vestibulitis. American Journal of Obstetrics and Gynecology. 2005;192:1549-53.

24. Zyczynski HM, Culbertson S, Gruss J, Degroat WC. Substance P and the pathophysiology of vulvar vestibulitis. Journal of the Society for Gynecologic Investigation. 1997;4:107A.

25. Bornstein J, Pascal B, Abramovici H. Treatment of a patient with vulvar vestibulitis by intramuscular interferon beta: A case report. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1991;42:237-9.

26. Bornstein J, Pascal B, Abramovici H. Intramuscular beta-interferon treatment for severe vulvar vestibulitis. Journal of Reproductive Medicine. 1993;38:117-20.

27. Holt LH, Bukar M, Ragin A. Sustained improvement in vulvodynia symptoms with interferon injections. Journal of Lower Genital Tract Disease. 1999;3:56.

28. Kent HL, Wisniewski PM. Interferon for vulvar vestibulitis. Journal of Reproductive Medicine. 1990;35:1138-40.

29. Larsen J, Peters K, Petersen CS, Damkjaer K, Albrectsen J, Weismann K. Interferon alpha-2b treatment of symptomatic chronic vulvodynia associated with koilocytosis. Acta Dermo-Venereologica. 1993;73:385-7.

30. Marinoff S, Turner M, Hirsch R, Richard G. Intralesional alpha interferon: Cost-effective therapy for vulvar vestibulitis syndrome. Journal of Reproductive Medicine. 1993;38:19-24.

31. Horowitz BJ. Interferon therapy for condylomatous vulvitis. Obstetrics & Gynecology. 1989;73:446-8.

32. Foster DC, Hasday JD. Elevated tissue levels of interleukin-1β and tumor necrosis factor-α in vulvar vestibulitis. Obstetrics & Gynecology. 1997;89:291-6.

33. Brown CS, Wan J, Bachmann G, Rosen R. Self-management, amitriptyline, and amitriptyline plus triamcinolone in the management of vulvodynia. Journal of Women's Health. 2009;18:163-9.

34. Munday PE. Treatment of vulval vestibulitis with a potent topical steroid. Sexually Transmitted Infections. 2004;80:154-5.

35. Dede M, Yenen MC, Yilmaz A, Baser M. Successful treatment of persistent vulvodynia with submucous infiltration of betamethasone and lidocaine. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2006;124:258-9.

36. Segal D, Tifheret H, Lazer S. Submucous infiltration of betamethasone and lidocaine in the treatment of vulvar vestibulitis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2003;107:105-6.

37. Murina F, Tassan P, Roberti P, Bianco V. Treatment of vulvar vestibulitis with submucous infiltrations of methylprednisolone and lidocaine. An alternative approach. Journal of Reproductive Medicine. 2001;46:713-6.

38. Bergeron S, Khalifé S, Dupuis MJ, McDuff P. A randomized clinical trial comparing group cognitive-behavioral therapy and a topical steroid for women with dyspareunia. Journal of Consulting and Clinical Psychology. 2016;84:259-68.

39. Nyirjesy P, Sobel JD, Weitz MV, Leaman DJ, Small MJ, Gelone SP. Cromolyn cream for recalcitrant idiopathic vulvar vestibulitis: Results of a placebo controlled study. Sexually Transmitted Infections. 2001;77:53-7.

40. Farajun Y, Zarfati D, Abramov L, Livoff A, Bornstein J. Enoxaparin treatment for vulvodynia: a randomized controlled trial. Obstetrics & Gynecology. 2012;120:565-72.

41. Donders GG, Bellen G. Cream with cutaneous fibroblast lysate for the treatment of provoked vestibulodynia: A double-blind randomized placebo-controlled crossover study. Journal of Lower Genital Tract Disease. 2012;16:427-36.

42. Kim R, Kelly KL, Olson M, Nickel JC. Early experience with topical meloxicam and lidocaine combination for the treatment of vulvodynia. Canadian Urological Association Journal. 2018;12.

43. Leo RJ. A systematic review of the utility of anticonvulsant pharmacotherapy in the treatment of vulvodynia pain. The Journal of Sexual Medicine. 2013;10:2000-8.

44. Spoelstra SK, Dijkstra JR, van Driel MF, Weijmar Schultz WC. Long-term results of an individualized, multifaceted, and multidisciplinary therapeutic approach to provoked vestibulodynia. The Journal of Sexual Medicine. 2011;8:489-96.

45. Bates CM, Timmins DJ. Vulvodynia: New and more effective approaches to management. International Journal of STD & AIDS. 2002;13:210-2.

46. Ben-David B, Friedman M. Gabapentin therapy for vulvodynia. Anesthesia & Analgesia. 1999;89:1459-60.

47. Boardman L, Cooper A, Blais L, Raker C. Topical gabapentin in the treatment of localized and generalized vulvodynia. Obstetrics & Gynecology. 2008;112:579-85.

48. Harris G, Horowitz B, Borgida A. Evaluation of gabapentin in the treatment of generalized vulvodynia, unprovoked. Journal of Reproductive Medicine. 2007;52:103-6.

49. Jeon Y, Kim Y, Shim B, Yoon H, Park Y, Shim B et al. A retrospective study of the management of vulvodynia. Korean Journal of Urology. 2013;54:48-52.

50. Keevil E, Khot S, Nunns D, Patel G, Hiom S, Hodgkinson V. Painful vulvodynia alleviated by topical gabapentin: A two center survey of treatment safety and efficacy. British Journal of Pain. 2018;12:5 –54.

51. van Beekhuizen HJ, Oost J, van der Meijden WI. Generalized unprovoked vulvodynia: A retrospective study on the efficacy of treatment with amitriptyline, gabapentin or pregabalin. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018;220:118-21.

52. Ventolini G, Barhan S, Duke J. Vulvodynia, a step-wise therapeutic prospective cohort study. Journal of Obstetrics and Gynaecology. 2009;29:648-50.

53. Brown CS, Bachmann GA, Wan J, Foster DC. Gabapentin for the treatment of vulvodynia: A randomized controlled trial. Obstetrics & Gynecology. 2018;131:1000-7.

54. Jerome L. Pregabalin-induced remission in a 62-year-old woman with a 20-year history of vulvodynia. Pain Research and Management. 2007;12:212-4.

55. Meltzer-Brody SE, Zolnoun D, Steege JF, Rinaldi KL, Leserman J. Open-label trial of lamotrigine focusing on efficacy in vulvodynia. Journal of Reproductive Medicine. 2009;54:171-8.

56. Pagano R. Vulvar vestibulitis syndrome: an often unrecognized cause of dyspareunia. Australian and New Zealand Journal of Obstetrics and Gynaecology. 1999;39:79-83.

57. Pagano R, Wong S. Use of amitriptyline cream in the management of entry dyspareunia due to provoked vestibulodynia. Journal of Lower Genital Tract Disease. 2012;16:394-7.

58. McKay M. Dysesthetic ("essential") vulvodynia. Journal of Reproductive Medicine. 1993;38:9-13.

59. Munday PE. Response to treatment in dysaesthetic vulvodynia. Journal of Obstetrics and Gynaecology. 2001;21:610-3.

60. Nyirjesy P, Halpern M. Medical management of vulvar vestibulitis: Results of a sequential treatment plan. Infectious Diseases in Obstetrics and Gynecology. 1995;3:193–7.

61. Tribó MJ, Andión O, Ros S, Gilaberte M, Gallardo F, Toll A et al. Clinical characteristics and psychopathological profile of patients with vulvodynia: An observational and descriptive study. Dermatology. 2008;216:24-30.

62. Reed BD, Caron AM, Gorenflo DW, Haefner HK. Treatment of vulvodynia with tricyclic antidepressants: Efficacy and associated factors. Journal of Lower Genital Tract Disease. 2006;10:245-51.

63. Friedman M, Ben-David B, Siegler E. Amitriptyline vs. placebo for treatment of vulvodynia: A prospective study. Journal of Lower Genital Tract Disease. 1999;3:36.

64. Eisen A. Venlafaxine therapy for vulvodynia. Pain Clinic. 1996;8:365-7.

65. Nyirjesy P, Lev-Sagie A, Mathew L, Culhane J. Topical amitriptyline-baclofen cream for the treatment of provoked vestibulodynia. Journal of Lower Genital Tract Disease. 2009;12:230-6.

66. Moga MA, Dimienescu OG, Bălan A, Scîrneciu I, Barabaș B, Liana P. Therapeutic approaches of botulinum toxin in gynecology. Toxins. 2018;10:169.

67. Casale R, Tugnoli V. Botulinum toxin for pain. Drugs in R & D. 2008;9:11-27.

68. Dykstra DD, Presthus J. Botulinum toxin type A for thetreatment of provoked vestibulodynia: An open-label pilot study. Journal of Reproductive Medicine. 2006;51:467-70.

69. Pelletier F, Girardin M, Humbert P, Puyraveau M, Aubin F, Parratte B. Long-term assessment of effectiveness and quality of life of Onabotulinumtoxin A injections in provoked vestibulodynia. Journal of the European Academy of Dermatology and Venereology. 2016;30:106-11.

70. Pelletier F, Parratte B, Penz S, Moreno JP, Aubin F, Humbert P. Efficacy of high doses of botulinum toxin A for treating provoked vestibulodynia. British Journal of Dermatology. 2011;164:617-22.

71. Gunter J, Brewer A, Tawfik O. Botulinum toxin A for vulvodynia: A case report. The Journal of Pain. 2004;5:238-40.

72. Brown CS, Glazer HI, Vog V, Menkes D, Bachmann G. Subjective and objective outcomes of botulinum toxin type A treatment in vestibulodynia: Pilot data. Journal of Reproductive Medicine. 2006;51:635-41.

73. Yoon H, Chung WS, Shim BS. Botulinum toxin A for the management of vulvodynia. International Journal of Impotence Research. 2007;19:84–7.

74. Petersen CD, Giraldi A, Lundvall L, Kristensen E. Botulinum toxin type A - A novel treatment for provoked vestibulodynia? Results from a randomized, placebo controlled, double blinded study. The Journal of Sexual Medicine. 2009;6:2523-37.

75. Carrico D, Peters K. Vaginal diazepam use with urogenital pain/pelvic floor dysfunction: serum diazepam levels and efficacy data. Urologic Nursing. 2011;31:279-84.

76. Murina F, Felice R, Di Francesco S, Oneda S. Vaginal diazepam plus transcutaneous electrical nerve stimulation to treat vestibulodynia: A randomized controlled trial European Journal of Obstetrics and Gynecology and Reproductive Biology. 2018;228:148-53.

77. Burrows LJ, Basha M, Goldstein AT. The effects of hormonal contraceptives on female sexuality: a review. The Journal of Sexual Medicine. 2012;9:2213-23.

78. Bazin S, Lefebvre J, Fortier M, Brisson J, Brouillette F, Bujold E et al. Evaluation of an estrogen vaginal cream for the treatment of dyspareunia: A double-blind randomized trial. Journal of Obstetrics and Gynaecology Canada. 2011;33:838-43.

79. Langlais EL, Lefebvre J, Maheux-Lacroix S, Bujold E, Fortier M, Bouchard C. Treatment of secondary vestibulodynia with conjugated estrogen cream: A pilot, double-blind, randomized placebo-controlled Trial. Journal of Obstetrics and Gynaecology Canada. 2017;39:453-8.

80. Burrows LJ, Goldstein AT. The treatment vestibulodynia with topical estradiol and testosterone. The Journal of Sexual Medicine. 2013;1:30-3.

81. Bergeron S, Merwin K, Dubé J, Rosen NO. Couple sex therapy versus group therapy for women with genito-pelvic pain. Current Sexual Health Reports. 2018;10:79-87.

82. Bergeron S, Binik YM, Khalife S, Pagidas K, Glazer HI, Meana M et al. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain. 2001;91:297-306.

83. Masheb RM, Kerns RD, Lozano C, Minkin MJ, Richman S. A randomized clinical trial for women with vulvodynia: Cognitive-behavioral therapy vs. supportive psychotherapy. Pain. 2009;141:31-40.

84. Corsini-Munt S, Bergeron S, Rosen NO, Steben M, Mayrand M, Delisle I et al. A comparison of cognitive-behavioral couple therapy and lidocaine in the treatment of provoked vesibulodynia: Study protocol for a randomized clinical trial. Trials. 2014;15:506-16.

85. Corsini-Munt S, Bergeron S, Rosen NO, Mayrand M, Delisle I. Feasibility and preliminary effectiveness of a novel cognitive-behavioral couple therapy for provoked vestibulodynia: A pilot study. The Journal of Sexual Medicine. 2014;11:2515-27.

86. Brotto LA, Basson R, Smith KB, Driscoll M, Sadownik L. Mindfulness-based group therapy for women with provoked vestibulodynia. Mindfulness. 2015;6:417-32.

87. Dunkley CR, Brotto LA. Psychological treatments for provoked vestibulodynia: Integration of mindfulness-based and cognitive-behavioral therapies. Journal of Clinical Psychology. 2016;28:637-50.

88. Brotto LA, Basson R, Carlson M, Zhu C. Impact of an integrated mindfulness and cognitive behavioural treatment for provoked vestibulodynia (IMPROVED): A qualitative study. Sex and Relationship Therapy. 2013;28:3-19.

89. Veehof MM, Trompetter HR, Bohlmeijer ET, Schnreurs KMG. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: A meta-analytic review. Cognitive Behaviour Therapy. 2016;45:5-31.

90. Reissing ED, Brown C, Lord MJ, Binik YM, Khalife S. Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. Journal of Psychosomatic Obstetrics and Gynaecology. 2005;26:107-13.

91. Thibault‐Gagnon S, Morin M. Active and passive components of pelvic floor muscle tone in women with provoked vestibulodynia: a perspective based on a review of the literature. The Journal of Sexual Medicine. 2015;12:2178-89.

92. Morin M, Carroll MS, Bergeron S. Systematic review of the effectiveness of physical therapy modalities in women with provoked vestibulodynia. Sexual Medicine Reviews. 2017;5:295-322.

93. Idama DW, Pring T. Vaginal dilator therapy-an outpatient gynaecological option in the management of dyspareunia. Journal of Obstetrics and Gynaecology. 2000;20:303-5.

94. Murina F, Bianco V, Radici G, Felice R, Di Martino M, Nicolini U. Transcutaneous electrical nerve stimulation to treat vestibulodynia: a randomised controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology. 2008;115:1165-70.

95. Smith M, Gillmer K. Amielle vaginal trainers-a patient evaluation. Journal of Obstetrics and Gynaecology. 1998;18:146-7.

96. FitzGerald MP, Anderson RU, Potts J, Payne CK, Peters KM, Clemens JQ et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. The Journal of Urology. 2013;189:175-85.

97. Dionisi B, Anglana F, Inghirami P, Lippa P, Senatori R. Use of transcutaneous electrical stimulation and biofeedback for the treatment of vulvodynia (vulvar vestibular syndrome): result of 3 years of experience. Minerva Ginecologica. 2008;60:485-91.

98. Dionisi B, Senatori R. Effect of transcutaneous electrical nerve stimulation on the postpartum dyspareunia treatment. Journal of Obstetrics and Gynaecology Research. 2011;37:750-3.

99. Vallinga MS, Spoelstra SK, Hemel IL, van de Wiel HB, Schultz WCW. Transcutaneous electrical nerve stimulation as an additional treatment for women suffering from therapy‐resistant provoked vestibulodynia: a feasibility study. The Journal of Sexual Medicine. 2015;12:228-37.

100. Murina F, Graziottin A, Felice R, Radici G, Tognocchi C. Vestibulodynia: synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation. Journal of Lower Genital Tract Disease. 2013;17:111-6.

101. Morin A, Léonard G, Gougeon V, Cyr MP, Waddell G, Bureau YA et al. Efficacy of transcranial direct-current stimulation in women with provoked vestibulodynia. American Journal of Obstetrics and Gynecology. 2017;216.

102. Glazer HI, Rodke G, Swencionis C, Hertz R, Young AW. Treatment of vulvar vestibulitis syndrome with electromyographic biofeedback of pelvic floor musculature. Journal of Reproductive Medicine. 1995;40:283-90.

103. McKay E, Kaufman RH, Doctor U, Berkova Z, Glazer H, Redko V. Treating vulvar vestibulitis with electromyographic biofeedback of pelvic floor musculature. The Journal of Reproductive Medicine. 2001;46:337-42.

104. Bergeron S, Binik YM, Khalife S, Pagidas K, Glazer HI, Meana M et al. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain. 2001;91:297-306.

105. Bergeron S, Brown C, Lord MJ, Oala M, Binik YM, Khalife S. Physical therapy for vulvar vestibulitis syndrome: A retrospective study. Journal of Sex and Marital Therapy. 2002;28:183-92.

106. Forth HL, Cramp MC, Drechsler WI. Does physiotherapy treatment improve the self-reported pain levels and quality of life of women with vulvodynia? A pilot study. Journal of Obstetrics and Gynaecology. 2009;29:423-9.

107. Gentilcore-Saulnier E, McLean L, Goldfinger C, Pukall CF, Chamberlain S. Pelvic floor muscle assessment outcomes in women with and without provoked vestibulodynia and the impact of a physical therapy program. The Journal of Sexual Medicine. 2010;7:1003-22.

108. Goldfinger C, Pukall CF, Gentilcore-Saulnier E, McLean L, Chamberlain S. A prospective study of pelvic floor physical therapy: Pain and psychosexual outcomes in provoked vestibulodynia. The Journal of Sexual Medicine. 2009;6:1955-68.

109. Hartmann EH, Nelson C. The perceived effectiveness of physical therapy treatment on women complaining of chronic vulvar pain and diagnosed with either vulvar vestibulitis syndrome or dysesthetic vulvodynia. Journal of Women's Health. 2001;25:13-8.

110. Miletta M, Bogliatto F. Role of the physical therapy in the multidisciplinary approach to vulvodynia: preliminary results. Working Paper of Public Health. 2015;4.

111. Tommola P, Unkila-Kallio L, Paavonen J. Long-term well-being after surgical or conservative treatment of severe vulvar vestibulitis. Acta Obstetricia et Gynecologica Scandinavica. 2012;91:1086-93.

112. Goldfinger C, Pukall CF, Thibault-Gagnon S, McLean L, Chamberlain S. Effectiveness of cognitive-behavioral therapy and physical therapy for provoked vestibulodynia: a randomized pilot study. The Journal of Sexual Medicine. 2016;13:88-94.

113. Prendergast SA. Pelvic floor physical therapy for vulvodynia: A clinician's guide. Obstetrics and Gynecology Clinics. 2017;44:509-22.

114. Nwanodi OB, Tidman MM. Vulvodynia treated with acupuncture or electromyographic biofeedback. Chinese Medicine. 2014;5:61-70.

115. Curran S, Brotto LA, Fisher H, Knudson G, Cohen T. The ACTIV study: acupuncture treatment in provoked vestibulodynia. The Journal of Sexual Medicine. 2010;7:981-95.

116. Danielsson I, Sjöberg I, Östman C. Acupuncture for the treatment of vulvar vestibulitis: a pilot study. Acta Obstetricia et Gynecologica Scandinavica. 2001;80:1360-7.

117. Powell J, Wojnarowska F. Acupuncture for vulvodynia. Journal of the Royal Society of Medicine. 1999;92:579-81.

118. Schlaeger JM, Xu N, Mejta CL, Park CG, Wilkie DJ. Acupuncture for the treatment of vulvodynia: a randomized wait-list controlled pilot study. The Journal of Sexual Medicine. 2015;12:1019-27.

119. Pukall C, Kandyba K, Amsel R, Khalifé S, Binik Y. Sexual pain disorders: effectiveness of hypnosis for the treatment of vulvar vestibulitis syndrome: a preliminary investigation. The Journal of Sexual Medicine. 2007;4:417-25.

120. Kandyba K, Binik YM. Hypnotherapy as a treatment for vulvar vestibulitis syndrome: a case report. Journal of Sex & Marital Therapy. 2003;29:237-42.

121. Murina F, Karram M, Salvatore S, Felice R. Fractional CO2 laser treatment of the vestibule for patients with vestibulodynia and genitourinary syndrome of menopause: a pilot study. The Journal of Sexual Medicine. 2016;13:1915-7.

122. Lev-Sagie A, Kopitman A, Brzezinski A. Low-level laser therapy for the treatment of provoked vestibulodynia—A randomized, placebo-controlled pilot trial. The Journal of Sexual Medicine. 2017;14:1403-11.

123. King MA, Mitchell LS, Belkin Z, Goldstein AT. Vulvar vestibulectomy for neuroproliferative-associated provoked vestibulodynia: A retrospective analysis. Journal of Gynecologic Surgery. 2018;34:58-62.

124. Tommola P, Unkila‐Kallio L, Paavonen J. Surgical treatment of vulvar vestibulitis: a review. Acta Obstetricia et Gynecologica Scandinavica. 2010;89:1385-95.

125. Goetsch M. Surgery combined with muscle therapy for dyspareunia from vulvar vestibulitis. Journal of Reproductive Medicine. 2007;52:597-603.

126. Abramov L, Wolman I, David MP. Vaginismus: an important factor in the evaluation and management of vulvar vestibulitis syndrome. Gynecologic and Obstetric Investigation. 1994;38:194-7.

127. Bergeron S, Binik YM, Khalife S, Pagidas K, Glazer HI, Meana M et al. A randomized comparison of group cognitive--behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain. 2001;91:297-306.

128. Bergeron S, Binik YM, Khalifé S, Meana M, Berkley KJ, Pagidas K. The treatment of vulvar vestibulitis syndrome: towards a multimodal approach. Sexual & Marital Therapy. 1997;12:305-11.

129. Bergeron S, Khalifé S, Glazer HI, Binik YM. Surgical and behavioral treatments for vestibulodynia: two-and-one-half–year follow-up and predictors of outcome. Obstetrics & Gynecology. 2008;111:159-66.

130. Michlewitz H, Kennison RD, Turksoy RN, Fertitta LC. Vulvar vestibulitis-subgroup with Bartholin gland duct inflammation. Obstetrics & Gynecology. 1989;73:410-3.

131. Eva LJ, Narain S, Orakwue CO, Luesley DM. Is modified vestibulectomy for localized provoked vulvodynia an effective long-term treatment? A follow-up study. The Journal of Reproductive Medicine. 2008;53:435-40.

132. Goldstein AT, Klingman D, Christopher K, Johnson C, Marinoff SC. Surgical treatment of vulvar vestibulitis syndrome: Outcome assessment derived from a postoperative questionnaire The Journal of Sexual Medicine. 2006;3:923-31.

133. Pukall CF, Mitchell LS, Goldstein A. Non-medical, medical, and surgical approaches for the treatment of provoked vestibulodynia. Current Sexual Health Reports. 2016;8:240-8.

134. Backman H, Widenbrant M, Bohm-Starke N, Dahlof LG. Combining physical and psychosexual therapy for provoked vestibulodynia - an evaluation of a multidisciplinary model. Journal of Sex Research. 2008;45:378-85.

135. Brotto LA, Yong P, Smith KB, Sadownik L. Impact of a multidisciplinary vulvodynia program on sexual functioning and dyspareunia. The Journal of Sexual Medicine. 2015;12:238-47.

136. Lindström S, Kvist LJ. Treatment of provoked vestibulodynia in a Swedish cohort using desensitization exercises and cognitive-behavioral therapy. BMC Women's Health. 2015;15:108.

137. Sadownik L, Smith KB, Hui A, Brotto LA. The Impact of a Woman's Dyspareunia and Its Treatment on Her Intimate Partner: A Qualitative Analysis. Journal of Sex & Marital Therapy. 2017;43:529-42.

138. Sadownik L, Seal BN, Brotto LA. Provoked vestibulodynia—women's experience of participating in a multidisciplinary vulvodynia program. The Journal of Sexual Medicine. 2012;9:1086-93.

139. Munday P, Buchan A, Ravenhill G, Wiggs A, Brooks F. A qualitative study of women with vulvodynia II. Response to a multidisciplinary approach to management. Journal of Reproductive Medicine. 2007;52:19-22.

140. Tommola P, Unkila-Kallio L, Paavonen J. Long-term follow up of posterior vestibulectomy for treating vulvar vestibulitis. Acta Obstetrica et Gynecologica Scandanavia. 2011;90:1225-31.

141. Miranda GVP, Soriano MM, Silveira ZNR, Vale MDCM. A systematic review of drug treatment of vulvodynia: evidence of a strong placebo effect. A BJOG: An International Journal of Obstetrics and Gynaecology. 2018;125:1216-24.

142. Bergeron S, Meana M, Binik YM, Khalife S. Painful Sex. In: Levine SB, Risen CB, Althof SE, editors. Handbook of Clinical Sexuality for Mental Health Professionals. 2 ed. New York: Routledge - Taylor & Francis Group; 2010. p. 193-214.

143. Reed BD, Plegue MA, Williams DA, Sen A. Presence of spontaneous pain and comorbid pain conditions identifies vulvodynia subgroups. Journal of Lower Genital Tract Disease. 2016;20:57-63.

144. Reed BD, Harlow BL, Sen A, Edwards RM, Chen D, Haefner HK. Relationship between vulvodynia and chronic comorbid pain conditions. Obstetrics & Gynecology. 2012;120:145-51.

145. Pukall CF. Primary and secondary provoked vestibulodynia: A review of overlapping and distinct factors. Sexual Medicine Reviews. 2016;4:36-44.

146. Gerber S, Bongiovanni AM, Ledger WJ, Witkin SS. Interleukin-1 beta gene polymorphism in women with vulvar vestibulitis syndrome. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2003;107:74-7.

147. King M, Rubin R, Goldstein A. Current uses of surgery in the treatment of genital pain. Current Sexual Health Reports. 2014;6:252-8.

148. Corsini-Munt S, Rancourt K, Dubé J, Rossi M, Rosen NO. Vulvodynia: A consideration of clinical and methodological research challenges and recommended solutions. The Journal of Pain Research. 2017;10:2425-36.