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IS THERE A PATH TO LASTING RELIEF? A REVIEW OF PHARMACOLOGICAL TREATMENT FOR VULVODYNIA

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ABSTRACT

Introduction: Vulvodynia is defined as discomfort of the vulva that lasts for at least three months and is clinically considered an idiopathic pain syndrome, presenting both diagnostic and therapeutic challenges.While non-pharmacological interventions such as pelvic floor physical therapy and psychotherapy provide relief for some patients, many require pharmacological treatment for persistent discomfort. Despite the availability of various pharmaceutical options, standardized treatment protocols are lacking, and comparative efficacy data remain limited. This review examines current pharmacological approaches for vulvodynia and assesses their effectiveness in managing symptoms.
Results: Following a rigorous selection process, 29 articles met the inclusion criteria. The available evidence supports the efficacy of oral medications, particularly amitriptyline as a first-line treatment, and topical lidocaine in managing vulvodynia. Furthermore, the integration of physiotherapy alongside pharmacological management appears to enhance patient outcomes. Botulinum toxin injections did not yield statistically significant improvement in the studies included in the review.
Conclusions: Amitriptyline and topical lidocaine have demonstrated efficacy for vulvodynia, particularly when combined with physiotherapy. Future research should focus on investigating the long-term efficacy of combined therapies and exploring the underlying mechanisms of vulvodynia to develop targeted treatments.

KEYWORDS

Pharmacology, Treatment Outcome, Vulvar Disease, Vulvar Vestibulitis, Vulvodynia

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Introduction

Vulvodynia is defined as vulvar discomfort, often described as burning, persisting for at least three months without a clear identifiable cause. The diagnosis of vulvodynia is reached by eliminating other known causes of vulvar pain, making it an idiopathic pain syndrome [1]. Vulvodynia can affect women of all ages, epidemiological research suggests the highest incidence of new cases occurs between the ages of 18 and 24 [2]. Chronic pain significantly impacts women's quality of life, including physical functioning, sexual health (dyspareunia, reduced satisfaction), and psychosocial well-being. Diagnostic and treatment obstacles contribute to frustration, isolation, and invalidation. The condition's "hidden" nature exacerbates these challenges, promoting shame and embarrassment that impede help-seeking behaviors [3]. The etiology of vulvodynia is currently unknown, however, several factors are potentially associated with its development. The International Society for the Study of Vulvovaginal Disease and the International Society for the Study of Women's Sexual Health and the International Pelvic Pain Society have revised the current terminology and classification of persistent vulvar pain and vulvodynia. In the consensus version, experts presented the range of possible causes of vulvar pain and vulvodynia in Table 1., and also modified the terms and descriptors of vulvar pain and vulvodynia features in Table 2. [4]. The absence of a single, identifiable cause underscores the need for a multimodal treatment strategy that addresses both pharmacological and non-pharmacological interventions tailored to the individual's specific needs [5, 6]. Non-pharmacological methods include: pelvic floor muscle physiotherapy, psychotherapy, neurostimulation and, in certain cases, surgery [4]. Currently, there is no standardized treatment protocol or combination of therapeutic approaches that reliably ensures sustained symptom reduction in vulvodynia [7]. Available evidence recommend non-invasive therapies, such as pelvic floor physical therapy and psychotherapy, as the first-line treatment, however, for many patients, this approach proves insufficient [8]. While these non-invasive therapies offer valuable initial management strategies, a substantial portion of individuals with vulvodynia experience persistent or recurrent symptoms despite these interventions. Pharmacotherapy demonstrates efficacy in the treatment of vulvodynia and serves as a primary therapeutic option when first-line treatments fail, potentially providing significant pain relief and improving quality of life [9]. This review explores pharmacological treatment options for vulvodynia, with drug classifications in Table 3. Despite the potential of pharmacological interventions, more rigorous research is needed to establish their efficacy and optimize treatment protocols [9, 10]. The aim of this review is to analyze the existing evidence for different pharmacological interventions for vulvodynia and determine which pharmacological approach demonstrates the greatest effectiveness in alleviating symptoms of this condition.

Table 1. Causes of vulvar pain [4]. The 2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia.

1. Vulvar pain caused by a specific disorders	
Infectious	recurrent Candidiasis, herpes simplex virus infection, trichomoniasis
Inflammatory	Lichen sclerosus, lichen planus, lichen simplex, contact or allergic urticaria, immunobullous disorders
Neoplastic disorders	Paget's disease and squamous cell carcinoma
Neurologic disorders	Postherpetic neuralgia, neuralgia caused by herpes simplex virus infection, nerve compression or injury, neuroma
Trauma	Obstetric trauma, injuries to the external genitalia
Iatrogenic causes	Pain after surgery or caused by chemotherapy or radiation therapy
Hormonal deficiencies	Menopausal urogenital syndrome, lactational amenorrhea, estrogen deficiencies, vulvovaginal atrophy

Table 2. Features describing the vulvodynia [4]. The 2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia.

1. Location	a. Limited to a specific area of the vulva (e.g. vestibulodynia, clitorodynia) b. Generalized, affecting the entire vulva c. Mixed, with limited and generalized pain
2. Provocation	a. Provoked (e.g. physical contact, clothing, insertional) b. Spontaneous c. Mixed, both provoked and spontaneous
3. Onset of disease complaints	a. Primary - complaints occurred during the first sexual or non-sexual contact (e.g. tampon application) b. Secondary - the discomfort occurs after a period of time without pain
4. Temporal pattern	a. Persistent - the condition persists over a period of at least 3 months b. Intermittent - the symptoms are not always present c. Constant - the symptoms are always present d. Immediate - the symptoms occur during the provoking physical contact e. Delayed - the symptoms occur after the provoking physical contact

Table 3. Pharmacological substances included in the review.

Substance	Drug Class	Primary Use
Gabapentin	Anticonvulsant/Neuropathic Pain	Neuropathic pain, seizures
Pregabalin		
Amitriptyline		
Ospemifene	Selective Estrogen Receptor Modulator	Painful intercourse in postmenopausal women
Itraconazole	Antifungal	Fungal infections
Lignocaine	Local Anesthetic	Local anesthesia
Xylocaine		
Procaine		
Spermidine	Polyamine/Nutritional Supplement	Cellular health, anti-aging research
Estrogens	Hormone	Hormone replacement therapy
Capsaicin	Topical Analgesic	Arthritis, neuropathic pain
Botulinum Toxin A	Neuromuscular Blocking Agent	Muscle spasms, migraines, cosmetic applications
Hyaluronic Acid	Lubricant/Joint Supplement	Joint pain, skin hydration, wound healing

Methodology

This literature review was conducted through a systematic search of PubMed and Google Scholar for articles published within the past decade. The search strategy included the keywords “vulvodynia” and “treatment.” A total of 490 records were retrieved from PubMed and 7,940 from Google Scholar. Due to the limited search functionality and relevance-ranking algorithm of Google Scholar, only the first 500 results were screened, yielding a total of 990 records. After removing 251 duplicates, 739 unique records were reviewed by title and abstract. Exclusion criteria included non-original articles, review papers, non-English publications, and studies not addressing pharmacological management of vulvodynia. Following the screening, 35 full-text articles were assessed for eligibility, of which six could not be accessed. Ultimately, 29 studies met all inclusion criteria and were included in the review. Eligible studies focused on the pharmacological treatment

of vulvodynia, regardless of subtype, and included both monotherapy and combination approaches. Randomized controlled trials were prioritized, but observational and case-based studies were also considered. Interventions were categorized as oral, topical, or injectable treatments, with combination therapies analyzed separately. The study identification and selection process followed PRISMA 2020 recommendations and is illustrated in the PRISMA flow diagram below (Figure 1).

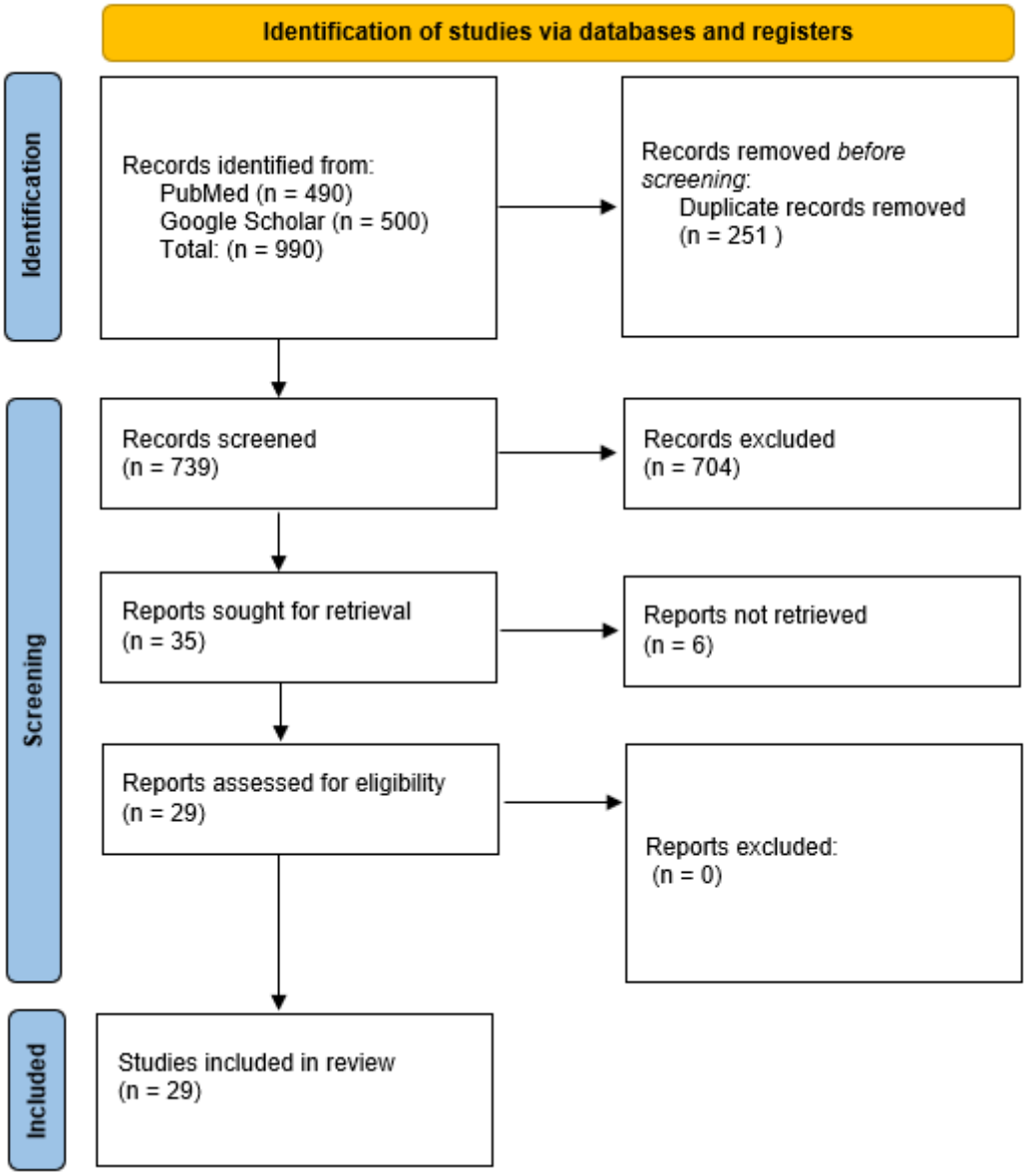

Fig. 1. *PRISMA flow diagram illustrating the process of study selection.*

Oral medications for the management of vulvodynia

Gabapentin

Two randomized, double-blind, placebo-controlled trials investigated the efficacy of gabapentin in treating provoked vulvodynia. Bachmann et al. focused on sexual function using the Female Sexual Function Index (FSFI) and pain levels via algometer and Numeric Rating Scale (NRS). While gabapentin significantly improved FSFI domains of desire, arousal, and satisfaction, it didn't affect lubrication, orgasm, or pain. Post-treatment, FSFI scores remained lower than a control group without vulvodynia. Gabapentin correlated with improved FSFI scores in participants with high, but not low, pelvic muscle pain. This study included 89 women (18-50 years old) experiencing vestibular pain >4/10 NRS during intercourse or vulvar contact for at least three months, with most (n=66) reporting pain for ≥5 years. The sample was diverse, with some reporting prior

sexual abuse, contraceptive/hormone therapy, and selective serotonin reuptake inhibitors use. 66 of 89 participants completed the study [18]. Brown et al. used a multicentre, randomised, crossover design with similar participant characteristics. Daily and intercourse-related pain was tracked using the NRS, and a tampon test provided an objective measure of pain. Gabapentin was titrated for four weeks (maximum five tablets per day), maintained for a fortnight and then reduced. Despite the rigorous design, this study, unlike the earlier one, did not demonstrate efficacy . No significant pain reduction with gabapentin compared to placebo based on the tampon test and reports of pain associated with sexual intercourse, concluding that gabapentin monotherapy may not be effective [19].

Amitriptyline

Two randomized controlled trials explored amitriptyline's efficacy in treating vulvodynia and related conditions. One study focused on vestibulodynia/painful bladder syndrome, enrolling 84 women without other neurological issues, vulvovaginal atrophy (VVA), skin conditions, or infections. Pain was assessed using the McGill Pain Questionnaire, dyspareunia severity with the Marinoff and Turner scale, and pelvic floor muscle tension was also considered. Participants received either amitriptyline alone or combined with an alpha-lipoic acid/n-3 polyunsaturated fatty acid supplement (including vitamins D and E, magnesium, docosahexaenoic acid. Amitriptyline was titrated to 30 mg nightly, and the supplement taken twice daily. Both groups experienced significant pain relief, but the combination therapy yielded greater improvement, particularly for dyspareunia (47% vs. 22% reporting less pain) [20].The second trial involved 86 women (18-45 years old) with severe vulvar pain (NRS >5) for at least three months and dyspareunia more than half the time. A gynecologist confirmed the diagnosis, excluding other conditions, infections, pregnancy/breastfeeding, premature ovarian insufficiency, prior oophorectomy/vulvar/vaginal surgery, malignancy, contraindicating medications, or cognitive impairments. Pain was assessed using the Friedrich scale (dyspareunia, burning, itching, Q-tip test, erythema) and NRS, while sexual function was evaluated with the FSFI. Participants received amitriptyline alone, with electrotherapy, or with pelvic floor exercises. All groups experienced some pain relief, but the electrotherapy group showed greater improvement in dyspareunia than medication alone. The physiotherapy group demonstrated the most significant improvements in sexual function (lubrication, orgasm, satisfaction, pain) and dyspareunia. This suggests that physiotherapy, targeting pelvic floor muscle tension through relaxation, tissue mobilization, and myofascial release, may be a valuable primary treatment approach for vulvodynia [11]. Continuing the discussion on vulvodynia treatments amitriptyline, a retrospective observational study evaluated the long-term efficacy and tolerability of amitriptyline, gabapentin, and pregabalin for generalized unprovoked vulvodynia (GUV). This study, conducted at three specialized vulvar disease clinics in Rotterdam, included 241 women diagnosed with generalized unprovoked vulvodynia between 1996 and 2013. Patient-reported pain reduction served as the primary outcome, with 60% achieving long-term relief. Amitriptyline was the most common first-line treatment, while gabapentin and pregabalin were used in cases of amitriptyline intolerance or inefficacy. Notably, 43% of participants presented with comorbid vulvar dermatoses (e.g., lichen sclerosus, lichen planus). The study analyzed the efficacy of each medication, considering factors like symptom duration, patient age, and comorbid vulvar conditions. Results indicated these medications' effectiveness even with coexisting dermatological issues [21].

Ospemifene

In a pilot study involving 55 postmenopausal women with vulvovaginal atrophy symptoms such as dryness, burning, dyspareunia, ospemifene was tested. Exclusion criteria included Body Mass Index > 37, other gynaecological conditions, taking hormonal medication, hypersensitivity to the drug and severe/chronic illness. Participants received 60 mg of ospemifene daily for 60 days. Symptoms were assessed by Visual Analogue Scale (VAS), swab test, visual examination (petechiae, pallor, tenderness, dryness, erythema) and current perception threshold (CPT) test. Treatment with ospemifene for two months showed reduced sensitivity of C, Aβ and Aδ nerve fibres in women with vulvovaginal atrophy, as evidenced by reduced current perception threshold values at 2000 Hz and 250 Hz. After treatment, patients reported an improvement in VVA symptoms such as dryness, burning and dyspareunia. A swab test conducted at the end of treatment confirmed a statistically significant reduction in pain. This treatment is an alternative for women who cannot undergo vaginal oestrogen therapy [12].

Itraconazole

A retrospective cohort study evaluated the efficacy of itraconazole in patients suffering from vulvodynia looking for an explanation of its effect had two hypotheses targeting a non-culturable pathogen or inhibiting angiogenesis and excessive innervation, which could reduce vulvar pain. Patients with negative fungal cultures and also non-responsive to fluconazole (200 mg for 6-8 weeks) were included in the study. Exclusion criteria included other vulvovaginal pathologies (lichen sclerosus, lichen planus, lichen simplex chronicus), previous treatment of vulvodynia, liver disease, concomitant antibiotic use and absence of pain during baseline swab assessment. Pain was assessed using a 10-point scale after swabbing the labia major, labia minor and six vestibular sites. Participants received 400 mg of itraconazole daily and liver function was monitored. Among 106 participants, itraconazole resulted in an average pain reduction of 60.7%, with peak efficacy (69.7%) after five to six weeks. 37.7% achieved remission and 53.8% experienced >60% pain reduction. Further studies are needed to clarify the exact mechanism of action, as the standard antifungal mechanism does not fully explain the observed effects [13].

Topical medications for the management of vulvodynia

Spermidine

A preliminary investigation explored the potential of topical spermidine hyaluronate as a treatment for provoked vestibulodynia (PVD). The study involved 26 women with provoked vestibulodynia who applied the gel. Patients were divided into two groups: the first group received 2 ml of spermidine hyaluronate with low viscosity in the vestibule area, while the second group received the gel with high viscosity. The treatment period lasted eight weeks. Pain levels (VAS) and dyspareunia (Marinoffa scale). No significant adverse effects were observed. The second group, which received the higher viscosity spermidine hyaluronate formulation, exhibited a statistically significant improvement compared to the first group, suggesting enhanced efficacy with increased viscosity [15].

Lidocaine

Forty-two patients with vulvodynia participated in a multi-center cohort study evaluating the effectiveness of manual perineal rehabilitation combined with 2% lidocaine. Treatment sessions were conducted a minimum of once per week, with the majority of participants performing daily self-massage. Pre- and post-treatment questionnaires assessed general well-being, pain, sexual function, and vaginal penetration, with the latter questionnaire also gauging treatment impact. The comprehensive intervention included strategies for managing penetration anxiety (such as dilators and breathing exercises), guidance on lifestyle and hygiene, and sexual coaching. Patients were advised to practice gentle genital hygiene, use appropriate lubricants, and opt for cotton undergarments and menstrual products. A 95% improvement rate was reported, highlighting the potential benefits of pelvic floor muscle relaxation [14]. A multi-center randomized controlled trial compared multimodal physiotherapy to topical lidocaine for the treatment of vulvodynia. Participants were assigned to one of two groups: a physiotherapy group receiving a 10-week program encompassing vulvar desensitization, pelvic floor muscle stretching, myofascial release, connective tissue manipulation, neuromuscular re-education, and home exercises (including vaginal dilators); Second group applying 5% lidocaine to the vulvar vestibule before bed. Outcomes were measured using the NRS, FSFI, Female Sexual Distress Scale, McGill-Melzack Pain Questionnaire, pain during intercourse ratings, and sexual function assessments. Multimodal physiotherapy proved significantly more effective than topical lidocaine, with sustained improvements observed at 6 months [22].

Xylocaine

Xylocaine, a local anesthetic exerts its analgesic activity through a mechanism involving the blockade of sodium channels on peripheral nociceptors and the inhibition of discharge transmission from peripheral sensory nerves [6]. Gupta and Shekhar conducted a prospective study of 520 women (20-65 years old) with a vulvodynia diagnosis based on Friedrich's criteria. Participants, most of whom had not found lasting relief from prior therapies (topical medications, amitriptyline, herbal remedies, revised perineal incisions, etc.), applied 5% xylocaine ointment to affected areas at bedtime and placed a medicated cotton swab in the vaginal vestibule for at least eight hours. At six months, 88% (458/520) reported intercourse without significant discomfort, compared to 34% (177/520) pretreatment. Both daily and intercourse-related pain scores, measured using a VAS, decreased significantly from a mean of 8.6 to 2.5. Eighty-eight percent of participants expressed complete satisfaction at six-month follow-up [7].

Estrogen

In an observational study, Goetsch investigated the impact of prolonged estrogen therapy on postmenopausal women experiencing persistent genital pain, potentially related to vulvar atrophy (including cases stemming from premenopausal oophorectomy). Participants, all over 44 years old, demonstrated significant (70-100%) pain reduction with a 4% lidocaine test and underwent assessment for vulvar atrophy. Treatment consisted of topical or transdermal estradiol, sometimes combined. Patients were categorized based on pain-related activity limitations, with 44% experiencing severe disruptions to basic functions like sitting. A correlation between vulvar pain and urological symptoms (e.g., dysuria) was observed in half the participants. Two patients reported positive outcomes with adjunctive gabapentin [23]. Langlais et al. conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of conjugated equine estrogen cream in alleviating dyspareunia related to secondary provoked vestibulodynia. Utilizing the NRS, FSFI, and the McGill Pain Questionnaire, the study compared the effects of nightly intravaginal application of the estrogen cream versus placebo over an 8-week period in women aged 18-45. While the McGill Pain Questionnaire revealed a significant reduction in dyspareunia among participants receiving the estrogen cream, no such improvement was detected using the NRS or FSFI. The authors acknowledge the limited generalizability of their findings due to the small sample size, which also restricts the formulation of robust treatment guidelines [16].

Capsaicin

The analgesic action of topical capsaicin, a Transient Receptor Potential Vanilloid 1 (TRPV1) agonist, involves a unique mechanism. Capsaicin first stimulates primary sensory neurons, leading to a burning sensation. This stimulation, however, induces a reversible desensitization of the neurons, rendering them unresponsive to further stimuli. This desensitization of TRPV1 receptors underlies the therapeutic potential of capsaicin for pain relief [24]. A 2024 study Kopits et al., evaluated the efficacy and tolerability of topical 0.025% capsaicin in 25 women with neuroproliferative provoked vestibulodynia. Participants applied VersaBase capsaicin cream daily to the vulvar vestibule, gradually increasing the duration to 20 minutes over 12 weeks. Lidocaine 2% ointment was permitted for pretreatment discomfort management. Pain and sexual function were assessed using the VAS and FSFI, respectively, before, during, and after treatment. Eighty percent of participants achieved the target 20-minute application within one to two weeks. Mean vulvar pain scores (11-point scale) significantly decreased from 8.2 at baseline to 5.35 ($p < 0.0001$). Although overall sexual function did not change significantly, sexual distress improved from 35.96 to 25.09 ($p < 0.0001$), with a corresponding improvement in dyspareunia. While 64% reported pain improvement and 56% would recommend capsaicin, tolerability varied, underscoring the need for thorough patient counseling [17].

Diazepam

A randomized, double-blind, placebo-controlled trial investigated vaginal diazepam plus transcutaneous electrical nerve stimulation (TENS) for vestibulodynia treatment. Forty two women diagnosed with vestibulodynia were randomly assigned to receive either 5 mg intravaginal diazepam or a placebo, with both cohorts concurrently undergoing Transcutaneous electrical nerve stimulation for a duration of 60 days. Outcome measures encompassed pain intensity (VAS), dyspareunia severity, vaginal surface electromyographic activity, and vestibular current perception threshold. Both groups showed significant improvements in pain, sexual function, pelvic floor muscle tone, and vestibular current perception threshold, though intergroup differences were limited. The diazepam group experienced greater reductions in dyspareunia and changes in pelvic floor muscle activity. Therefore, while both treatments appear to offer some benefit, the added benefit of diazepam may be marginal for some individuals [25].

Injectable interventions for the management of vulvodynia

Botulinum Toxin A

Botulinum toxin blocks acetylcholine release at the neuromuscular junction, temporarily weakening or paralyzing targeted muscles. This mechanism may be beneficial for treating vestibulodynia, as it may help alleviate muscle spasm and tension in the affected area, thereby reducing the associated pain and discomfort experienced by patients [26]. Haraldson et al. evaluated the effectiveness of Botulinum Toxin A (BoNT/A) injections for PVD in a randomized, double-blind, placebo-controlled trial. Eighty-eight women were divided into two groups of 44 participants each. One group received two injections of 50 units of BoNT/A into the bulbocavernosus muscles, with a three-month interval between injections, while the other group received

placebo injections. The primary outcome, a reduction in dyspareunia severity and pain during tampon use (VAS), showed no advantage of botulinum toxin injection over placebo. Analysis of secondary outcomes showed a positive effect of BoNT/A injection in reducing pelvic floor muscle tension and increasing the number of women attempting vaginal intercourse. Extending this work, Haraldson and colleagues conducted a 12-month follow-up study, which confirmed the initial findings, showing no statistically significant difference in pain levels (related to tampon use or dyspareunia) between the BoNT/A and placebo groups. Despite the lack of significant pain reduction, participants receiving BoNT/A reported a higher inclination towards sexual activity and improved sexual function [27]. Diomande et al. conducted a three-arm, placebo-controlled study with an exploratory analysis phase to examine a novel protocol for treating PVD in women. Thirty-three participants were divided into three groups, receiving either 50 units (arm A), 100 units (arm B) of BoNT/A, or placebo (arm C) via subcutaneous injection into the vulvar vestibule. Pain assessment using cotton swab-provoked VAS, von Frey filaments, and the Marinoff dyspareunia scale, occurred every three months. Initial results at three months showed no significant difference in pain reduction between the botulinum toxin and placebo groups, failing to demonstrate the efficacy of a single botulinum toxin injection. Subsequently, the study proceeded to an unblinded exploratory phase, where all participants received a second 100-unit BoNT/A injection. At six months pain was reassessed, and arm C participants received an additional 100-unit BoNT/A injection, with a final assessment at nine months. Repeat injections of 100 units of BoNT/A led to significant pain reduction, with 41% to 58% of patients experiencing at least a 2-point reduction on the VAS or reporting the absence of dyspareunia. The study suggests that repeated, high-dose BoNT/A injections may be more effective than a single dose in treating PVD [28]. A case-control study conducted at Aarhus University Hospital included 79 patients with locally provoked vulvodynia, refractory to 6-12 months of non-invasive treatment (desensitization, physiotherapy, contraceptive pill discontinuation, vaginal estrogen treatment in postmenopausal patients). Patients received a single 100-unit BoNT/A injection into the levator ani muscle under Electromyography (EMG) guidance. Pain (dyspareunia), quality of life, and cotton swab test results were assessed at 6 months post-injection. Statistically significant improvements were observed in both dyspareunia (NRS decreased from 7.82 to 5.82, $p < 0.001$) and quality of life (Negative Interference in Quality of Life decreased from 7.88 to 6.19, $p < 0.001$) [9]. Pelletier et al. examined the long-term effects of OnabotulinumtoxinA on provoked vestibulodynia in 19 women. Pain, quality of life, and sexual function were assessed before treatment and at 3 and 24 months post-injection. Participants received bilateral injections of 50 units of OnabotulinumtoxinA into each bulbospongiosus muscle, totaling 100 units, under EMG guidance. At 24 months, seven patients reported complete pain resolution (VAS = 0), while the remaining 12 experienced significant pain reduction, with 75% reporting only superficial pain. Furthermore, both sexual function and quality of life improved significantly, as evidenced by a 16.67-point increase in FSFI scores and a 10-point decrease in Dermatology Life Quality Index scores from baseline to 24 months [10]. Villa-Muñoz et al. investigated the efficacy of incobotulinumtoxinA injections (up to 200 units) for vestibulodynia treatment, also exploring patient characteristics influencing treatment response. Factors associated with poorer outcomes included smoking, painful comorbidities, and high score in the orgasmic domain of the FSFI. Conversely, pain localized to the 3 o'clock position in the vulvar vestibule and higher baseline VAS scores during swab testing predicted greater improvement. At 24 weeks, significant improvements were observed in pain (VAS, $p < 0.01$), sexual function (FSFI, $p < 0.01$), and psychological status (Hospital Anxiety and Depression Scale , $p < 0.01$) [29]. A retrospective case series explored the potential of botulinum toxin for vulvodynia in younger patients. The series described three female adolescents (aged 12, 15, and 18) with treatment-refractory vulvodynia who received transvaginal botulinum toxin injections into the pelvic floor [30].

Hyaluronic acid

Eserdag et al. conducted a retrospective study evaluating the efficacy of hyaluronic acid injections for provoked vestibulodynia in 12 women. One milliliter of hyaluronic acid (19 mg/mL) was injected into painful vestibular areas. Sexual function and pain were assessed at baseline and 45 days post-treatment. Significant improvements were observed in both FSFI scores (17.8 to 23.3, p=0.003) and VAS scores (7.2 to 4.1, p=0.002). Telephone follow-up at three months revealed pain recurrence in five patients, with pain levels returning to baseline, suggesting that the effects of this form of therapy may be short-lived [8].

Procaine

In a study by Weinschenk et al., the effectiveness of topical local anesthetic therapy with procaine was evaluated in 45 women experiencing severe, chronic vulvodynia. Participants reporting pain levels of 6 or higher on the Nominal Assessment Scale (NAS) for at least six months received 3-20 mL of a 1% procaine solution per session for a maximum of 12 sessions, or until a sustained NAS score of 4 or less was achieved. The treatment protocol involved bilateral vulvar nerve blocks for the first three sessions, with the potential addition of other nerve blocks (such as the genitofemoral nerve or the hypogastric plexus) if pain relief was insufficient. Using the NAS daily, patients' pain was assessed during treatment and again at least six months post-treatment. 80% of participants achieved therapeutic success (defined as a sustained NAS score ≤ 4), with average scores decreasing significantly from 7.9 to 2.4 ($p < 0.001$) [31].

Integrated treatment modalities for managing vulvodynia

Given the complex and often multifaceted nature of vulvodynia, where monotherapy frequently proves insufficient [32]. A pilot study at Queen's University investigated a topical combination of meloxicam and lidocaine for vulvodynia in patients who hadn't responded to standard treatments (lidocaine and amitriptyline). Six out of eight participants reported improvement after one week, with pain scores decreasing by 1-4 points on a Likert scale. While promising, the small sample size limits the reliability of these findings [33]. De Leo and colleagues performed an initial pilot study with an expanded group of patients. The study enrolled 35 postmenopausal women with vulvar vestibulodynia, 30 completed a 90-day treatment regimen of tibolone and Respecta®. Tibolone, a synthetic steroid with estrogenic, progestogenic, and androgenic properties, addresses the hormonal component often associated with postmenopausal vulvovaginal atrophy. Respecta®, a blend of Lactobacillus acidophilus GLA-14, Lactobacillus rhamnosus HN001, and bovine lactoferrin, aims to restore a healthy vaginal microbiota and reduce inflammation, potentially contributing to pain relief. Significant improvements in pain were observed using both a visual analog scale and a cotton swab test. The VAS score decreased notably from 8.0 to 3.7, and the cotton swab test scores dropped from 15.1 to 10.3. Both reductions were statistically significant ($p < 0.01$) [34]. A retrospective single-clinic audit evaluated the effectiveness of topical amitriptyline 0.5% plus oestriol 0.03% (AOO) in organogel for vulvodynia, dyspareunia, and pudendal neuralgia. Of 1174 patients prescribed AOO, 376 (35.7%) completed the survey. Dyspareunia (70.2%) was the most common indication for AOO use. Overall, 51.2% of respondents found AOO effective, with effectiveness rates of 48.4% for dyspareunia, 52.4% for vulvodynia, 50.8% for introital dyspareunia, and 53.2% for provoked vestibulodynia. Most patients (84.6%) applied AOO once daily, and 11.7% applied it twice daily. Mild, transient burning was the most reported side effect (10.1%), with no serious adverse events observed [35].

The combination pharmacological therapy was often reached when more often used methods with confirmed effectiveness disappointed. This is confirmed by the cases of patients described in the following articles. A case study describes the effective treatment of a 33-year-old woman suffering from both chronic vulvar and anal pain. After three months of using a topical baclofen cream and oral palmitoylethanolamide (PEA), her pain decreased significantly (by more than half). This treatment strategy leverages baclofen's ability to affect pain signaling pathways and the analgesic and anti-inflammatory properties of PEA. The study's positive result indicates that this combined treatment approach may be a useful option for managing these chronic pain conditions [36]. A small study investigated ganglion impar block (GIB) for chronic vulvodynia in four women unresponsive to standard treatments, all experiencing long-standing vulvar pain (6 months to 10 years) with allodynia and hyperalgesia. The GIB procedure, guided by fluoroscopy, was performed, with the number of injections (5 ml of 0.5% lidocaine and 10 mg triamcinolone). The injections varying between patients (one patient received one injection, another received three, and one received four, the last of which was an alcoholic neurolysis). Post-GIB, all participants reported significant pain reduction, with VAS scores dropping from 8–9 to below 2 and Leeds Assessment of Neuropathic Symptoms and Signs, scores declining from over 12 to under 5. Sustained relief was observed in two patients for up to two years, while the other two maintained pain control with medication post-GIB [32].

Discussion

This review included 29 publications, with the studies examining oral interventions being predominantly randomized controlled trials, thereby offering a higher level of evidentiary support. In contrast, the research on topical and injectable treatments tended to feature observational case series and uncontrolled studies, which inherently possess a higher risk of bias and have more limited generalizability. Studies exploring gabapentin's impact on women's sexual function and pain levels divided their research into two publications with the same

sample. Results suggest gabapentin improves sexual function, measured by the FSFI, though scores remained below those of women without vulvodynia. The lack of significant pain reduction during tampon tests led authors to discourage gabapentin monotherapy, hypothesizing that sexual function may correlate more with muscle dysfunction severity than overall pain/tenderness due to peripheral muscle intervention effects [18, 19]. Amitriptyline has shown efficacy in alleviating vulvodynia symptoms [21]. Research consistently indicates that combining amitriptyline with Alpha-linolenic acid N-3 Polyunsaturated fatty acids [20], electrotherapy, or pelvic floor exercises significantly enhances outcomes, allowing for lower doses and minimized side effects. The authors state that increased pelvic floor muscle tension contributes to vulvodynia [11]. Therefore, physiotherapy, by addressing this underlying cause, offers a better long-term treatment improving the quality of life of patients compared to lidocaine, which only provides temporary, local relief [22]. Self-administered massage with topical 2% lidocaine has shown a 95% efficacy rate. When used topically, lidocaine can be a helpful adjunct to other treatments [14]. The Kopits et al. study found that regular use of capsaicin significantly relieved vulvar pain and sexual discomfort among patients with neuroproliferative provoked vestibulodynia who could tolerate the therapy. However, tolerance to capsaicin exhibited substantial variability. 80% of participants were able to endure 20 minutes of application with 0.025% cream. Participants reported that rinsing the capsaicin with cold water, applying 2 % lidocaine, or using an ice pack to the vulva helped mitigate the associated pain [17]. An earlier study with a comparable protocol also employed 2% lidocaine prior to capsaicin application and ice packs for participants who experienced difficulty tolerating the capsaicin therapy [37]. Overall, capsaicin appears to be an effective treatment option for vulvodynia, but it necessitates careful patient selection and management to address the variable tolerance. Another approach that has been investigated for managing vulvodynia is the use of injectable medications. Among these, botulinum toxin has been the most extensively studied substance for this condition. Of the 7 studies investigating the application of botulinum toxin for the management of vestibulodynia, 3 were randomized controlled trials [27, 28, 38]. Several studies have suggested that botulinum toxin injections may provide relief for individuals with vulvodynia, as evidenced by decreased self-reported pain levels and enhanced sexual function and quality of life [10, 29]. However, these were small-scale pilot investigations involving limited patient populations and brief follow-up durations, lacking the rigorous randomization typically required for more definitive conclusions. Nevertheless, studies with more rigorous methodologies have reported contradictory results. They showed no statistically significant differences in post-treatment pain reduction between patients who received botulinum toxin and those in the placebo groups [27, 28, 38]. The heterogeneity in study designs, outcome measures, injection techniques and patient populations likely contributes to the varied results. A standardized protocol for botulinum toxin administration, including the optimal dosage, frequency of repetition, and interval between doses, is currently lacking in the literature on the treatment of vulvodynia. Diomande and colleagues proposed that repeated subcutaneous administration of high-dose botulinum toxin could be an effective treatment approach for provoked vulvodynia, based on the encouraging results observed in their exploratory analysis. They speculated that this intervention may lead to substantial reductions in pain experienced by patients [28]. Further research is needed to establish the most effective and safe protocol for the use of BoNT/A in patients with vulvodynia. The oral medications amitriptyline, gabapentin, and pregabalin often cause drowsiness and dizziness as common side effects. While these side effects are typically mild and transient, they occasionally led some patients to discontinue treatment or lower their dosage, potentially compromising the overall effectiveness of the therapy [19, 20, 21]. Topical application of lidocaine, while generally considered well-tolerated, has the potential to induce localized cutaneous reactions, such as minor skin irritation, burning sensations, and in rare instances, dermatitis [14, 22]. Studies on botulinum toxin injections for vulvodynia reported no serious adverse events and no significant difference in side effects between treatment and placebo groups. Side effects, primarily temporary injection site pain and occasional [38], transient urinary control difficulties during physical activity, were likely procedure-related, not drug-related [9, 27, 29]. A key challenge in evaluating vulvodynia treatments is the lack of consistency in outcome measures across studies. While various approaches have been employed, a standardized methodology is lacking. Existing research has assessed parameters such as pain levels, sexual function, and quality of life [10]. The importance of incorporating multiple outcome measures beyond pain alone is highlighted by Steinberg et al.'s 2005 study on capsaicin treatment for vulvar vestibulitis syndrome, which recognized the significant impact of vulvar vestibulitis syndrome on quality of life, particularly sexual function in sexually active women, and included sexual function as a primary endpoint [37]. Current evaluation methods frequently rely on subjective patient-reported assessments, such as the Visual Analog Scale, which gauges parameters like dyspareunia or pain intensity, and self-administered clinical questionnaires assessing changes in physical,

mental, and social well-being. While valuable, these subjective measures underscore the need for standardized and validated tools to assess vulvodynia-specific clinical outcomes. Such standardization would facilitate meaningful comparisons and more reliable conclusions across studies. To complement subjective assessments, clinicians can utilize objective assessment tools. Examples include algometers, which measure pressure applied during a vulvar swab test, and surface electromyography, which provides physiological and electrical data on the pelvic floor muscles [29]. Incorporating these objective measures can enhance the rigor and comprehensiveness of treatment evaluations. Limiting the review to studies less than 10 years old, while prioritizing current research, introduced a trade-off between recency and the breadth of available evidence. The need for larger sample sizes to achieve statistical significance has been highlighted in several studies [21, 38]. In our analysis, we gave priority to the findings from randomized controlled trials, as studies with limited sample sizes or lacking randomization raise concerns about the broader applicability and reliability of the results.

Conclusions

Vulvodynia is a complex condition with an unclear underlying cause and potential associated factors, precluding a single, standardized treatment approach. Personalized therapeutic management, involving a multidisciplinary team, should be guided by a comprehensive evaluation of each patient's medical history. Randomized controlled trials have demonstrated the efficacy of oral medications and topical lidocaine for vulvodynia, with oral amitriptyline showing the strongest evidence as a first-line treatment. Combining pharmacological treatments with self-massage, kinesitherapy, and physiotherapy has been shown to enhance patients' quality of life. Studies including physiotherapy have reported improved outcomes, supporting the integration of physiotherapy-based protocols. Although preliminary studies indicated possible benefits, botulinum toxin injections did not yield statistically significant improvement and appear to require repeated treatments for sustained relief. Given the diagnostic and therapeutic challenges of vulvodynia and its substantial impact on patients, further research is essential to refine treatment options.

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