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Vulvodynia Interventions—Systematic Review and Evidence Grading

Jeffrey C. Andrews, MD, FRCSC

Associate Professor, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN; and Vanderbilt Center for Evidence-Based Medicine, Vanderbilt Institute for Global Health, Nashville, TN

Introduction: State of the art guidance exists for management of vulvodynia, but the scientific basis for interventions has not been well described. Although there are many interventional therapies, and their use is increasing, there is also uncertainty or controversy about their efficacy.

Objective: To systematically assess benefits and harms of interventional therapies for vulvodynia and vestibulodynia.

Methods: The following databases were searched, using MeSH terms for studies related to the treatment of vulvodynia or vulva pain/pruritus/dysesthesia/hyperesthesia/hypersensitivity: MEDLINE, PsycINFO, Scopus, Cochrane Library, EBSCO Academic, and Google Scholar. Using Medical Subject Reference sections of relevant original articles, reviews, and evidence-based guidelines were screened manually. Manual searching for indirect evidence supporting interventions was done whenever no direct evidence was found for a treatment described within a review or guideline. Each modality is assessed with a grading system similar to the Grades of Recommendation, Assessment, Development, and Evaluation system. The grading system assesses study quality, effect size, benefits, risks, burdens, and costs.

Results: For improvement of pain and/or function in women with vestibulodynia (provoked localized vulvodynia), there was fair evidence that vestibulectomy was of benefit, but the size of the effect cannot be determined with confidence. There was good evidence of a placebo effect from multiple studies of nonsurgical interventions. There was fair evidence of lack of efficacy for several nonsurgical interventions. There were several interventions for which there were insufficient evidence to reliably evaluate. There was insufficient evidence to judge harms or to judge long-term benefits.

For clinically meaningful improvement of pain in women with generalized unprovoked vulvodynia, there was insufficient evidence for benefit of any intervention. There was fair evidence of a placebo effect in people with neuropathic pain and functional pain syndromes, from multiple studies of interventions. Based on indirect evidences from studies of patients with other pain disorders, interventions may be selected for future research.

Conclusion: There is fair evidence for effectiveness of vestibulectomy for vestibulodynia; however, there is uncertainty about the size of the absolute effect, because of the risk of bias inherent in studies of pain interventions without a placebo control group. Providers and patients looking for evidence-based interventions for generalized unprovoked vulvodynia may need to rely on indirect evidences from studies of neuropathic pain and functional pain syndromes.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this educational activity, the obstetrician/gynecologist should be better able to identify potential causes of vulvar pain to facilitate diagnosis of vulvodynia and vestibulodynia, distinguish between the symptoms of localized, provoked vulvodynia and generalized unprovoked vulvodynia to select the most appropriate therapies, evaluate the efficacy of surgical and nonsurgical interventions for the treatment of generalized unprovoked and localized, provoked vulvodynia. In addition, assess the benefits and risks of interventional therapies for vulvodynia and vestibulodynia to improve patient care.

The author, faculty, and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interest in, any commercial organizations pertaining to this educational activity.

Dr. Andrews has disclosed that the U.S. Food and Drug Administration has not approved the use of botulinum toxin, Interferon, Cromolyn, Nifedipine, Montelukast, TENS, Nitroglycerin, Photodynamic therapy, and Magnetic field therapy for the treatment of vestibulodynia as discussed in this article. Please consult the product's labeling for approved information.

The author is solely responsible for the content of this article and the decision to submit for publication. No statement in this article should be construed as an official position of the Vanderbilt Evidence Practice Center, the International Society for the Study of Vulvovaginal Disease, nor the GRADE Working Group.

Correspondence requests to: Jeff Andrews, MD, 719 Thompson Lane, Suite 27166, Nashville, TN 37204–3195. E-mail: jeff.andrews@vanderbilt.edu.

Vulvodynia is a condition of vulvar discomfort that affects millions of women each year.[1,2] These women and their providers are challenged to find effective therapeutic interventions. The International Society for the Study of Vulvar Disease (ISSVD) terminology for classification of vulvodynia distinguishes between generalized and localized findings.[3,4] Each of these 2 subgroups is further subdivided into provoked, unprovoked, or mixed (continuous pain, exacerbated by touch).[5] The majority of clinical presentations are either vestibulodynia (localized provoked vulvodynia) or generalized unprovoked vulvodynia.

Vestibulodynia is a term describing a syndrome of provoked, localized allodynia of the vestibule of the vulva, not explained by another condition, and lasting more than 3 months. Prevalence of vestibulodynia is estimated to be in 11% to 16% of women.[1–5] Even if this estimate is inflated, there are still millions of women who experience this syndrome. The pain is not present all of the time; rather it is evoked by touch: attempted intercourse, physical examination, or other direct contact. Most patients with vestibulodynia complain of dyspareunia; pain with intercourse or the inability to have intercourse due to pain. Often vestibulodynia is associated with vaginismus; a recurrent or persistent involuntary spasm of the muscles of the pelvic floor, which narrows the introitus and is associated with painful intercourse.

Vestibulodynia is not one disorder; it is a symptomatic description of several disease states.[6] Current theories about the various disease states include: hormonally mediated vestibulodynia, hypertonic pelvic floor dysfunction, neuroproliferative vestibulodynia.[7] Vestibulodynia was first described as a syndrome in 1987 by Dr Edward Friedrich.[8] Friedrich's criteria were: (1) severe pain in the vulvar vestibule upon touch or attempted vaginal entry; (2) tenderness to pressure localized within the vulvar vestibule; and (3) vulvar erythema (inflammation) of various degrees. In the past, patients with a similar condition were described as having vulvar vestibulitis.[9] Inflammation is often not found; therefore the term vestibulitis was misleading and has been replaced.[10] Diagnosis is typically made by examination with a cotton swab, used to place gentle pressure in the vestibule, which elicits severe pain or discomfort for the patient. Vestibulodynia may be primary (began with sexual debut, or first attempts to use a tampon), or secondary (began after a period of time, during which the same provocation did not evoke pain).

Generalized unprovoked vulvodynia replaces older terminology such as dysesthetic vulvodynia, essential vulvodynia, and burning vulva syndrome.[4] The patient reports an unpleasant and abnormal pain sensation of a continuous nature. The onset can be acute or gradual.[11] The quality of the pain is usually described as burning, or sometimes as stinging, irritation, itching, or a feeling of rawness. Most often the location of the pain is diffuse, without clear borders. The pain intensity is generally reported as moderate to severe.[12] Any stimulus which results in pressure on the vulva can exacerbate the pain, including intercourse, tampon insertion, speculum insertion, tight-fitting clothing, bicycling, horseback riding, and even sitting, walking, or exercising. Varying degrees of erythema have been reported; however, little or no physical findings are common.[11]

Vestibulodynia and vulvodynia are diagnoses of exclusion. Exclusions include vulvar pain which is related to a specific recognized disorder: (1) infectious (e.g., candidiasis, herpes, etc.); (2) inflammatory or dermatoses (e.g., lichen planus, immunobullous disorders, etc.); (3) neoplastic (e.g., Paget disease, squamous cell carcinoma, etc.); or (4) neurologic (e.g., herpes neuralgia, spinal nerve compression, etc.). Patients with vulvar pain, in whom there is not a recognized disorder, are diagnosed with vulvodynia. This description is "essential," meaning there is not an identified etiology, and there are no specific findings. The term "vulvodynia" may be used to describe a symptom, or an idiopathic pain disorder.

Vulvodynia is often associated with comorbid conditions, including interstitial cystitis, painful bladder syndrome, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, depression, headache, and posttraumatic stress disorder.[13–16]

Because the diagnosis of vulvodynia is so nonspecific, treatment of vulvodynia is not evidence based, and proceeds on a trial and error basis. At least 30 different types of therapy interventions have been used in the treatment and management of vulvodynia, yet evidence from clinical trials and studies remains largely inconclusive.

Current modalities of treatment include vulvar care measures; topical, oral, and injectable medications; surgery (vestibulectomy); dietary modifications; and physical therapy. It is common for these patients to seek management from a long series of gynecologists, other clinicians, and pain management specialists, because of the lack of successful treatment of their symptoms.[1] The state-of-the-art of vulvodynia management is described in "The Vulvodynia Guideline," developed by an expert panel organized by the International Society for the Study of Vulvar Diseases.[17] However, this guideline does not clearly state the risk of bias or quality of the supportive evidence.

A critical review was reported previously by Landry and colleagues.[18] Many patients continue one or more interventions over a prolonged period while reporting persistent symptoms. In this systematic review, we evaluate all published studies and provide evidence-based grading of the treatments for vulvodynia, and will inform the evolving clinical consensus for treatment recommendations for this disorder.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and checklist methodology was used for the preparation and presentation of this systematic review.[19] The population of interest is women with vulvodynia. The subset population of women with vestibulodynia (localized, provoked vulvodynia) was analyzed separately. Interventions under consideration were oral, topical, local, or regional medications, physical therapy, surgery, psychosocial interventions, and lifestyle changes. Placebo-controlled randomized trials were sought. Because of sparse data, studies with no comparator were included; in most of these studies, the data analyzed was a pretreatment assessment versus a post-treatment assessment. Eligible studies reported original descriptive or analytic treatment research. The primary outcome being assessed was reduction in pain. Other outcomes included change in sexual function, quality of life improvement, adverse effects, and side effects.

The following databases were searched, using MeSH terms for studies related to the treatment of vestibulodynia, vulvar vestibulitis, vulvodynia, or vulva pain/pruritus/dysesthesia/hyperesthesia/hypersensitivity: MEDLINE, PsycINFO, Scopus, Cochrane Library, EBSCO Academic, and Google Scholar. Sections of relevant original articles, reviews, and evidence-based guidelines were screened manually. Manual searching for indirect evidence supporting interventions was done whenever no direct evidence was found for a treatment described within a review or guideline. Four hundred and forty-seven treatment articles were identified and screened for the present paper. Using the population/intervention/comparator/outcome and study design criteria, 71 studies were eligible and included in the qualitative synthesis.

The comparative analysis of the studies focused on the methodology employed and the key outcome results. The quality of evidence was assessed with a grading system similar to the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.[20,21] The grading system assesses study quality and limitations, effect size, benefits, risks, imprecision, reporting bias, indirectness of evidence, and consistency of results. The GRADE system classifies the quality of evidence in 1 of 4 levels: high, moderate, low, and very low. With high quality, further research is very unlikely to change our confidence in the estimate of effect. With moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. In the case of low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. In the very low quality category, any estimate of effect is very uncertain.

To assign a description of the overall strength of evidence as good, fair, or poor, consideration was given to the number of patients, quality of research, consistency of results between studies, and directness of evidence. Consistent results from a number of higher quality studies across a broad range of populations would support a high degree of certainty that the results of the studies are true; and the entire body of evidence would be considered "good quality." For a "fair-quality" body of evidence, results could be due to true effects or due to biases operating across some or all of the studies. For a "poor-quality" body of evidence, any conclusion would be uncertain.

When reported, a clinically meaningful reduction in pain was defined as greater than or equal to 50% reduction in a validated pain score.[22] A determination of an absolute effect of an intervention would be based on evidence showing that the intervention was more effective than placebo or sham therapy for one or more of the following outcomes: pain, functional status, or overall improvement. For visual analogue scales for pain, mean improvements of greater than 50% reduction would be large effect; 30% to 50% would be moderate effect; less than 30% would be small effect.

Results

Vestibulodynia Results

Evidence Summary Tables 1 and 2 present nonsurgical and surgical interventions for vestibulodynia. Of the 71 eligible articles, 55 reported an evaluation of an intervention for therapy of vestibulodynia. Twenty-eight interventions for vestibulodynia were evaluated. Success rates varied from no effect to 100% improvement. Most of the studies had several methodological weaknesses, including lack of: con-

trol or placebo group, double-blind evaluation, pretreatment pain and functional status evaluation, validated outcome measures of pain and sexual functioning, and long-term outcomes.

The majority of the published studies were case series, and almost all reported an effect, when comparing the pretreatment data to the post-treatment data (before and after data). There were 11 randomized trials; of these, 6 were not placebo-controlled.[23–28] There were 3 nonblinded randomized trials of surgical interventions, compared with other surgical interventions or compared with cognitive behavioral therapy or electromyographic biofeedback.[26–28] Two nonblinded randomized trials of medical interventions demonstrated no absolute effect.[23,25] The 5 placebo-controlled randomized trials of medical interventions all showed no effect of the target intervention, when compared to placebo.[29–33] Logically, the placebo effect that is seen in the placebo-controlled trials is also present in case series. When considering before and after data from the case series studies, inductive reasoning can use the placebo-controlled randomized trials that reported before-and-after data for the placebo group, to gauge the size of the placebo effect. The placebo intervention effect, described as a greater than 50% decline in the pain score(s) ranged from 40% to 50% of subjects.[29,31–33]

Vestibulodynia Results: Nonsurgical Interventions (Table 1)

Injections. There was fair evidence of a lack of efficacy for botulinum toxin injections.[33–37] The body of evidence for other injections was poor; there was insufficient evidence regarding: steroid and "caine"-drug mixed injections,[38,39] multilevel nerve blocks,[40] intramuscular interferon,[41,42] and intralesional interferon.[43,44]

Topical Applications. There was fair evidence of a lack of efficacy for 5% xylocaine topical application,[23,29,45] for topical cromolyn,[31] and for topical nifedipine.[32] The body of evidence for other topical applications was poor; there was insufficient evidence regarding: capsaicin,[46,47] montelukast,[48] steroid,[24] gabapentin,[49] and ketoconazole.[50]

Oral Medications. There was fair evidence of a lack of efficacy for oral desipramine,[29] and for oral fluconazole.[25] There was insufficient evidence regarding oral calcium citrate.[51]

Cognitive Behavioral Therapy. There was insufficient evidence regarding cognitive behavioral therapy.[18,27,52,53]

Physical Therapy. There was insufficient evidence for use of dilators[55] and for pelvic floor physiotherapy.[56–59]

Acupuncture/TENS. There was insufficient evidence for electronic stimulation,[30,60] and for acupuncture.[61]

Vestibulodynia Results: Surgical Interventions

There was fair evidence of effect of vestibulectomy surgery (Table 2).[18,26–28,52,53,62–78] There was insufficient evidence to describe the size of the effect with certainty, due to risk of bias inherent in pain intervention studies without placebo controls. Case series of 1138 patients and randomized trials of 118 patients reported an effect of 31% to 100%, with a median of 79% for patients who reported at least some improvement to complete relief. For 12 studies reporting complete relief as an outcome, the median effect size was 67%.[26,28,64,66–69,71,72,74–76] The absolute effect was estimated to be 30% from 1 randomized controlled trial (RCT).[27] The effect size from this single RCT could be consistent with the effect size seen with case series, on the basis that surgery has been reported to have a placebo effect of 35%,[79–81] and the placebo effect seen with vestibulodynia in RCTs of nonsurgical interventions was 40% to 50%.[29,31–33] If the presumptive bias inherent in uncontrolled studies due to selection and placebo effect is deducted from the observed effect reported from the vestibulectomy case series, the absolute difference would approximate 30%. There is insufficient evidence to support that any specific vestibulectomy surgical technique is superior to another vestibulectomy surgical technique. There may be subsets of patients who are more likely to experience a benefit from vestibulectomy surgery; patients with secondary dyspareunia had greater odds of improvement than patients with primary dyspareunia.[77]

Generalized Unprovoked Vulvodynia Results

Evidence Summary Table 3 presents interventions for generalized unprovoked vulvodynia. Of the 71 eligible articles, 16 reported an evaluation of a therapy for vulvodynia; predominantly generalized unprovoked vulvodynia.[49,82–96] Twelve interventions for generalized unprovoked vulvodynia were evaluated. All the vulvodynia studies had several methodological weaknesses, including lack of: control or placebo group, double-blind evaluation, pretreatment pain and functional status evaluation, validated outcome measures of pain and sexual functioning, and long-

Table 1
Evidence Summary Table of Nonsurgical Interventions for Vestibulodynia

Citation	Study Type	No. Patients	Patient Characteristics*	Intervention/Exposure	Comparison	Outcome Measures†	Time: Length of Follow-Up	Effect Size: Relative/Absolute	Source of Funding	Evidence Quality‡ (Range)
Analytic studies										
Foster et al[29]	DBRPCT	133	Vestibulodynia	Topical 5% lidocaine and/or Oral desipramine	Placebo tablet and/or placebo cream	Tampon test, standard numeric pain rating scale, pain score	12 mo	No difference between intervention groups; Placebo: absolute effect of >50% decline in score: 40%	Gov't grant	High
Petersen et al[33]	DBRPCT	64	Vestibulodynia	Botulinum toxin A injection	Placebo (saline) injection	Pain VAS 10-point Likert scale, FSFI, FSDS, SF-36	6 mo	No difference between intervention groups: Fifty percent (50%) of the participants in each group experienced a clinical meaningful improvement	Prof society + gov't grant + unrestricted Pharma grant	High
Nyirjesy et al[31]	DBRPCT	26	Vestibulodynia	Cromolyn cream	Placebo cream	Symptom scale; dyspareunia score	>6 mo	No difference between intervention groups; Placebo: absolute effect of >50% decline in score: 46% Cromolyn: absolute effect of >50% decline in score: 38% (no withdrawals)	Nil	Mod 5
Bornstein[32]	RPCT	30	Vestibulodynia	Nifedipine (topical)	Placebo	Pain score; sexual function score	3 mo	No difference between intervention groups; Placebo: absolute effect of >50% decline in score: >50%	None stated	Low 1, 5
Murina et al[30]	RPCT (single-blind)	40	Vestibulodynia	ES via vaginal probe (TENS)	"Sham" vaginal probe	VAS and FSFI; Marinoff dyspareunia scale	3 mo	No difference between intervention groups	N/A	Low 1, 5
Danielsson[23]	RCT (non-blinded)	46	Vestibulodynia	Topical 5% lidocaine ointment	EMG	Vulvar-algesiometer; SF36; QOL VAS	12 mo	No difference between intervention groups	Gov't grant	Low 2
Bornstein et al[25]	RCT (non-blinded)	40	Vestibulodynia	Fluconazole (oral)	No tablet	Subjective change in dyspareunia	>3 mo	No difference between intervention groups (no withdrawals)	Nil	Low 1, 5
Munday[24]	RCT (randomized double blind crossover study terminated due to inadequate enrolment)	14	Vestibulodynia	Topical steroid (potent)	Topical steroid (mild)	Pain, tenderness, erythema scales	>8 wk	No difference between intervention groups (inadequate power)	Nil	Very low 2, 5
Descriptive studies										
Zolnoun et al[45]	Case series (prospective)	61	Vestibulodynia	Topical 5% lidocaine ointment	None	Pain VAS		Absolute effect of >50% decline in dyspareunia score: 59%	Nil	Very low 1
Murina et al[38]	Case series (retrospective)	22	Vestibulodynia	Methylprednisolone and lidocaine: submucosal infiltrations	None	Subjective remission of symptoms	9–24 mo	68% some improvement (32% no symptoms)	N/A	Very low 2, 5, 6

(*Continued*)

Table 1
Continued

Citation	Study Type	No. Patients	Patient Characteristics*	Intervention/Exposure	Comparison	Outcome Measures†	Time: Length of Follow-Up	Effect Size: Relative/Absolute	Source of Funding	Evidence Quality‡ (Range)
Segal[39]	Case study	1	Vestibulodynia	Betamethasone and lidocaine: submucosal infiltration	None	"Complete resolution"	6 wk	1/1 complete resolution	Nil	Very low 2, 5, 6
Rapkin et al[40]	Case series (prospective)	27	Vestibulodynia	Multilevel local anesthetic nerve blockade	None	Vulva algesiometer and several scales	6 mo	Absolute effect of >50% decline in dyspareunia score: 49%	N/A	Very low 1
Nappi et al[60]	Case series (prospective)	29	Vestibulodynia	TENS	None	VAS and FSFI; coital activity	>10 wk	Most patients had some improvement	N/A	Very low 1
Danielsson 2001[61]	Case series	13	Vestibulodynia	Acupuncture	None	QOL on VAS	3 mo	Most patients had some improvement	Gov't grant	Very low 2, 5, 6
Murina et al[46]	Case series (prospective)	33	Vestibulodynia	Capsaicin (topical, following 5% lidocaine)	None	Analog scale	18 mo	59% some improvement (1/33 withdrew due to adverse effects)	Nil	Very low 1
Steinberg et al[47]	Case series (retrospective)	52	Vestibulodynia	Capsaicin (topical, following 5% lidocaine)	None	Kaufman touch test and Marinoff dyspareunia scale	18 wk	Most patients had some improvement (1/11 withdrew due to adverse effects)	N/A	Very low 2, 6
Kamdar et al[48]	Quasi-experiment nonrandomized	47	Vestibulodynia	Montelukast (oral) (29)	"Treated with standard therapies" (18)	Symptom score		Absolute: 52% Relative: 37%	N/A	Very low 2
Boardman et al[49]	Case series (retrospective)	51	Vestibulodynia and/or vulvodynia	Gabapentin (topical)	None	Pain score	>3 mo	Absolute effect of >50% decline in dyspareunia score: 80% (1/7 withdrew due to adverse effect)	Nil	Very low 1
Morrison et al[50]	Case series (prospective)	31	Vestibulodynia	Ketoconazole (topical)	None	"Complete recovery or improvement"		44% complete recovery	N/A	Very low 1, 5
Bornstein et al[41]	Case study	1	Vestibulodynia	Interferon IM	None	"Cure"	2 mo	1/1 cured	Nil	Very low 2, 5, 6
Bornstein et al[42]	Case series (retrospective)	7	Vestibulodynia	Interferon IM	None	"Complete remission"	6–18 mo	5/7 patients in remission	Nil	Very low 2, 5, 6
Kent and Wisniewski[43]	Case series (retrospective)	8	Vestibulodynia	Interferon intralesional	None	"Complete remission"	>4 wk	5/8 patients in remission	Nil	Very low 2, 5, 6
Marinoff et al[44]	Case series (prospective)	55	Vestibulodynia	Interferon intralesional ± surgery	With HPV vs. without HPV	Introital dyspareunia subjective		49% some improvement	N/A	Very low 2
Bennani et al[34]	Case report	1	Vestibulodynia	Botulinum toxin A injection	None	Complete recovery		1/1 complete recovery	Nil	Very low 2, 5, 6
Romito et al[35]	Case reports	2	Vestibulodynia	Botulinum toxin A injection	None	Pain score	6 mo	N/A	Nil	Very low 2, 5, 6
Brown et al[36]	Case reports	2	Vestibulodynia	Botulinum toxin A injection	None	Pelvic floor hypertonicity and variability; vestibular hyperalgesia		½ modest improvement	Nil	Very low 2, 5, 6
Dykstra et al[37]	Case series (retrospective)	19	Vestibulodynia	Botulinum toxin A injection	None	Standard numeric pain rating scale	14 wk	Most patients had some improvement	Nil	Very low 2, 6

(*Continued*)

Table 1
Continued

Citation	Study Type	No. Patients	Patient Characteristics*	Intervention/Exposure	Comparison	Outcome Measures†	Time: Length of Follow-Up	Effect Size: Relative/Absolute	Source of Funding	Evidence Quality‡ (Range)
Solomons et al[51]	Case report	1	Vestibulodynia with high urinary oxalate	Calcium citrate (oral)	None	"Pain free"	>1 y	1/1 pain-free	Nil	Very Low 2, 5, 6
Murina et al[55]	Case series (retrospective)	15	Vestibulodynia	Graduated vaginal dilators	None	Marinoff dyspareunia scale; FSFI	>6 mo	Most patients had some improvement	Not stated	Very low 2, 5, 6
Goldfinger et al[56]	Case series (prospective)	13	Vestibulodynia	Pelvic floor physiotherapy	None	vestibular pain threshold testing, structured interviews, standardized questionnaire	3 mo	Most patients had some improvement	Nil	Very low 2, 5, 6
Forth et al[57]	Case series (retrospective)	14	Vulvodynia	Pelvic floor physiotherapy	None	McGill Pain Questionnaire and Short Form 36	3 mo	No difference (before and after)	Nil	Very low 2, 5, 6
Bergeron et al[58]	Case series (retrospective)	35	Vulvar vestibulitis	Physiotherapy	None	Phone interview		51% great improvement, 20% moderate improvement	Nil	Very low 2, 6
Fisher[59]	Case report	1	Dyspareunia and vaginismus	Physiotherapy	None		3 mo	1/1 pain-free	Nil	Very low 2, 5, 6

Consistency/inconsistency does not apply to a single study; publication bias does not apply to a single study; Strong dose-response requires at least 2 studies.

NNT (>50% reduction in primary symptom/outcome/score)—could only be determined from RCTs and all RCTs showed no effect of target intervention compared to control, therefore NNT not included on table.

NNH—withdrawals from intervention due to adverse effects, intolerability—described within Effects column.

*Vestibulodynia is a current terminology, older publications may use terms such as vulvar vestibulitis, vulvar vestibulitis, also Friedrich's criteria.

†EMG, electromyogram biofeedback therapy.

‡Evidence quality rated as high, moderate, low, or very low. Numeric code: (1) Serious Study limitations (design, execution, risk of bias), (2) Very serious study limitations, (3) Indirectness—some uncertainty, (4) Indirectness—major uncertainty, (5) Imprecision or sparse data, (6) Selective outcome reporting bias, (7) Strong dose-response relationship

RCT indicates randomized controlled trial; RPCT, randomized placebo-controlled trial; DB, double-blind; FSFI, Female Sexual Function Index; FSDS, Female Sexual Distress Scale; SF-36, 36-item short-form survey; VAS, visual analog scale; Likert, numeric scale anchored at the endpoints with the words "No pain" and at the right end with "Worst pain ever experienced."

Table 2
Evidence Summary Table of Surgical Interventions for Vestibulodynia

Citation PMID	Study Type	No. Patients	Patient Characteristics*	Intervention/Exposure	Comparison	Outcome Measures†	Time: Length of Follow-Up	Effect Size: Relative/Absolute	Evidence Quality‡ (Range)
Analytic studies									
Bergeron et al[27]	RCT (nonblinded)	78	Dyspareunia >6 mo, pain limited to intercourse and other activities involving vestibular pressure, moderate to severe pain in one or more locations of the vestibule during cotton-swab test; 18–50 yo	Vestibulectomy	Cognitive-behavioral group therapy; electromyographic biofeedback	Pain: cotton-swab test, self-reported Dyspareunia, MPQ. Sexual function: SHF, SIS, SFI, self-reported Frequency of intercourse per month. Psychological adjustment: BSI	6 mo	Vestibulectomy: 68% at least great improvement of pain; (9% had worsening of pain) Cognitive-behavioral therapy: 40% at least great improvement of pain; Biofeedback: 36% at least great improvement of pain	Low 2
Bornstein et al[28]	RCT (nonblinded)	21	Vestibulodynia	Vestibuloplasty	Perineoplasty	Self-reported		Perineoplasty 9/11 complete resolution Vestibuloplasty 10/10 failed to relieve symptoms	Low 1, 5, 6
Bornstein et al[72]	RCT (nonblinded)	19	Friedrich's criteria, pain severe enough to prevent from having intercourse >6 mo	Total perineoplasty	Subtotal perineoplasty + Interferon-α 2b injections	Not reported	3 mo–1 y	No difference between intervention groups: Total perineoplasty: 69% complete relief subtotal perineoplasty + Interferon-α 2b injections: 67%	Low 2
Descriptive studies									
Bergeron et al[53]	Observational: prospective cohort	51	Dyspareunia >6 mo, pain limited to intercourse and other activities involving vestibular pressure, moderate to severe pain in one or more locations of the vestibule during cotton-swab test; 18–50 y	Vestibulectomy	Cognitive-behavioral group therapy; electromyographic biofeedback	Pain: cotton-swab test, self-reported Dyspareunia, MPQ. Sexual function: SHF, SIS, SFI, self-reported frequency of intercourse per mo	2.5 y	"Sustained improvement"	Very low 2, 6
Granot et al[70]	Case series (prospective) (patient selection of treatment group)	90	Pain during intercourse >6 mo, severe pain During cotton-swab test in more than one location of 6 vestibular sites, 18–40 y	Vestibulectomy	Nonsurgical treatments (biofeedback, or cognitive-behavioral therapy, or use of hypoallergic agents), No treatment	Self-reported dyspareunia	7–8 mo	79% some improvement (vestibulectomy), 48% some improvement (nonsurgical treatments), 12% some improvement (no treatment)	Very low 1

(*Continued*)

Table 2
Continued

Citation PMID	Study Type	No. Patients	Patient Characteristics*	Intervention/Exposure	Comparison	Outcome Measures†	Time: Length of Follow-Up	Effect Size: Relative/Absolute	Evidence Quality‡ (Range)
Bornstein et al[72]	Case series (prospective)	79	Friedrich's criteria	Modified perineoplasty	None	Self-reported dyspareunia	1 y	76% complete relief	Very low 1
Schneider et al[69]	Case series (prospective)	54	Superficial dyspareunia, sensitive to cotton-swab touch	Vestibulectomy	None	Self-reported dyspareunia	6 mo	83% some improvement (minor postsurgery complications 15%; second surgery required for 17% of participants)	Very low 2
Kehoe and Luesley[52]	Case series (prospective)	54	Friedrich's criteria, subjective pain relief from application of topical lidocaine	Modified vestibulectomy	None	Self-reported dyspareunia	Mean 1 y	61% complete relief, 30% some improvement	Very low 1, 6
Goetsch[68]	Case series (prospective)	12	Friedrich's criteria, Westrom criteria, pain relief from application of topical lidocaine 4%, 22–35 y	Vestibulectomy and modified vestibulectomy	None	Self-reported dyspareunia	Mean 3 y	83% "complete relief", 17% some improvement. (42% declared suffering from vaginismus)	Very low 2, 5, 6
Traas et al[65]	Case series (retrospective)	126	18–39 y, Friedrich's criteria	Vestibulectomy	None	Self-reported dyspareunia	Mean 3 y	60% some improvement	Very low 2, 6
Goetsch[75]	Case series (retrospective)	111	Vestibulodynia	Modified superficial vestibulectomy and post-op physiotherapy	None	Self-reported pain and cotton-swab test	Mean 3.7 y	64% complete relief, 24% some improvement	Very low 2, 6
Goetsch[76]	Case series (retrospective)	133 (overlaps 2007 publ.)	Vestibulodynia	Modified superficial vestibulectomy	None	Self-reported pain		61% complete relief, 21% some improvement	Very low 2, 6
Eva et al[73]	Case series (retrospective)	110	Localized provoked vulvodynia	Vestibulectomy	None	Self-reported pain	1 y	Patient satisfaction was 83%	Very low 2, 6
Goldstein et al[66]	Case series (retrospective)	104	Pain limited to the vulvar vestibule	Vestibulectomy	None	Self-reported dyspareunia	Mean 2.2 y	52% no dyspareunia	Very low 2, 6
Bohm-Starke and Rylander[77]	Case series (retrospective)	67	Localized provoked vestibulodynia, 18–56 y; both primary and secondary onset of vestibulodynia	Vestibulectomy	None	Self-reported dyspareunia (VAS)	Mean 3.5 y	56% at least major improvement in patients with secondary vestibulodynia; 17% at least major improvement in patients with primary vestibulodynia	Very low 2, 6
Lavy et al[71]	Case series (retrospective)	53	Friedrich's criteria	Modified vestibulectomy	None	Self-reported dyspareunia	6 mo–10 y	74% complete relief, 13% some improvement	Very low 2, 6

(*Continued*)

Table 2
Continued

Citation PMID	Study Type	No. Patients	Patient Characteristics*	Intervention/Exposure	Comparison	Outcome Measures†	Time: Length of Follow-Up	Effect Size: Relative/Absolute	Evidence Quality‡ (Range)
Gaunt et al[63]	Case series (retrospective)	45	Friedrich's criteria, median age 29	Vestibulectomy	None	Pain score before/after surgery based on subjective symptom description by participant and objective findings from physician	Mean 2.5 y	90% total or some improvement	Very low 2, 6
McCormack and Spence[67]	Case series (retrospective)	42	Friedrich's criteria	Perineoplasty	None	Self-reported dyspareunia and vulvar discomfort	Mean 4.8 y	31% complete relief, 36% some improvement	Very low 2, 6
Bergeron et al[64]	Case series (retrospective)	38	19–52 y, Friedrich's criteria, moderate to severe interference with intercourse, symptoms >6 mo	Vestibulectomy	None	Self-reported dyspareunia, 5-point Likert scale	Mean 3.3 y	37% complete relief, 39% some improvement	Very low 2, 6
Leclair et al[78]	Case series (retrospective)	37	Vestibulodynia	KTP-nd: YAG laser	None	Self-reported pain scale	Mean 2.8 y	65% some improvement (35% underwent vestibulectomy following laser therapy—see Goetsch 2008)	Very low 2, 6
Rettenmaier et al[74]	Case series (retrospective)	27	Vulvar vestibulitis	Vestibulectomy	None	Self-reported pain	Up to 14 y	52% complete relief	Very low 2, 6
Chaim et al[62]	Case series (retrospective)	16	20–36 y, Friedrich's criteria, vulvar burning, failure of nonsurgical methods	Modified perineoplasty	None	Self-reported dyspareunia	6 mo–7 y, mean 3.5 y	94% some improvement	Very low 2, 5, 6

Consistency/inconsistency does not apply to a single study; publication bias does not apply to a single study; Strong dose-response requires at least 2 studies.

NNT (>50% reduction in primary symptom/ outcome /score)—could only be determined from RCTs and there are no valid randomized controlled trials of surgical interventions, therefore NNT not included on table. NNH—not reliably reported in studies.

Friedrich's criteria for vestibulodynia: Severe pain in the vulvar vestibule upon touch or attempted vaginal entry, Tenderness to pressure localized within the vulvar vestibule, Vulvar erythema (inflammation) of various degrees.[8]

*Vestibulodynia is a current terminology, older publications may use terms such as vulvar vestibulitis, vulvar vestibulitis, also Friedrich's Criteria.

†EMG, electromyogram biofeedback therapy.

‡Evidence quality rated as high, moderate, low, or very low. Numeric code: (1) Serious study limitations (design, execution, risk of bias), (2) very serious study limitations, (3) indirectness—some uncertainty, (4) indirectness—major uncertainty, (5) imprecision or sparse data, (6) selective outcome reporting bias, (7) strong dose-response relationship.

FSFI indicates Female Sexual Function Index; FSDS, Female Sexual Distress Scale; SF-36, 36-item short-form survey; VAS, visual analog scale; Likert, numeric scale anchored at the endpoints with the words "No pain" and at the right end with "Worst pain ever experienced"; MPQ, McGill Pain Questionnaire; SHF, Sexual History Form; SIS, Sexual Information Scale; SFI, Sexual Functioning Inventory; BSI, Brief Symptom Inventory.

Table 3
Evidence Summary Table of Interventions for Vulvodynia

Citation PMID	Study Type	No. Patients	Patient Characteristics	Intervention/Exposure	Comparison	Outcome Measures	Time: Length of Follow-up	Effect Size: Relative/Absolute	Source of Funding	Evidence Quality*
Descriptive studies										
Harris et al[83]	Case series (retrospective)	601	Generalized unprovoked vulvodynia	Gabapentin oral	None	Resolution of pain	>30 mo	64% had adequate resolution; 11% discontinued due to adverse effects	Nil	Very low 2, 6
Ben-David and Friedman[82]	Case series (retrospective)	17	Vulvodynia	Gabapentin oral	None	Improvement in pain	>6 mo	Most patients had some improvement; 7/17 complete relief, 7/17 significant relief	Nil	Very low 2, 5, 6
Boardman et al[49]	Case series (retrospective)	19	Vulvodynia (generalized [19] and localized [32], mixed unprovoked and provoked)	Gabapentin topical (2%–4%-6%)	None	VAS for pain, pre/post treatment	8 wk	Mean pain score reduction −4.77 (CI: −5.47 to −4.07) Absolute effect of >50% decline in dyspareunia score: 80% Discontinuation due to side-effects 14%	NVA	Very low 2, 3, 6
McKay[84]	Case series (retrospective)	20	Vulvodynia (dysesthetic) patients who had responded to amitriptyline	Amitriptyline oral	None	Improvement in pain		Only responsive patients were included in the series	Nil	Very low 2, 5, 6
Munday[85]	Case series (retrospective)	33	Vulvodynia (mix of patient characteristics)							
Reed et al[86]	Case series (prospective)	209	Vulvodynia (mix of patient characteristics)	TCAs (amitriptyline 183, desipramine 23, other TCA 3)	None	Pain score	Variable	Absolute effect of >50% decline in pain score: 53%	NIH	Very low 2, 3, 6
Gunter et al[87]	Case report	1	Vulvodynia	Botulinum and surgery	None	"Successfully managed"		1/1 patient improved	Nil	Very low 2, 5, 6
Yoon et al[88]	Case series (retrospective)	7	Vulvodynia	Botulinum	None	"Pain disappeared"	>11 mo	All patients improved	Nil	Very low 2, 5, 6
Powell and Wojnarowskal[89]	Case series	12	Vulvodynia	Acupuncture	None	Pain scores	5 wk	2/12 patients with 'good response'	Nil	Very low 2, 5, 6
Walsh et al[90]	Case series (prospective)	34	Vulvodynia	Nitroglycerin topical 0.2%	None	Pain scale	6 wk	Most patients had some improvement	Nil	Very low 2
Zawislak et al[91]	Case series (prospective)	11	Vulvodynia	Photodynamic therapy/5-aminolevulinic acid	None	"Overall symptoms" and dyspareunia		Most patients had some improvement	Nil	Very low 2, 5, 6
Whiteside et al[92]	Case report	1	Intractable burning vulvar pain	Spinal cord stimulation	None	Sustained symptom relief		1/1	Nil	Very low 2, 5, 6
Nair et al[93]	Case report	1	Vulvovaginal burning and deep pelvic pain	Spinal cord stimulator	None	Pain scale	3 mo	Reduction in pain from 10/10 to 2/10	Nil	Very low 2, 3, 5, 6
Langford et al[94]	Case series (retrospective)	18	Chronic pelvic pain and levator ani trigger points	Trigger point injections (levator ani)	None	VAS, PGC, PGS scores		Absolute effect of >50% decline in pain scores: 72%	Nil	Very low 2, 3, 5, 6
Holcomb et al[95]	Case reports	2	Back pain, pelvic pain, vulvodynia	Magnetic field	None	"Relief"	>2 y	2/2 patients had relief	Nil	Very low 2, 3, 5, 6

(Continued)

Table 3
Continued

Citation PMID	Study Type	No. Patients	Patient Characteristics	Intervention/Exposure	Comparison	Outcome Measures	Time: Length of Follow-Up	Effect Size: Relative/Absolute	Source of Funding	Evidence Quality*
Glazer[86]	Case series (retrospective)	43	Patients who responded to a follow-up survey after prior successful treatment for dysesthetic vulvodynia (43/62)	EMG-assisted pelvic floor muscle rehabilitation	None	Pain, daily functioning, sexual status	Mean 39.5 mo	43/43 pain-free	N/A	Very low 2, 6

Consistency/inconsistency does not apply to a single study; publication bias does not apply to a single study; strong dose-response requires at least 2 studies.

NNT (>50% reduction in primary symptom/outcome/score)–could only be determined from RCTs and all RCTs showed no effect of target intervention compared to control, therefore NNT not included on table.

NNH—withdrawals from intervention due to adverse effects, intolerability—described within Effects column.

*Evidence quality rated as high, moderate, low, or very low. Numeric code: (1) serious study limitations (design, execution, risk of bias), (2) very serious study limitations, (3) indirectness—some uncertainty, (4) indirectness—major uncertainty, (5) imprecision or sparse data, (6) selective outcome reporting bias, (7) strong dose-response relationship.

EMG indicates electromyogram biofeedback therapy; VAS, visual analog scale; Likert, numeric scale anchored at the endpoints with the words "No pain" and at the right end with "Worst pain ever experienced"; FSFI, Female Sexual Function Index; FSDS, Female Sexual Distress Scale; SF-36, 36-item short-form survey; NIH, National Institute of Health; NVA, National Vulvodynia Association.

term outcomes, sparse data, and selective outcome bias.[49,82–96] There were no analytic studies; no RCTs. All the studies reported a beneficial effect. Most of these studies reported before and after treatment data (Table 3). The body of evidence was poor. There was insufficient evidence for efficacy of: topical gabapentin,[49] topical nitroglycerin,[90] oral gabapentin,[82,83] tricyclic antidepressant (TCA) medications,[84,86] botulinum toxin injections,[87,88] and trigger point injections.[94] There was insufficient evidence for use of electromyogram biofeedback therapy-assisted pelvic floor physiotherapy,[96] acupuncture,[91] photodynamic therapy,[91] magnetic field therapy,[95] and spinal cord stimulation.[92,93] There was no evidence regarding cognitive behavioral therapy.

COMMENTARY

Limitations

This evidence synthesis has several potential limitations. Vulvodynia is an idiopathic disorder; in such conditions, there may be multiple etiologies which are different, and the appropriate treatment for each also may be different. Grouping patients with different conditions under one syndrome, and then studying an intervention that might only help one subset of the conditions, could lead to a demonstration of an apparent lack of effect, due to dilution of the patient subpopulation.

Descriptive studies can provide important insight into the effectiveness of interventions in real-world practice, but these types of studies are also more susceptible to confounding and bias,[97–100] particularly with subjective pain outcomes.

This analysis highlights the challenge of making necessary informed clinical decisions in the absence of high quality evidence. As Bornstein observed, "It is astonishing that the currently available vestibulitis treatments have been introduced without first establishing their effectiveness in a prospective randomized study. Every new treatment is introduced as the state-of-the-art approach, without subjecting it to thorough evaluation. This phenomenon results from our desire to provide our patients quick relief from the misery of vestibulitis, especially if the treatment seems noninvasive."[25]

Placebo Effect

The high quality indirect evidence from double-blind placebo-controlled randomized trials demonstrates that there is a placebo effect of interventions

for neuropathic pain and functional pain disorders. The placebo effect, described as an absolute effect of >50% decline in the pain score(s) ranged from 14% to 33%, with a median of 22%: 100 (14%), 101 (15%, 20%), 102 (22%), 103 (23%), 104 (31%), 105 (33%). The placebo effect emphasizes the quality of evidence weakness of a nonrandomized study without a placebo group. Placebo responses have also been large across a number of clinical trials for treatment of women's sexual dysfunction.[101,102]

Several studies in this review found no difference in pain measures between nonsurgical intervention groups and placebo groups; however, they did report a significant placebo effect.[29–33]

A challenge in interpreting observation trials of surgery, or randomized trials of surgery versus nonsurgical therapy[18,27,53] is that patients could not reasonably be blinded to the intervention. This probably is responsible for some overestimation of benefits[97,98] as surgery can be associated with important placebo effects,[79] particularly when assessing a subjective outcome such as pain.

The Etiology of Vulvodynia: Idiopathic, Neuropathic, Functional, or Somatoform Disorder?

Perhaps the management of vulvodynia could be improved if the etiology of the pain could be identified or at least classified. The ISSVD approach to terminology was largely informed by a gynecology, dermatology, and pathology perspective.[3,4] The experience of pain involves the nervous system, and the nosology of neurology uses different descriptors and terms to describe similar conditions. Using a neurologic classification, once the known causes (such as nociception and inflammation) have been ruled out, chronic pain is subdivided into neuropathic or functional.[1,16,103–106]

Neuropathic Pain

Neuropathic pain is a complex type of pain initiated or caused by a primary lesion or dysfunction in the nervous system.[106,107] Neuropathic pain manifests as a constant, burning pain with spontaneous sharp exacerbations and worsening upon normal sensory triggers causing considerable effect on the quality of life; persons must have experienced pain for at least 3 months, with a mean pain intensity greater than 3/10 on a pain scale.[107] A wide range of factors is known to precipitate neuropathic pain, including diabetes, peripheral trauma and traumatic nerve lesion, postsurgical nerve lesion, spinal cord trauma, central nervous system trauma, infections such as herpes zoster and HIV, and mechanical pressure such as compression and entrapment syndromes. Numerous treatment studies exist for patients with painful diabetic peripheral neuropathy (DPN) and for postherpetic neuropathy (PHN), due to the prevalence of these conditions. This has resulted in medications being registered in many countries with 1 or 2 indications for specific neuropathic pain syndromes (DPN, PHN). Supported by positive clinical empiricism, drugs demonstrated to have efficacy in DPN and PHN are prescribed by physicians for other painful peripheral and central neuropathic conditions, where there is absence of, or scarce scientific evidence for efficacy.[108] Vulvodynia does not fit into the classic definition of neuropathic pain, based on clinical evidence of underlying neurologic disease or site of the lesion in the somatosensory pathway.[108–110] Also, vulvodynia is usually bilateral and well-recognized neuropathic pain syndromes are usually unilateral (PHN, DPN, TGN [trigeminal neuralgia], etc). As a comparison, atypical facial pain syndrome usually begins unilateral and less than one-third of patients develop bilateral symptoms.[111] Generalized unprovoked vulvodynia may represent an entity within the spectrum of neuropathic pain syndromes, if understood as maladaptive nociception, neurogenic dysfunction in the form of dysregulation of inhibitory control.

Due to the lack of evidence that vulvodynia is a neuropathic pain disorder, evidence for efficacy of interventions for neuropathic pain disorders would have to be considered very indirect for patients with vulvodynia.

Functional Pain

Vulvodynia may also represent functional pain. Functional pain is a disorder in which a person experiences chronic pain for which there is no known cause or any visible physical injury or disease: the pain is attributable to a functional disorder rather than organic disease; of at least 3 months duration; and the pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The functional pain disorders can be further characterized into somatic pain syndromes, such as fibromyalgia and vulvodynia, and visceral pain syndromes, such as interstitial cystitis, painful bladder syndrome, irritable bowel syndrome, functional abdominal pain syndrome, and chronic pelvic pain. The functional pain symptom or

deficit is not intentionally produced or feigned (as in factitious disorder or malingering.

Mental Disorder Classification

A diagnostic overlap is found within the classification of female sexual disorders in the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-IV-TR),[112] which includes categories for dyspareunia not due to a medical condition (302.76) and for vaginismus not due to a medical condition (306.51). Many patients with vestibulodynia, who wish to be sexually active, report dyspareunia. Also, a condition of chronic pain without a recognized etiology may be described within the psychiatric perspective. Using a psychiatric classification, various somatoform pain disorders (300.81) are identified by specific criteria.[105,112] The ISSVD classification of vulvodynia overlaps with the neurologic category of functional pain and with the category of pain disorder (307.80) and somatoform disorders (300.81) in the DSMV-IV-TR.[16,105,112] The common feature of the somatoform disorders is the presence of physical symptoms that suggest a general medical condition, and are not fully explained by a general medical condition.[112]

CONCLUSIONS

Vestibulodynia

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

There is fair evidence that vestibulectomy surgery provides a benefit for patients with vestibulodynia, but the size of this effect cannot be determined with confidence, and the number-needed-to-treat is not known. The reason the size of absolute effect cannot be determined is that there is not adequate data about the placebo effect. Based on the very small number of placebo-controlled randomized trials, the magnitude of the placebo effect of surgery is about 35%.[79,80] Using this estimate of the placebo effect, the estimate of the percentage of patients who could have a substantial improvement in their vestibulodynia following vestibulectomy would be in the range of 30% to 50%.

Generalized Unprovoked Vulvodynia

There is insufficient direct evidence for efficacy of any intervention for generalized unprovoked vulvodynia. Clinicians and patients confronted with generalized unprovoked vulvodynia disorder today must rely upon this poor quality direct evidence and upon high quality indirect evidence derived from intervention studies for other types of pain.

Indirect Evidence From Neuropathic and Functional Pain Studies

Based upon high quality evidence of effect in neuropathic and functional pain disorders, the following medications could be selected for future controlled trials in patients with generalized unprovoked vulvodynia: 5% xylocaine topical,[113,114] pregabalin,[115,116–118,119,120] gabapentin,[114,115,117] duloxetine,[114,117,121] and selective serotonin reuptake inhibitors (SSRI) (bupropion, citalopram, paroxetine, fluoxetine).[114,117,121]

Future Research

The majority of reported studies were descriptive, and very few women have been previously enrolled in placebo-controlled randomized trials.[31–33] Given the high placebo response rate of around 50%, the only data that will give confidence about a beneficial effect will need to come from placebo-controlled randomized trials. Intervention controlled trials for vulvodynia could be modeled after studies performed to evaluate neuropathic and functional pain disorders.[113–124] Individual centers will take longer to enroll adequate numbers, so centers should consider collaborating in large multicenter trials. When determining the number of patients needed in a future study to demonstrate a difference between the target intervention and placebo, the absolute benefit of these interventions in studies of neuropathic pain and functional pain disorders expressed as greater than 50% reduction in the pain score compared to placebo, ranged from 15% to 43%, with a median of 22.5%.[113–125] Better assessment and reporting of harms in future clinical trials would help provide data for number-needed-to-harm and more balanced assessments of net benefits. Standardization of outcomes reporting for vestibulodynia and vulvodynia research would be ideal. This could also permit future meta-analysis by decreasing heterogeneity. A recommendation is to focus on patient-centered clinically meaningful reductions in pain; the patients' pain scores rather than cotton swab pain scores.

Another recommendation is to consistently use a clinically meaningful reduction in pain defined as greater than or equal to 50% reduction on a validated pain score. There are set of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations that could be adopted by vulvodynia researchers.[126–131]

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