

## NVA Research Update E- Newsletter

June – July – August 2017

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### Vulvodynia

#### **Chronic vulvar pain in a cohort of post-menopausal women: Atrophy or Vulvodynia?**

Mitro SD, Harlow SD, Randolph JF, Reed BD.

*Womens Midlife Health*. 2016;2. pii: 4. doi: 10.1186/s40695-016-0017-z. Epub 2016 Jun 9.

<https://www.ncbi.nlm.nih.gov/pubmed/28127441>

**BACKGROUND:** Although postmenopausal vulvar pain is frequently attributed to vaginal atrophy, such symptoms may be due to vulvodynia, a chronic vulvar pain condition. Given the limited research on vulvodynia in postmenopausal women, the objective of this study was to provide preliminary population-based data on the associations of vaginal symptoms, serum hormone levels and hormone use with chronic vulvar pain in a multiethnic sample of post-menopausal women. **METHODS:** We used data from 371 participants at the Michigan site of the Study of Women's Health Across the Nation (SWAN) who participated in the 13th follow-up visit. Women completed a validated screening instrument for vulvodynia and provided information on additional vaginal symptoms as well as demographic characteristics, and hormone use by questionnaire. Blood samples were obtained to assess hormone levels. We compared women who screened positive for vulvodynia and women with past or short-duration vulvar pain to women without vulvar pain, using Chi-squared and Fisher's Exact tests. Relative odds ratios and 95 % confidence intervals were calculated using multinomial logistic regression models adjusting for age, body mass index, and race/ethnicity. **RESULTS:** Current chronic vulvar pain consistent with vulvodynia was reported by 4.0 % of women, while 13.7 % reported past but not current chronic vulvar pain or short-duration vulvar pain symptoms. One quarter of women who reported current chronic vulvar pain did not report vaginal dryness. Women with current chronic and with past/short duration vulvar pain symptoms were more likely to have used hormones during the preceding year than women without vulvar pain symptoms (13.3 %, 17.6 %, 2.0 %, respectively;  $p < .01$ ). Increased relative odds of current vulvar pain symptoms were associated with each log unit decrease in serum dehydroepiandrosterone-sulfate, estradiol and testosterone levels at the previous year's visit.

**CONCLUSION:** Some women who experience chronic vulvar pain symptoms do not report vaginal dryness, and others report continued or first onset of pain while using hormones. Vulvodynia should be considered in the differential diagnosis of postmenopausal women presenting with vulvar pain symptoms.

### **Vulvodynia-Younger Age and Combined Therapies Associate With Significant Reduction in Self-Reported Pain.**

Aalto AP, Vuoristo S, Tuomaala H, Niemi RJ, Staff SM, Mäenpää JU.

*J Low Genit Tract Dis.* 2017 Jul;21(3):209-214. doi: 10.1097/LGT.0000000000000318.

<https://www.ncbi.nlm.nih.gov/pubmed/28644192>

**OBJECTIVES:** Eight percent of women have vulvodynia (VD), a chronic pain disorder with unknown etiology. The aim of our study was to assess the efficacy of given VD treatments measured by numerical rating scale (NRS) for pain and patients' quality of life. **MATERIALS AND METHODS:** Study material consisted of a retrospective VD patient cohort (N = 70). Data were collected by postal questionnaires and review of the medical records. **RESULTS:** We report here a statistically significant reduction in NRS only with combination of therapies (median NRS before treatments 8 vs median NRS 4 after treatments,  $p < .001$ ) but not with any individual therapy alone, i.e., physiotherapy, topical medications, oral pharmaceutical therapy, sexual counseling by a trained nurse, sacral neuromodulation, and laser treatment or surgery. Older age (>30) and frequent ( $\geq 6$ ) outpatient clinic visits associated with a significantly minor reduction in NRS ( $p = .03$  and  $p = .04$ , respectively). **CONCLUSIONS:** The results of this retrospective study suggest that an effective, multimodality-based treatment is most beneficial for VD patients and VD at older age may represent a subtype more resistant to therapy.

### **Vulvodynia is not created equally: empirical classification of women with vulvodynia.**

*J Pain Res.* 2017 Jul 6;10:1601-1609. doi: 10.2147/JPR.S136751. eCollection 2017.

Alappattu M, Lamvu G, Feranec J, Witzeman K, Robinson M, Rapkin A.

<https://www.ncbi.nlm.nih.gov/pubmed/28740427>

**BACKGROUND:** Vulvodynia classification is based on the sensory dimensions of pain and does not include psychological factors associated with the pain experience and treatment outcomes. Previous work has shown that individuals with chronic pain can be classified into subgroups based on pain sensitivity, psychological distress, mood, and symptom severity. **OBJECTIVE:** The aim of this study was to identify distinct subgroups of women with vulvodynia enrolled in the National Vulvodynia Registry. We hypothesized that women with vulvodynia can be clustered into subgroups based on distress and pain sensitivity. **DESIGN:** A cross-sectional study. **METHODS:** We conducted an exploratory hierarchical agglomerative cluster analysis using Ward's cluster method and squared Euclidean distances to identify unique subgroups based on baseline psychological distress and pain sensitivity. The variables included the catastrophizing subscale of the Coping Strategies Questionnaire, the Beck Depression Inventory, the State Trait Anxiety Index-Trait scale, McGill Pain Questionnaire-Affective subscale, and vulvar and pelvic muscle pressure pain sensitivity. **SUBJECTS:** Eight sites enrolled women who presented with vaginal or vulval pain of at least 3-month duration. **RESULTS:** Two distinct subgroups, high pain sensitivity with high distress ( $n=27$ ) and low pain sensitivity with low distress ( $n=100$ ), emerged from the cluster analysis. Validation indicated that subgroups differed in terms of clinical pain intensity, sensory aspects of pain, and intercourse pain. **CONCLUSION:** Empirical classification indicates that unique subgroups

exist in women with vulvodynia. Providers should be aware of the heterogeneity of this condition with respect to pain-related distress and pain sensitivity.

## Provoked Vestibulodynia

### Provoked vestibulodynia: current perspectives

Henzell H, Berzins K, Langford JP

Received 17 April 2017

Accepted for publication 21 July 2017

Published 11 September 2017 Volume 2017:9 Pages 631–642

DOI <https://doi.org/10.2147/IJWH.S113416>

**Abstract:** Provoked vestibulodynia (PVD) refers to vulvar pain of at least 3 months duration, localized to the vestibule, provoked by touch and sexual activity and occurring in the absence of a clear identifiable cause. The clinical spectrum ranges from mild with distressing discomfort through to severe and disabling pain. Current understanding is that PVD is one of many chronic pain conditions characterized by sensitization of peripheral and central nociceptive pathways, with pain arising due to dysfunctional neuronal activity in the absence of painful stimuli. Pathophysiology is not well understood but is likely a complex interplay of environmental, genetic, psychological and immune factors. Care is multidisciplinary and follows general principles of chronic pain management with the addition of specific therapy tailored to address pelvic floor overactivity, and sexual and relationship difficulties. More recently, the therapeutic use of placebo is gaining traction in chronic pain research and is a very promising adjunctive therapy. The majority of women with PVD are managed outside of tertiary clinic settings, and care depends on availability and affordability of specialized services; however, much can be done by the primary health provider. PVD is common, and highly treatable, especially with early intervention, but unfortunately, many clinicians are unaware of this condition, and the biggest hurdle for women accessing treatment is obtaining a diagnosis. With treatment, most women can expect significant improvement, often with fairly simple interventions, although some women will benefit from referral to specialized centers. The aims of this article are twofold: firstly, to summarize current literature concerning PVD pathophysiology and management; secondly, to provide a framework for clinicians unfamiliar with vulvar medicine to understand and manage PVD.

## Co-morbid Disorders

### Biomechanical paradigm and interpretation of female pelvic floor conditions before a treatment.

Lucente V, van Raalte H, Murphy M, Egorov V.

*Int J Womens Health.* 2017 Aug 3;9:521-550. doi: 10.2147/IJWH.S136989. eCollection 2017.

<https://www.ncbi.nlm.nih.gov/pubmed/28831274>

**BACKGROUND:** Further progress in restoring a woman's health may be possible if a patient with a damaged pelvic floor could undergo medical imaging and biomechanical diagnostic tests. The results of such tests could contribute to the analysis of multiple treatment options and suggest the optimal one for that patient. **AIM:** To develop a new approach for the biomechanical characterization of vaginal conditions, muscles, and connective tissues in the female pelvic floor. **METHODS:** Vaginal tactile imaging

(VTI) allows biomechanical assessment of the soft tissue along the entire length of the anterior, posterior, and lateral vaginal walls at rest, with manually applied deflection pressures and with muscle contraction, muscle relaxation, and Valsalva maneuver. VTI allows a large body of measurements to evaluate individual variations in tissue elasticity, support defects, as well as pelvic muscle function. Presuming that 1) the female pelvic floor organs are suspended by ligaments against which muscles contract to open or close the outlets and 2) damaged ligaments weaken the support and may reduce the force of muscle contraction, we made an attempt to characterize multiple pelvic floor structures from VTI data. **RESULTS:** All of the 138 women enrolled in the study were successfully examined with the VTI. The study subjects have had normal pelvic support or pelvic organ prolapse (stages I-IV). The average age of this group of subjects was  $60 \pm 15$  years. We transposed a set of 31 VTI parameters into a quantitative characterization of pelvic muscles and ligamentous structures. Interpretation of the acquired VTI data for normal pelvic floor support and prolapse conditions is proposed based on biomechanical assessment of the functional anatomy. **CONCLUSION:** Vaginal tactile imaging allows biomechanical characterization of female pelvic floor structures and tissues in vivo, which may help to optimize treatment of the diseased conditions such as prolapse, incontinence, atrophy, and some forms of pelvic pain.

### **Pudendal Neuromodulation as a Treatment for Persistent Genital Arousal Disorder-A Case Series.**

Gaines N, Odom BD, Killinger KA, Peters KM.

*Female Pelvic Med Reconstr Surg.* 2017 Jun 27. doi: 10.1097/SPV.0000000000000435.

<https://www.ncbi.nlm.nih.gov/pubmed/28657994>

**BACKGROUND:** Persistent genital arousal disorder (PGAD) is a rare life-altering condition characterized by unwanted, uncomfortable genital sensations or spontaneous orgasms without physical or emotional stimulation. Its etiology remains unclear, and a variety of treatments have been attempted with incomplete resolution. We propose that chronic pudendal neuromodulation (CPN) may be a useful treatment for PGAD symptoms. **METHODS:** A retrospective chart review was performed for women older than 18 years with a diagnosis of PGAD that had staged neuromodulation with placement of a tined lead at the pudendal nerve. Demographic, operative, and postoperative data were collected. A survey was then sent to these women to assess additional demographic data, preoperative and postoperative symptoms, and patient satisfaction. Descriptive statistics were performed. **RESULTS:** Six women underwent CPN for PGAD. Mean age was 52 (SD, 9) years. Five (83%) of 6 were still implanted at time of survey, at a mean of 38 months after implantation; 1 device was removed for nonuse. Four of 6 completed surveys and were still using their device. Three of 4 had met their treatment goals and were satisfied with CPN; 3 of 4 felt CPN was the most useful treatment modality they had used overall. Chronic pudendal neuromodulation also improved chronic pelvic pain (4/4), bowel function (3/4), and bladder function (3/4). **CONCLUSIONS:** Chronic pudendal neuromodulation can be an effective treatment for decreasing frequency of PGAD symptoms and providing symptom relief.

### **Myotonometry Reliably Measures Muscle Stiffness in the Thenar and Perineal Muscles.**

Davidson MJ, Bryant AL, Bower WF, Frawley HC.

*Physiother Can.* 2017;69(2):104-112. doi: 10.3138/ptc.2015-85.

<https://www.ncbi.nlm.nih.gov/pubmed/28539690>

**Purpose:** The authors investigated the reliability of myotonometry-measured muscle tone in the thenar and perineal muscles. **Methods:** Participants were women aged 18-50 years who were asymptomatic for thumb and pelvic floor dysfunction (interrater study  $n=20$ ; intrarater study  $n=43$ ) or who were symptomatic for vulvodynia (interrater study  $n=14$ ; intrarater study  $n=32$ ). Mechanical properties (stiffness, frequency, decrement, relaxation time, and creep) of the muscles were measured using a myotonometer (MyotonPRO) while the muscles were in a relaxed state. Measures were performed twice by two assessors. Intra- and interrater reliability were determined using intra-class correlation coefficients (ICCs) and absolute reliability using the standard error of measurement and a minimum detectable change. **Results:** The primary property of interest, muscle stiffness, showed very good interrater (ICC 0.85-0.86) and intrarater (ICC 0.82-0.88) reliability in the thenar eminence. In the perineal muscles, reliability results ranged from good to very good for interrater (ICC 0.70-0.86) and intrarater (ICC 0.80-0.91) reliability for muscle stiffness. Absolute reliability was confirmed, with all measures showing minimal variance. **Conclusions:** Muscle stiffness of the smaller muscles of the body can be reliably measured using the MyotonPRO. The device could be used as a reference standard in the development of a digital palpation scale that would facilitate accurate diagnosis of muscle tone.

### **Botulinum toxin to treat pelvic pain.**

Zhang Y, Smith CP.

*Toxicon.* 2017 Aug 25. pii: S0041-0101(17)30262-3. doi: 10.1016/j.toxicon.2017.08.017.

<https://www.ncbi.nlm.nih.gov/pubmed/28847706>

Botulinum toxin's (BoNT) success in treating several pain disorders has triggered interest in its application for pelvic pain disorders. This article summarizes results presented at the recent Neurotoxins Meeting in Madrid, Spain, in January 2017. It does not include BoNT use for Interstitial Cystitis/Bladder Pain Syndrome, which was the topic of a separate lecture. It includes studies documenting the beneficial effects of OnaBoNTA for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men using both transrectal and transurethral injection techniques. It also focuses on research using OnaBoNTA to treat levator spasms in women with chronic pelvic pain. Finally, it presents a novel approach using high density quantitative surface EMG to map out innervation zones and allow for more precise targeting of hypertonic pelvic floor muscles.

### **Myofascial Pelvic Pain and Related Disorders.**

Bonder JH, Chi M, Rispoli L.

*Phys Med Rehabil Clin N Am.* 2017 Aug;28(3):501-515. doi: 10.1016/j.pmr.2017.03.005.

<https://www.ncbi.nlm.nih.gov/pubmed/28676361>

Myofascial pelvic pain refers to pain in the pelvic floor muscles, the pelvic floor connective tissue, and the surrounding fascia. The cause is often multifactorial and requires treatment that encompasses multiple modalities. This type of pain is often associated with other abdominopelvic disorders, so providers in these specialties need to be aware of these connections. A comprehensive musculoskeletal examination, including evaluation of the pelvic floor muscles, and history are key to diagnosing

myofascial pelvic pain. Treatments include physical therapy, muscle relaxers, oral neuromodulators, cognitive-behavioral therapy, and pelvic floor muscle injections.

### **Cystitis and pelvic pain management: guidelines versus real-world practice.**

C Goddard J.

Urologia. 2017 Aug 17;0. doi: 10.5301/uj.5000260.

<https://www.ncbi.nlm.nih.gov/pubmed/28862731>

Clinical practice guidelines for the management of bladder pain syndrome/chronic pelvic pain aim to help guide clinicians in diagnosing and treating patients they see on a day-to-day basis in the clinic. However, the approaches suggested by current clinical guidelines may not always align with the practicalities of routine clinical practice, where patient expectations must also be taken into consideration.

### **Integrative Women's Health.**

Chiaramonte D, Ring M, Locke AB.

Med Clin North Am. 2017 Sep;101(5):955-975. doi: 10.1016/j.mcna.2017.04.010. Epub 2017 Jul 14.

<https://www.ncbi.nlm.nih.gov/pubmed/28802473>

This article addresses the common women's health concerns of menopause-related symptoms, premenstrual syndrome, and chronic pelvic pain. Each can be effectively addressed with an integrative approach that incorporates interventions such as pharmaceuticals, nutraceuticals, mind-body approaches, acupuncture, and lifestyle modification.

### **Vulvovaginal Issues in Mature Women.**

Marnach ML, Torgerson RR.

Mayo Clin Proc. 2017 Mar;92(3):449-454. doi: 10.1016/j.mayocp.2016.10.031.

<https://www.ncbi.nlm.nih.gov/pubmed/28259230>

Mature women often present with symptomatic vulvovaginal atrophy and vulvar dermatoses, causing noncoital pain, dyspareunia, and sexual changes. Diagnosis of these conditions can be challenging, and long-term management is required to decrease morbidity and enhance quality of life. Vaginal estrogen therapies remain safe and effective for treating symptomatic vulvovaginal atrophy. A vulvar biopsy is easy to perform and generally well tolerated when indicated for the diagnosis of lichen simplex chronicus, lichen sclerosus, and lichen planus. Therapy with moderate- to high-potency corticosteroids is effective for these frequently debilitating conditions.

## Pudendal Neuralgia

### **[Magnetic resonance neurography for the identification of pudendal neuralgia].**

[Article in Spanish]

Cejas CP, Bordegaray S, Stefanoff NI, Rollán C, Escobar IT, Consigliere Rodríguez P. *Medicina (B Aires)*. 2017;77(3):227-232.

<https://www.ncbi.nlm.nih.gov/pubmed/28643681>

The pudendal nerve entrapment is an entity understudied by diagnosis imaging. Various causes are recognized in relation to difficult labors, rectal, perineal, urological and gynecological surgery, pelvic trauma fracture, bones tumors and compression by tumors or pelvic pseudotumors. Pudendal neuropathy should be clinically suspected, and confirmed by different methods such as electrofisiological testing: evoked potentials, terminal motor latency test and electromyogram, neuronal block and magnetic resonance imaging. The radiologist should be acquainted with the complex anatomy of the pelvic floor, particularly on the path of pudendal nerve studied by magnetic resonance imaging. High resolution magnetic resonance neurography should be used as a complementary diagnostic study along with clinical and electrophysiological examinations in patients with suspected pudendal nerve neuralgia.

## Dermatological Conditions

### **Therapeutic comparison between treatments for Vulvar Lichen Sclerosus: study protocol of a randomized prospective and controlled trial.**

Belotto RA, Chavantes MC, Tardivo JP, Euzébio Dos Santos R, Fernandes RCM, Horliana ACRT, Pavani C, Teixeira da Silva DF.

*BMC Womens Health*. 2017 Aug 10;17(1):61. doi: 10.1186/s12905-017-0414-y.

<https://www.ncbi.nlm.nih.gov/pubmed/28793884>

Vulvar lichen sclerosis (VLS) is a lymphocyte-mediated disease of unknown etiology that can cause intense itching as well stenosis, hindering the evacuation and urination. It can also limit the sex life due to severe local pruritus, pain and dyspareunia (pain during sexual intercourse). The standard treatment for this disease is the use of topical corticosteroids to reduce the clinical symptoms and to try to increase disease-free intervals. Photodynamic therapy (PDT), a treatment that associates a light radiation with a photosensitizing agent and photobiomodulation (PBM) are therapies that can promote effective immunomodulatory responses at the application site by means of photophysical and photochemical phenomena from the molecular to the systemic level, which promote their use in chronic dermatoses. The aim is to compare the effects of PDT, PBM, and topical corticosteroid in VLS evaluating clinical, histological, immunohistochemical and spectroscopic responses. **METHODS:** The study is prospective, randomized and controlled, in a population of 60 women with histological diagnoses of VLS. There will be 3 treatments groups: PDT, PBM and topical corticosteroid (control group), where will be allocated by randomization 20 patients in each one. The clinical course will be monitored by measuring local temperature, itching, atrophy, and the area of the lesion. Histologically, the slides will be classified and will have the ordering of collagen fibers quantified. Immunohistochemical analysis will be done

using the markers IFN- $\gamma$ , TGF- $\beta$ , CD4, CD8, IL-1, p53 and Ki-67. Finally, the spectroscopic evaluation will be done by reflectance. Descriptive and inferential statistical analyses will be conducted to compare the groups and make associations between different responses. The study is an open-label for patients with active symptomatic disease with a period of 1 year follow-up to determine the rate of recurrence in each groups. **DISCUSSION:** The immunological effects of PDT and PBM are described by several authors in inflammatory skin diseases, stimulating the production and organization of the associated collagen. Thus, it is reasonable to determine the efficacy and safety of these new treatments in VLS, in comparison to the control group, analyzing the recurrence time, the impact on the optical properties of the skin, and the benefit to patients.

#### **Intraepidermal nerve fiber density in vulvar lichen sclerosus and normal vulvar tissues.**

Milian-Ciesielska K, Chmura L, Dyduch G, Jagers C, Radwanska E, Adamek D.

*J Physiol Pharmacol*. 2017 Jun;68(3):453-458.

<https://www.ncbi.nlm.nih.gov/pubmed/28820401>

Lichen sclerosus (LS) is a chronic and inflammatory disease causing sensory symptoms such as itch and pain and affecting most frequently genital skin of women. Intraepidermal nerve fiber density (IENFD) was examined immunohistologically in 20 vulvar skin biopsies of patients affected by LS and in 20 control vulvar skin biopsies, in order to determine if these sensory sensations originate in changes in the epidermal innervation. Obtained results show fewer protein gene product 9.5 (PGP 9.5) positive intraepidermal nerve fibers (IENF) in LS tissues compared to controls ( $P = 0.004$ ), while the number of calcitonin gene-related peptide (CGRP) positive IENF in LS was increased compared to normal vulvar tissue ( $P = 0.03$ ). No differences in the number of vasoactive intestinal peptide (VIP) expressing IENF could be observed. To our best knowledge, this is the first study to describe intraepidermal nerve fiber density in vulvar LS. Significant differences in IENFD between LS and control skin samples, which have been found, point to the damage to the small nerve fibers in the disease process of LS, which may contribute to pathogenesis of LS sensory symptoms.

#### **Skin diseases of the vulva: inflammatory, erosive-ulcerating and apocrine gland diseases, zinc and vitamin deficiency, vulvodynia and vestibulodynia.**

Sand FL, Thomsen SF.

*J Obstet Gynaecol*. 2017 Aug 1:1-12. doi: 10.1080/01443615.2017.1328590.

<https://www.ncbi.nlm.nih.gov/pubmed/28764581>

Chronic, inflammatory and ulcerating mucocutaneous diseases that can affect the vulvar area are reviewed: lichen sclerosus, lichen planus, plasma cell vulvitis, complex aphthosis, Behcet's disease, pyoderma gangrenosum, metastatic Crohn's disease, dyskeratotic skin diseases (Hailey-Hailey disease and Darier's disease), autoimmune bullous diseases (mucous membrane pemphigoid and pemphigus vulgaris) and hidradenitis suppurativa. Also, vulvodynia and vestibulodynia, zinc and vitamin B deficiency are described.



### **Recurrent Yeast Infections and Vulvodynia: Can We Believe Associations Based on Self-Reported Data?**

Harlow BL, Caron RE, Parker SE, Chatterjea D, Fox MP, Nguyen RHN.  
J Womens Health (Larchmt). 2017 Jul 7. doi: 10.1089/jwh.2016.5777.  
<https://www.ncbi.nlm.nih.gov/pubmed/28686502>

**OBJECTIVE:** We determined whether self-reported new or recurrent yeast infections were a risk factor for and/or consequence of vulvodynia and then determined the extent to which various levels of misclassification of self-reported yeast infections influenced these results. **MATERIALS AND METHODS:** In this case-control study we retrospectively assessed self-reported new and recurrent yeast infections prior and subsequent to first vulvar pain onset among 216 clinically confirmed cases and during a similar time period for 224 general population controls. **RESULTS:** A history of >10 yeast infections before vulvodynia onset was strongly but imprecisely associated with currently diagnosed vulvodynia after adjustment for age, age at first intercourse, and history of urinary tract infections [adjusted odds ratio = 5.5, 95% confidence interval (CI) 1.7-17.8]. Likewise, a history of vulvodynia was associated with a twofold risk of subsequent new or recurrent onset of yeast infections after adjustment for age, age at first intercourse, and history of yeast infections before vulvodynia onset (comparable time period among controls, 95% CI 1.5-2.9). Bias analyses showed that our observed associations were an underestimation of the true association when nondifferential misclassification of self-reported yeast infections and certain differential misclassification scenarios were present. However, if women with vulvodynia more frequently misreported having them when they truly did not, our observed associations were an overestimate of the truth. **CONCLUSIONS:** There appears to be a positive relationship between yeast infections preceding and following the diagnosis of vulvodynia, but this relationship varies from strong to nonexistent depending on the relative accuracy of the recalled diagnosis of yeast infections among cases and controls. To better understand the bidirectional associations between yeast infections and vulvodynia, future validation studies are needed to determine the extent to which misclassification of self-reported yeast infections differs between women with and without vulvodynia.

### **Candida Vulvovaginitis and Vulvodynia: The Mystery Continues.**

J Womens Health (Larchmt). 2017 Aug 24. doi: 10.1089/jwh.2017.6620.  
Reed BD.  
<https://www.ncbi.nlm.nih.gov/pubmed/28836889>

(No abstract available.)