

Research Update E- Newsletter  
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## Vulvodynia

### **Vulvodynia: a neuroinflammatory pain syndrome originating in pelvic visceral nerve plexuses due to mechanical factors**

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<https://pubmed.ncbi.nlm.nih.gov/35147761/>

This short opinion aimed to present the evidence to support our hypothesis that vulvodynia is a neuroinflammatory pain syndrome originating in the pelvic visceral nerve plexuses caused by the failure of weakened uterosacral ligaments (USLs) to support the pelvic visceral nerve plexuses, i.e., T11-L2 sympathetic and S2-4 parasympathetic plexuses. These are supported by the USLs, 2 cm from their insertion to the cervix. They innervate the pelvic organs, glands, and muscles. If the USLs are weak or lax, gravitational force or even the muscles may distort and stimulate the unsupported plexuses. Inappropriate afferent signals could then be interpreted as originating from an end-organ site. Activation of sensory visceral nerves causes a neuro-inflammatory response in the affected tissues, leading to neuroproliferation of small peripheral sensory nerve fibers, which may cause hyperalgesia and allodynia in the territory of the damaged innervation. Repair of the primary abnormality of USL laxity, responsible for mechanical stimulation of the pelvic sensory plexus, may lead to resolution of the pain syndrome.

### **Menstrual Cycle Characteristics and Vulvodynia**

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J Womens Health (Larchmt). 2022 Jan 17. doi: 10.1089/jwh.2020.9011.  
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**Objective:** The menstrual cycle may influence vulvodynia through hormonal pathways or vulvar irritation due to menstruation or menstrual hygiene. We assessed menstrual cycle characteristics in those with and without clinically confirmed vulvodynia. **Materials and Methods:** Participants were recruited from the administrative database of a health care network serving ~27% of Minneapolis-Saint Paul residents. For 220 clinically confirmed cases and 224 controls, menstrual cycle characteristics were retrospectively assessed at three time points: before age 18, the year before onset of vulvar pain, and 3

months before study participation. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between menstrual characteristics at all three time points and vulvodynia. Models adjusted for prespecified confounders were evaluated against crude effect estimates. **Results:** Women with heavier menstrual flows had higher odds of vulvodynia compared with women with lighter menstrual flows during their adolescent years (OR 1.62, 95% CI 0.91-2.86), the year before onset of vulvar pain (OR = 2.11, 95% CI 1.10-4.02), and during the 3 months before study participation (OR = 1.67, 95% CI 0.91-3.06). Women with more severe cramps also had higher odds of vulvodynia compared with women with no or mild cramps during their adolescent years (OR = 2.45, 95% CI 1.45-4.15), the year before onset of vulvar pain (OR = 3.30, 95% CI 1.67-6.51), and during the 3 months before study participation (OR = 4.96, 95% CI 1.99-12.36). Women with specific premenstrual symptoms also reported higher odds of vulvodynia. Among those with vulvodynia, half reported a change in vulvar pain across the menstrual cycle, with 60% of these reporting greater pain just before and during menstruation. Furthermore, we observe a trend of decreased tampon use and increased use of sanitary pads as women with vulvodynia moved closer to their date of diagnosis. **Conclusions:** Menstrual cycle characteristics were associated with vulvodynia, and associations were consistent across different phases of the reproductive life cycle.

### **Therapy With Local Anesthetics to Treat Vulvodynia. A Pilot Study**

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<https://pubmed.ncbi.nlm.nih.gov/35063914/>

**Introduction:** Vulvodynia (chronic vulvar pain) is a sexually debilitating disorder with a prevalence of ~10%. **Aim:** To investigate the effectiveness of therapy with local anesthetics (TLA) in women with severe vulvodynia, we conducted a prospective, non-controlled observational study. **Methods:** 45 patients with severe chronic vulvodynia (primary and secondary vulvodynia, 0-10 numeric analogue scale (NAS)  $\geq 6$ , median 7.9, duration  $\geq 6$  months, median 65.2 months) in an outpatient practice in Germany were treated with TLA in 3-12 sessions using procaine 1% as local anesthetic. Effectiveness was analyzed with Wilcoxon signed rank tests and Wilcoxon rank sum tests. **Outcomes:** Therapeutic success as a reduction of pain to  $\leq 4$  NAS lasting for  $\geq 6$  months after end of therapy. **Results:** TLA successfully reduced vulvodynia in 36 of 45 patients (80 %, responders). The NAS reduction was from 7.9 to 2.4 ( $P < .001$ ). Even patients denominated as non-responders experienced a significant reduction in NAS ( $P = .03$ ). In responders, long-term success was observed for 6.8-125 months (median 24.1 months). No adverse events occurred. **Clinical translation:** A promising new treatment for a hard-to-treat chronic female pain disorder. **Strengths and limitations:** Limitation: Monocentric, non-controlled observational design; Strength: the high number of patients treated. **Conclusion:** The high success rate of TLA in this investigation offers new perspectives on the etiology of vulvodynia as a complex pain syndrome affecting several nerves of the pelvic floor, and also provides early insight into the effectiveness of TLA in women with vulvodynia.

### **A novel approach to vulvodynia using targeted neuromodulation**

Jacob R Stephens, Kenneth M Peters  
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Vulvodynia is a debilitating disorder which can prove extremely difficult to treat. Neuromodulation is increasingly becoming a frontline therapy in various chronic pain syndromes. We present a relatively simple surgical technique utilizing targeted neuromodulation leading to the successful treatment of vulvodynia.

### **Vulvodynia in prepubertal girls: diagnosis**

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Ginekol Pol. 2022 Jan 24. doi: 10.5603/GP.a2021.0190.

<https://pubmed.ncbi.nlm.nih.gov/35072227/>

**Objectives:** To identify specific features of vulvodynia in prepubertal girls, highlight potential triggers and concomitant diseases, outline diagnostic criteria is neglected problem in adolescent gynecology.

**Material and methods:** A retrospective study, based on medical records of an outpatient clinic, a cohort of 54 vulvodynia cases was evaluated, aged 3-10 years, seen between January 2016 and July 2018.

**Results:** The study cohort presented with pain (61%), sometimes aggravated at night, pruritus (44%) and a range of other varied and unusual vulvar complaints (26%). Concomitant diseases and/or psychological problems were present in 61% of cases. Overactive pelvic muscles accompanying symptoms like urological or gastrological problems were noted in half of children. Several potential triggers were identified in a third of the cases that were emotionally stressful to the children. From the commencement of symptoms, 93% of the girls have consulted more than one doctor with 43% seeing more than three doctors, without receiving a diagnosis of vulvodynia. **Conclusions:** A diagnosis of vulvodynia needs to be considered in the absence of vulva pathology with wide range of vulvar pain, pruritus and discomfort. All persistent or recurrent vulvar discomfort must be taken into consideration as a vulvodynia symptom, also various non-specific, worrisome complaints. Comorbid urological and gastrological symptoms associated with overactive pelvic muscles should not be overlooked. Chronic pain can be triggered by the psychological distress in some prepubertal girls. Proper diagnosis may prevent long-term negative sequelae, what emphasizes the need for professional education of healthcare providers in adolescent vulvar pain and discomfort.

### **Internet-based Treatment for Vulvodynia (EMBLA) - A Randomized Controlled Study**

Andrea Hess Engström, Nina Bohm-Starke, Merit Kullinger, Susanne Hesselman, Ulf Högberg, Monica Buhrman, Alkistis Skalkidou

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<https://pubmed.ncbi.nlm.nih.gov/34972640/>

**Background:** Internet-based ACT (Acceptance and commitment therapy) treatment may improve accessibility and reduce stigma related to seeking health care, but there are a lack of studies investigating internet-based treatment using ACT principles for women with vulvodynia. **Aim:** The aim of this study was to investigate the effects of an internet-based treatment of pain during intercourse for women with provoked vulvodynia compared with no intervention during the waiting period before clinical treatment. **Methods:** A multicenter randomized controlled trial was conducted during 2016 to 2020, in which 99 participants were included. Participants were randomized to either a 6 week guided internet-based treatment using ACT principles or usual care. Data were collected at baseline, 6 weeks after baseline, and approximately 10 months after baseline. **Outcomes:** Pain-related (pain during intercourse, tampon test, impact of pain on sexual function) and pain behavior-related outcomes (attempts at intercourse, sexual activities besides intercourse, willingness to perform the tampon test,

chronic pain acceptance questionnaire) were used as outcomes. **Results:** Treatment was efficacious in what concerns pain during intercourse and pain acceptance. Less pain during intercourse among women in the intervention group was observed at both post-treatment (primary endpoint,  $P = .01$ , Cohen's  $d = 1.4$ , 95% CI = 0.33, 2.4), and follow-up ( $P = .04$ ). Absolute mean difference between groups for pain during intercourse at post-treatment was -2.84, 95% CI = -4.91, -0.78), and -1.58 at follow-up, 95% CI = -3.17, 0.02), where the intervention group rated less pain than controls. No differences between groups over time were found for tampon test measures or impact of pain on sexual function. There was a significant difference between groups at all timepoints indicating fewer attempts at intercourse among participants in the intervention group. At post-treatment, women who underwent internet-based treatment reported higher pain acceptance and a rise in activity engagement compared with the control group. **Clinical implications:** There is an indication that internet-based treatment could be incorporated into clinical practice as a complement to clinical treatment. **Strengths & limitations:** Study strengths included using several forms of recruitment and an intervention built by different professions with long experience of treating patients with vulvodynia. High dropout rate was a limitation of this study. **Conclusion:** Internet-based treatment may have an impact on pain during intercourse and positive effects on pain acceptance. However, conclusions must be drawn with caution due to the small sample size.

## Provoked Vestibulodynia

### Where does postmenopausal dyspareunia hurt? A cross-sectional report

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[https://journals.lww.com/menopausejournal/Abstract/9000/Where\\_does\\_postmenopausal\\_dyspareunia\\_hurt\\_A.96805.aspx?fbclid=IwAR2CGIkBeJHXpnHDbeyjZL0sJ4UEfy0M6LVGtPSHpz-5LgfJNY8lz1ZqwtA#:~:text=Conclusions%3A,located%20at%20the%20vulvar%20vestibule](https://journals.lww.com/menopausejournal/Abstract/9000/Where_does_postmenopausal_dyspareunia_hurt_A.96805.aspx?fbclid=IwAR2CGIkBeJHXpnHDbeyjZL0sJ4UEfy0M6LVGtPSHpz-5LgfJNY8lz1ZqwtA#:~:text=Conclusions%3A,located%20at%20the%20vulvar%20vestibule)

**Objective:** A common symptom of genitourinary syndrome of menopause (GSM) is dyspareunia, attributed to vulvovaginal atrophy. Our objective was to systematically describe the pain characteristics and anatomic locations of tenderness in a cohort with moderate/severe dyspareunia likely due to GSM. **Methods:** This cross-sectional study reports the baseline data of postmenopausal women with dyspareunia screened for an intervention trial of topical estrogen. Postmenopausal women not using hormone therapy who had moderate or severe dyspareunia were eligible if estrogen was not contraindicated. Biopsychosocial assessments were performed using the Vulvar Pain Assessment Questionnaire, and participants underwent a systematic vulvovaginal examination that included a visual assessment and cotton swab testing for tenderness rated using the Numerical Rating Scale (0-10). Vaginal pH and mucosal sensitivity were assessed; pelvic floor muscles and pelvic viscera were palpated for tenderness. **Results:** Fifty-five eligible women were examined between July 2017 and August 2019. Mean age was  $59.5 \pm 6.8$  years, and duration of dyspareunia was  $6.2 \pm 4.3$  years. The mean intercourse pain score was  $7.3 \pm 1.8$ , most often described as "burning" and "raw." Ninety-eight percent had physical findings of vulvovaginal atrophy. Median pain scores from swab touch at the vulvar vestibule (just outside the hymen) were 4 to 5/10, and topical lidocaine extinguished pain. Median vaginal mucosal pain was zero. **Conclusions:** Participants described their pain as "burning" and "dry." Tenderness was most severe and most consistently located at the vulvar vestibule. Correlating the symptom of dyspareunia with genital examination findings may further our understanding of treatment outcomes for GSM.

## **A mucoadhesive biodissolvable thin film for localized and rapid delivery of lidocaine for the treatment of vestibulodynia**

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Vestibulodynia (VBD), an idiopathic pain disorder characterized by erythema and pain of the vulvar vestibule (the inner aspect of the labia minora and vaginal opening), is the most common cause of sexual pain for women of reproductive age. Women also feel discomfort with contact with clothing and tampon use. As most women with this disorder only have pain with provocation of the tissue, topical anesthetics applied to the vestibule are the current first line treatment for temporary pain relief. Treatment options are limited due to anatomical constraints of the vestibular region, poor drug retention time, imprecise dosing, leakage, and overall product messiness. In this study we report a novel approach to treatment of VBD using thin film designed to fit the vulvar vestibule and deliver lidocaine locally. Two use cases for VBD treatment were identified 1) rapid drug release (<5 min), for use prior to intercourse and 2) long-acting release ( $\geq 120$  min) for prolonged use and relief throughout the day. Cellulose-based mucoadhesive thin films were fabricated using a solvent casting method. Three polymers including hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), were selected owing to their biocompatibility and ideal properties for film casting. Films casted with HEC, HPC, and HPMC exhibited mucoadhesive properties relative to a control, with the highest mucoadhesive force recorded for films casted with HPC. Effect of media volume, pH, presence of mucin and presence of drug on film dissolution rates were investigated. Dissolution rates were independent of media volume, media pH or drug presence, whereas faster dissolution rates were obtained for all films in presence of mucin. In vitro lidocaine release kinetics were influenced by polymer type, percent drug loading and film casting thickness. Lidocaine release was based on a diffusion mechanism rather than through film dissolution and faster release ( $\sim 5$  min) was observed for HEC films compared HPC films ( $\sim 120$  min). Higher drug loading and film thickness resulted in slower and more prolonged release kinetics of lidocaine. All films were biocompatible and exhibited good mechanical properties. Two film formulations (9% w/w HPC with 12% w/w LHC, 5% w/w HEC with 6% w/w LHC) were optimized to meet the two use case scenarios for VBD treatment and moved into in vivo testing. In vivo testing demonstrated the safety of the films in BALB/c mice, and the pharmacokinetic analysis demonstrated the delivery of lidocaine primarily to the vaginal tissue. We demonstrate the ability to develop a mucoadhesive, biodissolvable thin film and fine-tune drug release kinetics to optimize local delivery of lidocaine to the vulva.

## **Clodronate Treatment Prevents Vaginal Hypersensitivity in a Mouse Model of Vestibulodynia**

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Front Cell Infect Microbiol. 2022 Jan 18;11:784972. doi: 10.3389/fcimb.2021.784972. eCollection 2021.

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**Introduction:** Improved understanding of vestibulodynia pathophysiology is required to develop appropriately targeted treatments. Established features include vulvovaginal hyperinnervation, increased nociceptive signalling and hypersensitivity. Emerging evidence indicates macrophage-neuron signalling contributes to chronic pain pathophysiology. Macrophages are broadly classified as M1 or M2,

demonstrating pro-nociceptive or anti-nociceptive effects respectively. This study investigates the impact of clodronate liposomes, a macrophage depleting agent, on nociceptive signalling in a mouse model of vestibulodynia. **Methods:** Microinjection of complete Freund's adjuvant (CFA) at the vaginal introitus induced mild chronic inflammation in C57Bl/6J mice. A subgroup was treated with the macrophage depleting agent clodronate. Control mice received saline. After 7 days, immunolabelling for PGP9.5, F4/80+CD11c+ and F4/80+CD206+ was used to compare innervation density and presence of M1 and M2 macrophages respectively in experimental groups. Nociceptive signalling evoked by vaginal distension was assessed using immunolabelling for phosphorylated MAP extracellular signal-related kinase (pERK) in spinal cord sections. Hyperalgesia was assessed by visceromotor response to graded vaginal distension. **Results:** CFA led to increased vaginal innervation ( $p < 0.05$ ), increased pERK-immunoreactive spinal cord dorsal horn neurons evoked by vaginal-distension ( $p < 0.01$ ) and enhanced visceromotor responses compared control mice ( $p < 0.01$ ). Clodronate did not reduce vaginal hyperinnervation but significantly reduced the abundance of M1 and M2 vaginal macrophages and restored vaginal nociceptive signalling and vaginal sensitivity to that of healthy control animals. **Conclusions:** We have developed a robust mouse model of vestibulodynia that demonstrates vaginal hyperinnervation, enhanced nociceptive signalling, hyperalgesia and allodynia. Macrophages contribute to hypersensitivity in this model. Macrophage-sensory neuron signalling pathways may present useful pathophysiological targets.

#### **[Multidisciplinary examination and treatment of vulvodynia]**

[Article in Danish]

Christina Damsted Petersen, Line Markdanner Lindgren

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Women suffering from chronic vulvar pain seek help in the healthcare system on numerous occasions. The most common type is provoked localized vulvodynia (PVD) in which the pain has been persistent for more than three months without identifiable cause. The aetiology of PVD is multifactorial and the diagnosis is based upon medical history and gynaecological assessment including a bio-psycho-social evaluation. Danish and international guidelines point to the advantages of a multidisciplinary approach, where physical, psycho-sexual assessment is integrated in a multidisciplinary treatment programme as summarized in this review.

#### **Sexual communication mediates cognitive-behavioral couple therapy outcomes: A randomized clinical trial for provoked vestibulodynia**

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<https://pubmed.ncbi.nlm.nih.gov/35191716/>

Provoked vestibulodynia (PVD) is a chronic vulvovaginal pain condition affecting 8%-10% of women and is associated with negative sexual sequelae. Our randomized clinical trial comparing cognitive-behavioral couple therapy (CBCT) to a medical intervention (lidocaine) found that both treatments improved affected women's pain and both affected women's and partners' sexual outcomes, with CBCT demonstrating more benefits (Bergeron et al., 2021). The goal of this study was to examine two putative mediators of CBCT's treatment effects: collaborative and negative sexual communication patterns

(SCPs). Women with PVD and their partners were randomly assigned to 12 weeks of CBCT ( $N = 53$ ) or lidocaine ( $N = 55$ ). Outcome measures (sexual satisfaction, function, and distress) were collected at pre-treatment, post-treatment, and 6-month follow-up, and in-treatment measures of the mediators were taken at Weeks 1, 4, 8, and 12 of treatment. Results showed that affected women's reports of improving collaborative communication mediated the effect of CBCT, but not lidocaine, on post-treatment sexual satisfaction (women with PVD and partners), sexual function (women with PVD), and sexual distress (women with PVD). For partners, collaborative communication improved equally in both treatments. Given that there were no differences in negative SCPs between the CBCT and lidocaine conditions, it was not possible to examine negative communication as a potential mediator. From the perspective of women with PVD, CBCT helped couples communicate about their sexual problems in more collaborative ways, which was in turn beneficial for improving the sexual well-being of both members of the couple.

## Co-morbid Disorders

### **The Vaginal Microbiome: III. The Vaginal Microbiome in Various Urogenital Disorders**

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J Low Genit Tract Dis. 2022 Jan 1;26(1):85-92. doi: 10.1097/LGT.0000000000000645.

<https://pubmed.ncbi.nlm.nih.gov/34928258/>

**Objective:** This series of articles, titled The Vaginal Microbiome (VMB), written on behalf of the International Society for the Study of Vulvovaginal Disease, aims to summarize the recent findings and understanding of the vaginal bacterial microbiota, mainly regarding areas relevant to clinicians specializing in vulvovaginal disorders. **Materials and methods:** A search of PubMed database was performed, using the search terms "vaginal microbiome" with "Candida," "vaginitis," "urinary microbiome," "recurrent urinary tract infections," "sexually transmitted infections," "human immunodeficiency virus," "human papillomavirus," "nonspecific vaginitis," "vulvodynia," and "vulvovaginal symptoms." Full article texts were reviewed. Reference lists were screened for additional articles. The third article in this series describes VMB in various urogenital disorders. **Results:** Variable patterns of the VMB are found in patients with vulvovaginal candidiasis, challenging the idea of a protective role of lactobacilli. Highly similar strains of health-associated commensal bacteria are shared in both the bladder and vagina of the same individual and may provide protection against urinary tract infections. Dysbiotic VMB increases the risk of urinary tract infection. Loss of vaginal lactic acid-producing bacteria combined with elevated pH, increase the risk for sexually transmitted infections, although the exact protective mechanisms of the VMB against sexually transmitted infections are still unknown. **Conclusions:** The VMB may constitute a biological barrier to pathogenic microorganisms. When the predominance of lactobacilli community is disrupted, there is an increased risk for the acquisition of various vaginal pathogens. Longitudinal studies are needed to describe the association between the host, bacterial, and fungal components of the VMB.

## **Pain-Related Worrying and Goal Preferences Determine Walking Persistence in Women with Fibromyalgia**

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<https://pubmed.ncbi.nlm.nih.gov/35162534/>

Physical activity and exercise are relevant behaviors for fibromyalgia health outcomes; however, patients have difficulties undertaking and maintaining an active lifestyle. With a cross-sectional design, this study explored the role of pain-related worrying and goal preferences in the walking persistence of women with fibromyalgia. The sample included 111 women who attended a tertiary health setting. We adapted the Six-Minute Walk Test where participants decided either to stop or continue walking in five voluntary 6 min bouts. Women who were categorized higher in pain-related worrying reported higher preference for pain avoidance goals ( $t = -2.44$ ,  $p = 0.02$ ) and performed worse in the walking task (LongRank = 4.21;  $p = 0.04$ ). Pain avoidance goal preference increased the likelihood of stopping after the first ( $OR = 1.443$ ), second ( $OR = 1.493$ ), and third ( $OR = 1.540$ ) 6 min walking bout, and the risk of ending the walking activity during the 30 min task ( $HR = 1.02$ , [1.0-1.03]). Influence of pain-related worrying on total walking distance was mediated by goal preferences ( $ab = -3.25$ ). In interventions targeting adherence in physical activity and exercise, special attention is needed for women who are particularly worried about pain to help decrease their preference for short-term pain avoidance goals relative to long-term goals such as being active through walking.

## **Extending the Common Sense Model to Explore the Impact of Visceral Sensitivity on Quality of Life in Inflammatory Bowel Disease**

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Turk J Gastroenterol. 2022 Feb 4. doi: 10.5152/tjg.2021.201158.

<https://pubmed.ncbi.nlm.nih.gov/35115287/>

**Background:** Inflammatory bowel disease is associated with poor quality of life. The aim of the cross-sectional study was to extend the common sense model to explore the impact of inflammatory bowel disease activity on quality of life and the potential mediating roles of illness perceptions, visceral sensitivity, coping styles, acceptance, and psychological distress. **Methods:** A total of 141 inflammatory bowel disease patients (86 with Crohn's disease and 55 with ulcerative colitis; 74 males, 65 females, and 2 gender non-specific, mean age 40.43 years) from 2 metropolitan hospital inflammatory bowel disease outpatient clinics participated. Measures included disease activity (Crohn's Disease Activity Index, Simple Clinical Colitis Activity Index), illness perceptions (Brief Illness Perceptions Questionnaire), visceral sensitivity (Visceral Sensitivity Index), coping styles (Brief Coping Operations Preference Enquiry), acceptance (Acceptance and Action Questionnaire-II), psychological distress (Depression, Anxiety, and Stress Scale), and European Health Interview Survey-Quality of Life (EUROHIS-QoL). **Results:** A structural equation model of the extended common sense model was found to have a good fit ( $\chi^2(10) = 10.07$ ,  $P = .43$ , root mean square error of approximation = 0.01, standardized root mean residual = 0.04, comparative index fit = 1.00, Tucker-Lewis index = 1.00, goodness-of-fit = 0.98). After controlling for irritable bowel syndrome diagnosis, the impact of disease activity on quality of life was statistically mediated by illness perceptions, maladaptive coping styles, and psychological distress. In addition, visceral sensitivity bordered on influencing the impact of disease activity and illness perceptions on quality of life through psychological distress. **Conclusions:** This study demonstrates that



together with illness perceptions and coping styles, visceral sensitivity plays an important role in an individual's adaption to living with inflammatory bowel disease.

### **Increased frequency of fibromyalgia among patients with chronic pain presenting to internal medicine clinics of a tertiary care hospital: A cross sectional study**

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J Pak Med Assoc. 2021 Dec;71(12):2740-2747. doi: 10.47391/JPMA.1682.

<https://pubmed.ncbi.nlm.nih.gov/35150531/>

**Objective:** To estimate fibromyalgia frequency among patients presenting with complaints of chronic fatigue and or generalised body pain for at least six weeks. **Methods:** The cross-sectional study was conducted at the Department of Internal Medicine, Indus Hospital, Karachi, between December 2016 and March 2018, and comprised patients of either gender presenting with complaints of chronic fatigue and or generalised body pain for at least six weeks. They were assessed for fibromyalgia according to the 2010 Fibromyalgia Diagnostic criteria questionnaire. The Data was analysed using SPSS 21. **Results:** Of the 267 patients, 197(73.8%) were females and 70(26.2%) were males. Fibromyalgia was detected in 149(55.80%) patients. The mean age of patients with fibromyalgia was 42.3±14.6 years and it was 38.9±13.7 years in patients without fibromyalgia ( $p < 0.05$ ). No significant association was found between gender and fibromyalgia ( $p > 0.05$ ). **Conclusions:** All patients with generalised pain should be evaluated for fibromyalgia and a diagnosis made to reduce the cost of further referrals and investigations, and delay in the management of this debilitating disorder.

### **Daily low dose of tadalafil improves pain and frequency in bladder pain syndrome/interstitial cystitis patients**

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Turk J Urol. 2022 Jan;48(1):82-87. doi: 10.5152/tud.2022.21292.

<https://pubmed.ncbi.nlm.nih.gov/35118993/>

**Objective:** Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic disease, with consequent high morbidity. Increasing evidence suggests that bladder afferent hyperexcitability, through neurogenic bladder inflammation and urothelial dysfunction, plays a key role in the pathophysiology of BPS/IC. The rationale of using phosphodiesterase type 5 inhibitors (PDE5i) would be to decrease bladder afferent hyperactivity. Detrusor relaxation, improvement of microcirculation, and a decrease in adrenergic nociceptive overactivity would be other effects in bladder tissue. We aimed to evaluate the efficacy, tolerability, and safety of a daily low dose of 5mg tadalafil in refractory BPS/IC patients. **Material and methods:** A total of 14 refractory BPS/IC female patients, previously evaluated with a physical examination, bladder diary, bladder-pain related visual analogue score, O'Leary-Sant Scores (OSS) for symptoms and problems, and quality of life (QoL) question from International Prostate Symptom Score, were treated with 5mg of tadalafil, for 3months. Re-evaluations occurred at 4 and 12weeks. Adverse events were assessed and recorded. **Results:** Urinary frequency, OSS, and QoL were significantly improved at 1-month follow-up (10.6 ± 2.5, 21.9 ± 4.1, and 4.6 ± 1.5, respectively,  $P < .05$ ). Pain intensity and volume voided were significantly improved at a 3-month follow-up (3.5 ± 2 and 266.7 ± 60.5,  $P < .05$ ). Patients referred to urinary frequency as the most important parameter improved at 4weeks, and pain at 3months. No differences between ulcerated and nonulcerated patients were observed. Two patients dropped out due to unsatisfactory results and two due to persistent headache and/or tachycardia, but both events were resolved after discontinuing the drug.

## Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review

Angela L Liang, Erin L Gingher, Jenell S Coleman

Obstet Gynecol. 2022 Feb 1;139(2):287-296. doi: 10.1097/AOG.0000000000004656.

<https://pubmed.ncbi.nlm.nih.gov/35104069/>

**Objective:** The endocannabinoid system is involved in pain perception and inflammation. Cannabis contains delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are cannabinoids that bind to endocannabinoid system receptors. A fatty acid amide called palmitoylethanolamide (PEA) enhances endogenous cannabinoids. Given that use of medical cannabis is increasing, we sought to characterize patterns of cannabis use for gynecologic pain and its effectiveness as an analgesic. **Data sources:** We searched PubMed, EMBASE, Scopus, Cochrane, and ClinicalTrials.gov using terms for "woman," "cannabis," and "pain" or "pelvic pain" or "endometriosis" or "bladder pain" or "cancer." The search was restricted to English-language articles published between January 1990 and April 2021 and excluded animal studies. **Methods of study selection:** The initial search yielded 5,189 articles with 3,822 unique citations. Studies were included if they evaluated nonpregnant adult women who used cannabinoids for gynecologic pain conditions (eg, chronic pelvic pain, vulvodynia, endometriosis, interstitial cystitis, malignancy). Study types included were randomized controlled trials (RCTs), cohort studies, and cross-sectional studies. Covidence systematic review software was used. **Tabulation, integration, and results:** Fifty-nine studies were considered for full review, and 16 met inclusion criteria. Prevalence of cannabis use ranged from 13% to 27%. Most women ingested or inhaled cannabis and used cannabis multiple times per week, with dosages of THC and CBD up to 70 mg and 2,000 mg, respectively. Sixty-one to 95.5% reported pain relief. All six prospective cohort studies and one RCT of PEA-combination medications reported significant pain relief, and the average decrease in pain after 3 months of treatment was  $3.35 \pm 1.39$  on the 10-point visual analog scale. However, one fatty acid amide enzyme inhibitor RCT did not show pain reduction. **Conclusion:** Survey data showed that most women reported that cannabis improved pain from numerous gynecologic conditions. Cohort studies and an RCT using PEA-combination medications reported pain reduction. However, interpretation of the studies is limited due to varying cannabis formulations, delivery methods, and dosages that preclude a definitive statement about cannabis for gynecologic pain relief.

## Miodesin™ Positively Modulates the Immune Response in Endometrial and Vaginal Cells

Carlos Rocha Oliveira, Hudson Polonini, Maria Cristina Marcucci, Rodolfo P Vieira

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Endometriosis presents high prevalence and its physiopathology involves hyperactivation of endometrial and vaginal cells, especially by bacteria. The disease has no cure and therapies aiming to inhibit its development are highly desirable. Therefore, this study investigated whether Miodesin™ (10 µg/mL = IC<sub>80</sub>; 200 µg/mL = IC<sub>50</sub>), a natural compound constituted by *Uncaria tomentosa*, *Endopleura uchi*, and astaxanthin, could exert anti-inflammatory and anti-proliferative effects against Lipopolysaccharides (LPS) stimulation in endometrial and *Candida albicans* vaginal cell lines. VK2 E6/E7 (vaginal) and KLE (epithelial) cell lines were stimulated with *Candida albicans* ( $1 \times 10^7$  to  $5 \times 10^7$ /mL) and LPS (1 µg/mL), respectively. Miodesin™ inhibited mRNA expression for Nuclear factor kappa B (NF-κB), ciclo-oxygenase 1 (COX-1), and phospholipase A2 (PLA2), beyond the C-C motif chemokine ligand 2 (CCL2), CCL3, and CCL5 in VK2 E6/E7 cells ( $p < 0.05$ ). In addition, the inhibitory effects of both doses of Miodesin™ (10 µg/mL and 200 µg/mL) resulted in reduced secretion of interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor α (TNF-α) (24 h, 48 h, and 72 h) and CCL2, CCL3, and CLL5 ( $p < 0.05$ ) by VK2 E6/E7 cells. In the

same way, COX-1 Miodesin™ inhibited LPS-induced hyperactivation of KLE cells, as demonstrated by reduced secretion of IL-1β, IL-6, IL-8, TNF-α (24 h, 48 h, and 72 h) and CCL2, CCL3, and CLL5 ( $p < 0.05$ ). Furthermore, Miodesin™ also inhibited mRNA expression and secretion of matrix metalloproteinase-2 (MMP-2), MMP-9, and vascular endothelial growth factor (VEGF), which are key regulators of invasion of endometrial cells. Thus, the study concludes that Miodesin™ presents beneficial effects in the context of endometriosis, positively affecting the inflammatory and proliferative response.

### **Association among Disorders of Gut-Brain Interaction (DGBI) and Fibromyalgia: A Prospective Study**

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The disorders of gut-brain interaction (DGBI) have been associated with Fibromyalgia (FM). However, there are no data about the relationship between FM and DGBI using Rome IV criteria. This study aimed to evaluate the prevalence of FM in patients with Irritable Bowel Syndrome (IBS) and/or Functional Dyspepsia (FD) and the prevalence of IBS and FD in FM patients using Rome IV criteria. DGBI patients and FM patients were recruited from two outpatient clinics devoted to DGBI and FM. All patients underwent a standardized gastrointestinal (GI) symptoms questionnaire. FM symptoms in DGBI patients were assessed through Fibromyalgia Rapid Screening Tool (FiRST) and Fibromyalgia Impact Questionnaire. Thereafter, the rheumatologists evaluated them. 49.0% of FM patients fulfilled the diagnostic criteria for IBS, 81.6% for FD with an overlap for both IBS/FD in 44.9%. IBS-C was the most prevalent IBS-subtype in DGBI patients, whereas IBS-M was the most prevalent in FM patients ( $p = 0.01$ ). 45.3% of DGBI patients reported pathological FiRST scores. DGBI patients with FM showed the highest score at the standardized GI questionnaire followed by FM patients with DGBI and DGBI without FM. In conclusion DGBI are common in FM patients and vice versa. The presence of FD is extremely frequent in FM patients. A multidisciplinary approach should be routinely used for the management of these patients.

### **Interactions between vulvovaginal disorders and urinary disorders: The case for an integrated view of the pelvis**

Gayle Fischer, Jennifer Bradford

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Lower urinary tract symptomatology is often difficult to categorize if history and investigation focus only on the urinary tract. Disease and dysfunction in organs more posteriorly can often cause or influence such bladder and urethral symptoms. Vulvovaginal skin diseases are an important but often missed influence on lower urinary tract symptomatology.

### **P048 Metastatic Crohn's Disease Debuting with Severe Oral Manifestation and Vulvar Involvement - A Diagnostic Challenge**

Viviana Parra Izquierdo, Juan Frias-Ordoñez, Consuelo Romero-Sanchez, Julio Alvarado, Cristian Florez  
Am J Gastroenterol . 2021 Dec 1;116(Suppl 1):S12. doi: 10.14309/01.ajg.0000798792.71403.36.

[https://www.researchgate.net/publication/356692387\\_P048\\_Metastatic\\_Crohn's\\_Disease\\_Debuting\\_w\\_ith\\_Severe\\_Oral\\_Manifestation\\_and\\_Vulvar\\_Involvement\\_-\\_A\\_Diagnostic\\_Challenge](https://www.researchgate.net/publication/356692387_P048_Metastatic_Crohn's_Disease_Debuting_w_ith_Severe_Oral_Manifestation_and_Vulvar_Involvement_-_A_Diagnostic_Challenge)

**Case:** Background: Metastatic Crohn's disease (MCD) is an unusual cutaneous manifestation in Crohn's disease (CD), and concomitant oral and vulvar involvement is even more unusual. It can debut with cavity lesions oral such as canker sores, ulcers, lip edema, granulomatosis, dry mouth, abscesses in the salivary ducts, erythema, gingivitis, glossitis, among others, however, simultaneous compromise with several oral lesions and so severe with loss of multiple pieces dental is very rare. **Case presentation:** Patient in the fourth decade of life with a family history of autoimmunity who debuts with severe oral manifestations with a requirement for extraction of 14 teeth, severe gingivitis, smooth tongue and glossitis, aphthous stomatitis, ulcers, lip edema and angular cheilitis, without clear cause, and in management by the oral pathology group. Associated with this, there was vulvo-perineal compromise with ulcerated, inflammatory, erythematous and infiltrated lesions. It was initially suspected of Behçet's disease, HLA B51 was performed, it was negative, also, negative pathergy test, and no other suggestive systemic findings. A vulvar biopsy was performed with marked edema of the dermis, dilated lymphatics with perivascular and interstitial lymphoplasmacytic infiltrate and noncaseating granulomas, negative for microorganisms. At this level, it was compatible with MCD, without presence of gastrointestinal symptoms and calprotectin levels in stool in normal range. High and low endoscopic studies and capsule endoscopy were performed in small intestine, without alterations, it was managed by dermatology with topical steroids and by dentistry with dental implants. It was considered patient with inflammatory bowel disease (IBD) type CD with severe extraintestinal manifestations (EIM), although it did not present compromise intestinal treatment, it was decided to start treatment with anti-TNF initially with adalimumab developing paradoxical psoriasis, later treatment with infliximab, again with presentation of severe paradoxical psoriasis, for which it was suspended. Cyclosporine was also used as an immunomodulator, presenting intolerable tachycardia. 18 months after these symptoms, she presented episcleritis of the left eye and begins with colicky abdominal pain and average diarrheal stools 5-a-day, it was performed high and low endoscopic studies without alterations and new capsule endoscopic of small intestine documenting Crohn's enteritis involving the duodenum, jejunum and ileum, considering a patient with IBD type CD, with EIM with vulvo-perineal compromise, severe oral involvement and episcleritis. Currently is under management with azathioprine and Ustekinumab, with clinical improvement significant. **Conclusions:** MCD represents a diagnostic challenge, it can debut without gastrointestinal involvement, and its clinical and histopathological findings simulate other entities. A timely diagnosis is required to seek early benefit in the patient.

### **The Link between Fibromyalgia Syndrome and Anger: A Systematic Review Revealing Research Gaps**

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Anger has been associated with increased pain perception, but its specific connection with Fibromyalgia Syndrome (FMS) has not yet been established in an integrated approach. Therefore, the present systematic review focuses on exploring this connection, and based on this connection, delimiting possible gaps in the research, altogether aimed at improving FMS clinical intervention and guiding future

research lines. Anger is considered a basic negative emotion that can be divided into two dimensions: anger-in (the tendency to repress anger when it is experienced) and anger-out (the leaning to express anger through verbal or physical means). The current systematic review was performed based on the guidelines of the PRISMA and Cochrane Collaborations. The Prospective Register of Systematic Reviews (PROSPERO) international database was forehand used to register the review protocol. The quality of chosen articles was assessed and the main limitations and research gaps resulting from each scientific article were discussed. The search included PubMed, Scopus, and Web of Science databases. The literature search identified 13 studies eligible for the systematic review. Levels of anger-in have been shown to be higher in FMS patients compared to healthy participants, as well as patients suffering from other pain conditions (e.g., rheumatoid arthritis). FMS patients had also showed higher levels of state and trait anxiety, worry and angry rumination than other chronic pain patients. Anger seems to amplify pain especially in women regardless FMS condition but with a particularly greater health-related quality of life's impact in FMS patients. In spite of the relevance of emotions in the treatment of chronic pain, including FMS, only two studies have proposed intervention programs focus on anger treatment. These two studies have observed a positive reduction in anger levels through mindfulness and a strength training program. In conclusion, anger might be a meaningful therapeutic target in the attenuation of pain sensitivity, and the improvement of the general treatment effects and health-related quality of life in FMS patients. More intervention programs directed to reduce anger and contribute to improve well-being in FMS patients are needed.

## Persistent Genital Arousal Disorder

### **Persistent Genital Arousal in Relationships: A Comparison of Relationship, Sexual, and Psychological Well-Being**

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<https://pubmed.ncbi.nlm.nih.gov/34903472/>

**Background:** Persistent Genital Arousal Disorder/Genitopelvic Dysesthesia (PGAD/GPD) is characterized by sensations of physiological genital sexual arousal (and/or other types of genitopelvic dysesthesia) that occur in the absence of subjective feelings of sexual desire. **Aims:** The aim of this study was to compare relationship, sexual, and psychological well-being in partnered individuals with and without distressing symptoms of PGAD/GPD. **Methods:** The sample (N = 65 individuals with vulvas and vaginas, N = 11 individuals with penises) of 152 partnered individuals (N = 76 with and 76 without PGAD/GPD symptoms) participated in a one-time anonymous online survey. **Outcomes:** The questionnaires assessed relationship satisfaction (Couple Satisfaction Index-Short Form, CSI); sexual satisfaction (Global Measure of Sexual Satisfaction, GMSEX); sexual functioning (Female Sexual Functioning Index, FSFI, or International Index of Erectile Functioning, IIEF); sexual distress (Sexual Distress Scale, SDS); and psychological well-being, as determined by the presence of depression and/or anxiety symptoms (Hospital Anxiety and Depression Scale, HADS). **Results:** Among individuals with vulvas and vaginas, those with PGAD/GPD symptoms reported significantly lower relationship and sexual satisfaction, greater sexual distress, and more symptoms of depression and anxiety than their counterparts in the control group. In addition, these individuals with PGAD/GPD symptoms also reported significantly worse sexual functioning (arousal, orgasm, satisfaction, and pain), and they were significantly more distressed about each aspect of their sexual functioning difficulties compared to those in the control group. Among the small sample of individuals with penises (N = 11), descriptive analyses revealed that total sexual

functioning scores did not differ across the PGAD/GPD symptom and control groups. In addition, 55.3% of the total sample with PGAD/GPD symptoms managed unwanted genital arousal by avoiding sex with their partner, while 64.5% managed their symptoms by having sex with their partner, and some individuals with PGAD/GPD used both strategies. **Clinical implications:** The finding that PGAD/GPD symptoms impact relationships indicates that treatment for PGAD/GPD should include consideration of the well-being of one's intimate relationship(s). **Strengths & limitations:** This study added to the small literature on experiences of PGAD/GPD in relationships, and it was the first to assess sexual satisfaction. Limitations include the small sample of individuals with penises, and the cross-sectional, correlational design, which does not allow for causal conclusions to be drawn. **Conclusion:** Results emphasize the importance of continued research of this population (and their partners) in order to improve diagnosis, intervention, and recognition within the medical community.

### **Persistent Genital Arousal Disorder (PGAD): A Clinical Review and Case Series in Support of Multidisciplinary Management**

Eric R Pease, Matthew Ziegelmann, Jennifer A Vencill, Susan N Kok, C Scott Collins, Hannah K Betcher  
Sex Med Rev. 2022 Jan;10(1):53-70. doi: 10.1016/j.sxmr.2021.05.001. Epub 2021 Aug 4.

<https://pubmed.ncbi.nlm.nih.gov/34362711/>

**Introduction:** Persistent genital arousal disorder (PGAD) is an uncommon condition resulting in intrusive, unwanted and distressing symptoms of genital arousal. Presentation can vary and most cases do not have an immediately identifiable etiology. **Objectives:** To present evaluation and treatment recommendations for PGAD from a multidisciplinary perspective and provide case examples.

**Methods:** A focused review of the literature on diagnosis, workup, and treatment of PGAD was completed. A case series of 3 varying presentations of PGAD is offered. **Results:** PGAD results in high levels of patient distress and is best managed with a multidisciplinary treatment approach. Identification and management of co-occurring symptoms or disease states is imperative, particularly psychologic and psychiatric comorbidities. With appropriate intervention, patients may achieve improvement of their physical symptoms and a decrease in associated psychological distress. **Conclusion:** PGAD is an uncommon and highly distressing condition that requires thoughtful evaluation for appropriate diagnosis and treatment. Multidisciplinary treatment approaches provide the best opportunity to address the needs of patients and optimizing treatment response.

## **Pudendal Neuralgia**

### **Pudendal Neuralgia: The Need for a Holistic Approach-Lessons From a Case Report**

Simon Gabriël Beerten, Rocco Salvatore Calabrò

Innov Clin Neurosci. Apr-Jun 2021;18(4-6):8-10.

<https://pubmed.ncbi.nlm.nih.gov/34980976/>

Pudendal neuralgia is a form of chronic pelvic pain, although the validity of this diagnosis has not been firmly established. It is characterized by unilateral pain in the pudendal nerve dermatome, mostly while sitting. In this case report, a 76-year-old female patient presented to her general practitioner with a 10-year history of unilateral buttock pain, which had been diagnosed as pudendal neuralgia. She tried various treatments and visited numerous specialists, but there was little improvement overall. Some medications seemed to have a positive effect, but pain ultimately persisted until psychological factors

were appropriately addressed. Management of pudendal neuralgia follows general chronic neuralgia principles, from medication over nerve block to definitive surgery. However, this case serves as a prime example of how the psychosocial approach is equally important. Given that psychological factors can make pain persist, it is imperative to properly address them. As pudendal neuralgia is uncommonly encountered in primary care, specific attention must be paid to psychological factors, which become significantly more important in long-standing chronic pelvic pain.

### **Overview of the anatomical basis of the piriformis syndrome-dissection with magnetic resonance correlation**

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Exp Ther Med. 2022 Feb;23(2):113. doi: 10.3892/etm.2021.11036. Epub 2021 Dec 3.  
<https://pubmed.ncbi.nlm.nih.gov/34970336/>

The piriformis syndrome is one of the most commonly misdiagnosed causes of lower back and gluteal pain caused by the compression of the sciatic nerve and the internal pudendal neurovascular bundle by the piriformis muscle. Although this syndrome was first suggested over 90 years ago, its diagnosis still represents a challenge for clinicians. In the present study, dissection was used to determine the intra- and extrapelvic anatomical course of the internal pudendal nerve and the data were compared with the information obtainable through MRI examination, in order to identify the piriformis syndrome and to differentiate it from other causes of internal pudendal neuralgia. Thorough dissections of the pelvis and deep gluteal region were conducted on female cadavers, which were correlated with MRI scans, in order to describe the course of the internal pudendal nerve in contact with the piriformis muscle. The dissection findings and MRI scans obtained allowed us to describe and demonstrate the compression points along the course of the sciatic nerve and the internal pudendal bundle, the anatomical correlations between the piriformis muscle and the nervous structures around it, emphasizing the areas most susceptible to possible nerve impingement syndromes. In the anatomic trajectory of the sciatic nerve and the internal pudendal bundle there are multiple contact points with anatomical structures that may lead to compression of the nerve structures, generating symptoms that comprise the piriformis syndrome. The present study sought to establish clear osseous landmarks that may help evaluate these associations and possible nerve compressions on pelvic MRI examination.

### **[Treatment of neuropathy of inferior gluteal and pudendal nerves following periarticular synovial cyst of the hip joint. A case report and literature review]**

[Article in Russian]

Zh Vopr Neurokhir Im N N Burdenko. 2021;85(4):64-68. doi: 10.17116/neiro20218504164.  
M Yu Kurnukhina, A A Gusev, F S Govenko, V Yu Cherebillo  
<https://pubmed.ncbi.nlm.nih.gov/34463452/>

The authors report a patient with neuropathy of inferior gluteal and pudendal nerves following periarticular synovial cyst of the hip joint. Effectiveness of treatment was analyzed. ENMG and MRI of pelvic soft tissues and hip joint were applied to confirm neuropathy of inferior gluteal and genital nerves. Periarticular synovial cyst of the hip joint followed by compression and ischemia of inferior gluteal and pudendal nerves was detected. In pre- and postoperative period, intensity of pain syndrome was assessed using visual-analogue scale. Neuropathic pain and quality of life were evaluated using the Leeds scale (LANSS) and NeuroQoL questionnaire, respectively. The patient underwent microsurgical

neurolysis and decompression of inferior gluteal and pudendal nerves and resection of periarticular synovial cyst of the hip joint. Complete regression of pain syndrome and improvement in quality of life were observed after surgery. Compression of neurovascular structures with periarticular hip cysts followed by clinical and neurological disorders is an indication for microsurgical neurolysis and resection of cyst.

### **Pudendal Nerve Entrapment Syndrome**

Jasmeen Kaur, Paramvir Singh

In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2021 Nov 14.

<https://pubmed.ncbi.nlm.nih.gov/31334992/>

Pudendal neuralgia caused by pudendal nerve entrapment (PNE) is a chronic and severely disabling neuropathic pain syndrome. It presents in the pudendal nerve region and affects both males and females. It is mostly underdiagnosed and inappropriately treated and causes significant impairment of quality of life.

Anatomy of the Pudendal Nerve:

The pudendal nerve emerges from the S2, S3, and S4 roots' ventral rami of the sacral plexus. It carries sensory, motor, and autonomic fibers; however, an injury to the pudendal nerve causes sensory deficits more than motor. It courses between two muscles, the piriformis and coccygeus muscles. It departs the pelvic cavity through the greater sciatic foramen ventral to the sacrotuberous ligament. It passes medial to and under the sacrospinous ligament at the ischial spine level to re-enter the pelvic cavity through a lesser sciatic foramen. The pudendal nerve then courses in the pudendal canal, which is also called the Alcock canal. The three last branches of the pudendal nerve terminate in the ischioanal fossa. These are the inferior rectal branch, perineal branch, and dorsal sensory nerve of the penis or clitoris. However, there are case reports which have shown variability in the anatomy of the pudendal nerve.

Pudendal nerve compression based on anatomy:

The pudendal nerve entrapment syndromes subdivide into four types based on the level of compression.

- Type I - Entrapment below the piriformis muscle as the pudendal nerve exits the greater sciatic notch.
- Type II - Entrapment between sacrospinous and sacrotuberous ligaments is the most common cause of nerve entrapment.
- Type III - Entrapment in the Alcock canal.
- Type IV - Entrapment of terminal branches.

## **Dermatological Conditions**

### **The efficacy of injecting hybrid cooperative complexes of hyaluronic acid for the treatment of vulvar lichen sclerosus: A preliminary study**

Marinella Tedesco, Valentina Garelli, Fulvia Elia, Francesca Sperati, Aldo Morrone, Emilia Migliano

<https://pubmed.ncbi.nlm.nih.gov/35094456/>

Lichen Sclerosus is a chronic-relapsing inflammatory skin disease usually involving the anogenital region lacking a resolute therapy. Potent to high-potent topical corticosteroids are considered to be the



standard first-line treatment. The objective of this preliminary study is to evaluate the efficacy of injecting Hybrid Cooperative Complexes of Hyaluronic Acid (HCC) in the treatment of Vulvar Lichen Sclerosus (VLS). Twenty-female patients (range 21-78 years) with histopathologic diagnosis of lichen sclerosus and good general conditions were enrolled. Patients underwent HCC infiltration every month, for three times. Patients had been assessed at baseline (T0) and after 1 and 6 months from treatment (T1 and T2, respectively). Clinical evaluation was executed in every visit. Itching, burning sensation, pain and dyspareunia were reported by a patient at T0, T1, and at T2. The effectiveness of the treatment on patients' quality life and sexual life was assessed using the Dermatology Life Quality Index (DLQI) at T0 and at T2. During or after the treatment no complications or side-effects were observed. All patients had a significant reduction in most symptoms after 1 and 6 months of HCC treatment. The reduction of patients with itching ( $p \leq 0.001$ ), pain ( $p = 0.031$ ), burning sensation ( $p = 0.004$ ) at 6 months is significant. The analysis of DLQI scores revealed a significant improvement in patients' quality of life. The DLQI mean score ( $\pm$ SD) at baseline and at follow-up was  $5.89 \pm 3.68$  and  $3.42 \pm 2.36$  ( $p = 0.002$ ), respectively. Our preliminary study has demonstrated the safety and tolerability of HCC infiltrations in patients with VLS, and the effectiveness of HCC in reducing symptoms and, thus, to improve patient Quality of Life.

### **[Established Genital and Extragenital Lichen Sclerosus:A Clinicopathological Analysis]**

[Article in Chinese]

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Zhongguo Yi Xue Ke Xue Yuan Xue Bao . 2021 Dec 30;43(6):849-855.

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<https://pubmed.ncbi.nlm.nih.gov/34980321/>

**Objective** To investigate the clinicopathological characteristics of established genital and extragenital lichen sclerosus(LS)and compare the differences between them. **Method** The clinicopathological data of 55 patients with established genital and extragenital LS diagnosed by pathological examination in the Department of Dermatology of Beijing Hospital were retrospectively analyzed. **Results** The 55 patients included 11 males and 44 females. Among them,38,15,and 2 patients had genital lesions, extragenital lesions, and both genital and extragenital lesions, respectively. Extragenital LS mainly involved the back(14.55%)and extremities(7.27%).Among the patients,28.30% were asymptomatic, and 73.58% and 24.53% felt itchy and painful, respectively. The asymptomatic patients had a higher proportion in extragenital cases( $\chi^2=31.224,P=0.000$ ),and the itchy symptom was more common in genital LS cases than in extragenital LS cases( $\chi^2=39.073,P=0.000$ ).Vulvar pain only appeared in the patients with genital LS.A total of 57 biopsy specimens from the 55 patients were reviewed, of which 40 were from genital lesions and 17 were from extragenital lesions. In addition to papillary dermal homogenization (100%),the common pathological changes include hyperkeratosis(98.25%),atrophy(50.88%),basal cell liquefaction degeneration (52.63%),dilated blood vessels(64.91%),a perivascular lymphocytic infiltrate(100%),histiocytic infiltrate(85.96%),and lichenoid inflammatory infiltrate(54.39%).Higher proportions of acanthosis ( $\chi^2=4.402,P=0.036$ ),dilated blood vessels ( $\chi^2=9.330,P=0.002$ ),and eosinophilic infiltrate ( $\chi^2=4.162,P=0.041$ ) were observed in genital LS cases. A higher proportion of follicular plugging appeared in extragenital LS cases ( $\chi^2=5.076,P=0.024$ ). **Conclusion** The established genital LS and extragenital LS showed some differences in clinical symptoms and pathological changes including acanthosis, dilated blood vessels, eosinophilic infiltrate, and follicular plugging.

## **The Effect of Lipofilling and Platelet-Rich Plasma on Patients with Moderate-Severe Vulvar Lichen Sclerosus who were Non-Responders to Topical Clobetasol Propionate: A Randomized Pilot Study**

P Gutierrez-Ontalvilla, F Giner, L Vidal, M Iborra

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<https://pubmed.ncbi.nlm.nih.gov/35048150/>

**Background:** The first-line treatment for vulvar lichen sclerosus (VLS) is 3 months of topical corticosteroid therapy. However, limited evidence is available concerning the use of fat grafting and platelet-rich plasma as a second-line treatment for patients who do not respond to first-line treatment.

**Methods:** This prospective single-center randomized pilot trial included 20 patients with a clinical and histological diagnosis of moderate to severe VLS. The patients in the treatment group (TG) received two infiltrations (at 3-month intervals) of nanofat mixed with platelet-rich plasma (PRP) into the vulvar area, while the control group (CG) received standard topical corticosteroid therapy. Fat was aspirated from the medial thigh or lower abdomen regions. Microfat was obtained after centrifugation and was emulsified to obtain a nanofat suspension. Treatment efficacy was determined by measuring changes in the vulvar skin elasticity, histopathology, and clinical signs, symptoms, and patient quality of life at after 1 year. **Results:** A total of 19 patients were finally assessed (9 TG and 10 CG). At the end of the study (1 year), there had been no significant improvement in vulvar skin elasticity. However, patients in the TG showed a significant improvement in their symptoms (itching, pain, burning, and dyspareunia) and clinical signs (cervical erosions, fissures, stenosis, and leukoderma). Analysis of skin biopsies revealed a significant decrease in all inflammatory cell types in the TG. No adverse events related to the autologous treatment were recorded. **Conclusions:** Compared with topical corticosteroids, two infiltrations delivered 3 months apart decreased the inflammation of the vulva and improved most of the clinical signs and symptoms associated with VLS. Nonetheless, no improvement in vulvar skin elasticity was derived from the autologous treatment.

## **Does compliance to topical corticosteroid therapy reduce the risk of development of permanent vulvar structural abnormalities in pediatric vulvar lichen sclerosus? A retrospective cohort study**

Ashod Kherlopian, Gayle Fischer

Pediatr Dermatol. 2022 Jan;39(1):22-30. doi: 10.1111/pde.14840. Epub 2021 Nov 4.

<https://pubmed.ncbi.nlm.nih.gov/34738263/>

**Background:** Vulvar lichen sclerosus (VLS) is a chronic inflammatory dermatosis of the genital skin, with up to 20% of cases in the pediatric age group. Limited data exist concerning the prognosis of pediatric VLS, particularly the likelihood of permanent architectural change and whether this can be prevented by compliance with topical corticosteroid treatment (TCS). **Objective:** To evaluate the extent to which compliance to TCS treatment influences the risk of developing vulvar structural abnormalities, including clitoral phimosis and diminutive or fused labia minora. **Methods:** A retrospective chart review of case records of pediatric-age females with VLS between January 31, 2004 and January 31, 2021. **Results:** One hundred eighteen cases of VLS were identified, with a mean age at diagnosis of 7.25 years and a mean follow-up period of 42.7 months. Thirty-four girls were "partially compliant," whereas 84 were "compliant." The risk ratio (RR) of developing any vulvar structural abnormality or clitoral phimosis was 5.76 (95% CI 2.96-11.3) and 21.2 (95%CI 5.23-85.9) times higher, respectively, in partially compliant compared with compliant subjects. The RR of a partially compliant female with pre-pubertal onset VLS having a vulvar structural abnormality persisting beyond menarche was increased 3.54-fold relative to compliant females (95% CI 1.75-7.17). **Limitations:** The retrospective nature of our data, lack of a control group, wide variability in follow-up duration, and nonstandardized method of stratifying compliance.

**Conclusion:** Vulvar structural abnormalities are common in prepubertal onset VLS. Compliance to TCS appears to be critical in the prognosis of pediatric VLS although attitudes underpinning noncompliance to TCS treatment require further elucidation.

### **Effects of Fractional CO<sub>2</sub> Laser Treatment on Patients Affected by Vulvar Lichen Sclerosus: A Prospective Study**

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**Background:** Fractional carbon dioxide (CO<sub>2</sub>) lasers are today considered the most effective and efficient treatment for many vulvovaginal disorders, providing mini-invasive procedures without side effects. Previous studies demonstrated the efficacy of fractional CO<sub>2</sub> lasers in vulvar lichen sclerosus (VLS), a chronic skin disorder characterized by itching and painful lesions. Complications include pain, sexual and/or urinary dysfunction, with a negative quality of life, and an increased risk of squamous cell carcinoma. A definitive VLS treatment is still lacking. **Objectives:** This is a prospective, single-center study aimed at evaluating the effect of fractional microablative CO<sub>2</sub> laser treatment on women affected by VLS. **Materials and methods:** Patients with histologically confirmed VLS underwent three fractional microablative CO<sub>2</sub> laser treatments, 4 weeks apart, on the genital affected areas. Clinical and VLS-related symptoms, side effects, and patient satisfaction index were assessed and recorded for all the patients using the visual analog scale (VAS). **Results:** Data from a total of 70 patients were included, paired at different time points and analyzed. VLS-related symptoms and other relevant parameters (pH, vaginal introitus discomfort, dyspareunia, vaginal dryness, itching, and burning) showed a statistically significant improvement ( $p < 0.001$ ) after the first laser treatment and kept improving after second and third sessions. According to VAS, the two most common symptoms, vaginal introitus discomfort and dyspareunia, went from (mean  $\pm$  standard deviation)  $8.2 \pm 2.3$  and  $8.3 \pm 2.2$ , respectively, at baseline, to  $3.6 \pm 2.6$  and  $3.8 \pm 2.6$ , respectively, 1 month after the last treatment. Vaginal dryness, itching, and burning were significantly improved as well. Most patients declared to be very satisfied with the results of the treatment. A total of 62.8% of the women expressed a satisfaction score  $\geq 8$  on a scale from 0 to 10. **Conclusions:** Fractional microablative CO<sub>2</sub> laser treatment seems to be safe and effective to treat VLS and improve VLS-related symptoms.

### **The SWIFT Model for Lichen Sclerosus Among Premenarchal Girls**

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**Objective/purpose:** Delay in diagnosis of childhood lichen sclerosus (LS) can be ameliorated with an efficient evaluation tool. We sought to create a useful prognostic tool for rapid and accurate risk stratification for LS in premenarchal girls. **Method:** We conducted a retrospective chart review at a single institution of premenarchal girls presenting with vulvovaginal complaints at a specialty pediatric and adolescent gynecology clinic at a major academic center. Sixty-nine patients seen between July 2019 and September 2020 were used as a pilot study to create a model for LS based on 18 signs and symptoms. Accuracy of the pilot model was confirmed in a larger data set (additional 105 patients, seen between January 2017 and December 2020), and model parameters were refined through cluster-based analytics. **Results:** Pilot study yielded 5 predictors for LS: soreness (S), whitening (W), urinary

incontinence (I), fissures (F), and thickening of the clitoral hood (T)-SWIFT. The final refined model is given as log odds (LS) =  $-7 + 3 \cdot S + 17 \cdot W + 3 \cdot I + 3 \cdot F + 18 \cdot T$ . This model yielded a >97% accuracy in predicting LS among 174 unique patients (LS prevalence = 18%). **Conclusions:** The SWIFT model accurately predicts clinical diagnosis of LS in premenarchal girls. Replication in other patient populations is highly encouraged. Awareness of LS is paramount, and an efficient, accurate evaluation tool will prove invaluable in assuring timely diagnosis and treatment for premenarchal patients.

### **Platelet-rich plasma for the treatment of lichen sclerosis**

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**Aim:** Evaluate the clinical effectiveness of platelet-rich plasma as a treatment for lichen sclerosis.

**Methods:** A systematic review was performed. The electronic databases PubMed, Ovid MEDLINE®, Web of Science, Cochrane, clinicaltrials.gov were used to identify case studies, case series, prospective uncontrolled, and randomized controlled studies published between 1946 and April 21, 2021. Six prospective uncontrolled studies, one randomized double-blind prospective study, and one case report were included. **Results:** Platelet-rich plasma treatment was subjectively reported to improve quality of life, but objective measures demonstrating treatment efficacy were not observed. In addition, platelet-rich plasma preparation and administration between studies lacked standardization.

**Conclusion:** Platelet-rich plasma may be used for symptomatic adjuvant treatment of lichen sclerosis, though additional double-blind controlled studies with standardized platelet-rich plasma protocols are needed to better characterize the efficacy of platelet-rich plasma.

### **Lymphocyte-Peppered Sclerotic Collagen: An Additional Histological Clue in Lichen Sclerosis, Morphea, and Systemic Sclerosis**

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Am J Dermatopathol. 2021 Dec 1;43(12):935-938. doi: 10.1097/DAD.0000000000002071.

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**Background:** "Line sign," "cookie cutter sign," "square biopsy sign," "high eccrine glands sign" have been previously described in morphea and lichen sclerosis. We found focal areas of thickened collagen bundles with lymphocytes interspersed between them in several biopsies of these conditions. **Materials and methods:** We reviewed slides of sclerosing disorders obtained from the archives of the pathology department in our hospital for the period 2013-2019. **Results:** A total of 73 slides including 40 of lichen sclerosis, 24 of morphea, 2 of lichen sclerosis-morphea overlap, and 7 of systemic sclerosis were evaluated. Lymphocytes were noted between sclerotic collagen bundles in 46 (63%) slides, being most common in lichen sclerosis (80%, 32/40) followed by morphea (50%, 12/24), whereas it was seen in one case each of lichen sclerosis with morphea overlap (50%, 1/2) and systemic sclerosis (14.3%, 1/7). The finding was noted in the upper dermis in 20 of 32 (62.5%) slides of lichen sclerosis and in both the superficial and deep dermis in 11 (91.7%) of 12 slides of morphea. **Conclusion:** Lymphocyte-peppered sclerotic collagen may be a useful histological clue to the diagnosis of lichen sclerosis, morphea, and systemic sclerosis.

## **Photodynamic Therapy in the Treatment of Vulvar Lichen Sclerosus: A Systematic Review of the Literature**

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J Clin Med. 2021 Nov 23;10(23):5491. doi: 10.3390/jcm10235491.

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Vulvar lichen sclerosus (VLS) is a chronic inflammatory disease involving the genital skin and mucous membrane. Patients exhibit focal atrophy and destructive scarring, with an increased risk of malignant transformation. Due to objective symptoms as well as subjective complaints, patients with VLS experience emotional distress, lowered mood, and sexual dysfunction, which is reflected in impaired health-related quality of life. Thus, the necessity of implementing appropriate therapy at the earliest possible stage of the disease in order to avoid serious complications is highlighted. We presented the systematic review of available literature, performed with MEDLINE, Cinahl, Central, Scopus, and Web of Science databases. We identified a total of twenty relevant studies which indicate that photodynamic therapy (PDT) is a valuable therapeutic modality in the treatment of VLS.

## **[The five more frequent inflammatory vulvar lesions]**

[Article in French]

F Plantier

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Lichen sclerosus, lichen planus, psoriasis and plasma cell vulvitis are the most common diagnosis amongst inflammatory vulval diseases, the most frequently suspected by the clinicians and the most frequently diagnosed by the pathologist. We expose their clinical and pathological aspects and detail the most recurrent diagnosis difficulties.

## **Meet the expert: Topical management of vulvar dermatoses**

Samantha H Jakuboski, Sarah J Noor

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Vulvar dermatoses are often debilitating chronic skin conditions associated with pain and pruritus. In oncologic patients, cancer treatments can precipitate and exacerbate vulvar dermatoses. Cytotoxic chemotherapy, hormonal therapies, and local pelvic radiation therapy can lead to vulvar symptoms, and cancer treatment-induced vulvar conditions include graft-versus-host-disease and radiation dermatitis. There have also been reports of lichen sclerosus development or exacerbation secondary to hormonal therapy and immune checkpoint inhibitors, attributed to proposed hormonal and immunologic pathogenesis of lichen sclerosus. Early recognition and treatment of these conditions can significantly improve quality of life. In this review, we summarize the clinical features and management characteristics of six types of common vulvar dermatoses that may present in the oncologic patient.

**Successful treatment of vulvovaginal lichen planus with tildrakizumab: A case series of 24 patients**

Ashod Kherlopian, Gayle Fischer

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Vulvovaginal lichen planus (VLP) is a chronic inflammatory dermatosis affecting the genital skin and mucosa that can have a profound negative impact on patient quality of life. Up to 43% of women with VLP require systemic immunosuppression to achieve disease remission, and some individuals prove to be highly treatment resistant. We present a case series of 24 women with severe VLP who successfully achieved remission using off-label treatment with the interleukin-23 (IL-23) monoclonal antibody blocker tildrakizumab, and highlight tildrakizumab as a treatment for women with recalcitrant VLP who have failed more conservative treatments.