

International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization for interstitial cystitis/bladder pain syndrome/hypersensitive bladder
www.painful-bladder.org

IPBF e-Newsletter and Research Update Issue 53, November 2019

An IPBF update, including Research Highlights, for patient support groups, healthcare professionals and friends around the world in the field of interstitial cystitis, bladder pain syndrome/painful bladder syndrome, hypersensitive bladder, Hunner lesion, ketamine cystitis, chronic pelvic pain and associated disorders.

This issue of the IPBF e-Newsletter includes the following topics:

- Upcoming meetings
- Meeting Reviews
- Calendar Overview
- Publications
- Research Update
- Donations & Sponsoring

UPCOMING MEETINGS

INTERNATIONAL SOCIETY FOR THE STUDY OF BPS/IC (ESSIC) ANNUAL SCIENTIFIC MEETING TO BE HELD IN AMSTERDAM 5-7 DECEMBER 2019

The 2019 annual meeting of ESSIC will be held 5-7 December in the heart of Amsterdam, The Netherlands, at the DoubleTree by Hilton Hotel (Oosterdoksstraat 4, 1011 DK Amsterdam), adjacent to Amsterdam Central Station with a direct rail link to Amsterdam's Schiphol Airport.

The theme running through this 2019 international meeting entirely devoted to IC/BPS will be the multidisciplinary approach to IC/BPS healthcare. Expert speakers will discuss state-of-the-art clinical diagnosis and treatment, including phenotyping and subtyping, to help clinicians achieve optimum treatment per patient and minimize the current trial and error situation. This not-to-be-missed meeting for anyone interested in improving clinical care for their IC/BPS patients will also include an update on the latest research developments and scientific evidence in this field, physical therapy, the role of the urology nurse, the complex problems of comorbidities and much more besides. This international conference gives you a chance to meet the experts. ESSIC 2019 is also a "must" for IC/BPS patient advocates who need to stay abreast of the latest developments and report back to their support group members.

Further information and preliminary programme can be found on the ESSIC congress website, [click here](#).

- PATIENT ADVOCACY NETWORKING MEETING TO BE HELD FOLLOWING ESSIC MEETING

The Dutch IC Patient Association (ICP) is taking this opportunity to host an informal lunch and networking event where patient advocates from different countries can connect and exchange information on supporting IC/BPS patients. This will take place on Saturday 7 December in the afternoon immediately following the ESSIC meeting. Dr Dick Janssen, meeting chair for this year's ESSIC annual meeting, has kindly agreed to chair this event for the ICP. After lunch, the programme will begin and each patient association will have the opportunity to provide a brief presentation about their own organization, highlighting their current challenges and presenting their most innovative projects. For further information, please contact [Mathilde Scholtes](#).

CONVERGENCES PP, 14-16 NOVEMBER 2019, MADRID, SPAIN.

Convergences in PelviPerineal Pain will be held this year in Madrid 14-16 November. This meeting will cover pelvic and perineal neuralgias including:

- Vulvar vestibulodynia
- Pelvipereineal pain after surgery for prolapse and incontinence
- New treatments in pelvipereineal pain

- Pain and Endometriosis

<http://www.convergencespp.com/wp-content/uploads/2019/09/CPGB2.pdf>
contact@convergencespp.com

9TH GLOBAL PATIENTS CONGRESS 2020 – SAVE THE DATE!

The International Alliance of Patients' Organizations (IAPO) has announced that IAPO's 9th Global Patients Congress will be held 16-18 April 2020 at the Surgeons Quarter in Edinburgh, Scotland. At the 2020 Global Patient Congress, members, patients and partners will share their experiences of working and promoting global health. Delegates will also have the opportunity to build their capacity through a string of talks, interactive discussions and expert workshops. More information can be found at: www.globalpatientscongress.org

MEETING REVIEWS

REVIEW OF THE INTERNATIONAL CONTINENCE SOCIETY (ICS) 49TH ANNUAL MEETING, 3-6 SEPTEMBER 2019, GOTHENBURG, SWEDEN

The 49th annual meeting of the [International Continence Society \(ICS\)](#) was held in Gothenburg, Sweden's second largest city, and the homebase of much research into Hunner lesion over a number of decades. This multidisciplinary conference was attended by 1,995 delegates including urologists, gynaecologists, neurologists, physiotherapists, nurses, basic scientists and patient advocates. In recent years, the ICS has developed an increasing interest in chronic pelvic pain, including IC/BPS, and now has a [School of Pelvic Pain](#), Director Kristene Whitmore MD, as part of the [ICS Institute](#) which is aimed at research and education. This is good news for the IC/BPS world which has tended to be rather side-lined in recent years by many urology societies.

This year's ICS conference programme included many podium presented research abstracts on IC/BPS, even prize-winners, along with several posters! Three workshops either focused on or included chronic pelvic pain and IC/BPS, while there was a one-hour Round Table Session on Hunner Lesion. All the sessions related to the field of IC/BPS were very well-attended. This is reassuring for the future.

Topics in our field discussed during the conference included: splitting off Hunner lesion from non-lesion at least for research and treatment purposes, phenotyping for better treatment, comorbidities, a multidisciplinary whole-body approach, the emotional and psychological impact of this bladder disease, the need for empathy and support, the continuing problems of non-reimbursement of treatments, while researchers and basic scientists showed that they are hard at work. A category prize was awarded to Jiang et al. from Taiwan for their abstract on potential urinary biomarkers to diagnose interstitial cystitis and overactive bladder. Wang *et al.*, also from Taiwan, received a category prize for their study on patients treated with repeat intravesical platelet rich plasma injections. [Read more....](#)

CALENDAR OVERVIEW

2019

CONVERGENCES pp

14-16 November 2019, Madrid, Spain.

contact@convergencespp.com

4TH ANNUAL MEETING OF THE SOCIETY FOR PELVIC RESEARCH (SPR 2019)

16/17 November 2019 Charleston, USA

www.pelvicresearch.com

ESSIC ANNUAL MEETING 2019

5-7 December, DoubleTree by Hilton Hotel, Amsterdam, The Netherlands

<https://www.essicmeeting.eu/>

2020

EAU 2020

20-24 March 2020, RAI Amsterdam, Europaplein 24, 1078 GZ Amsterdam, The Netherlands

<https://eaucongress.uroweb.org/eau20/>

9TH GLOBAL PATIENTS CONGRESS

16-18 April 2020

Surgeons Quarter, Edinburgh, Scotland.

www.globalpatientscongress.org

18TH WORLD CONGRESS ON PAIN

August 4-8, 2020, Amsterdam, The Netherlands

<https://www.iaspworldcongressonpain.org/amsterdam/>

50th INTERNATIONAL CONTINENCE SOCIETY ANNUAL MEETING 2020

26-29 August, Las Vegas, USA

<https://www.ics.org/2020>

GIBS 2020

Annual Congress on IC/BPS

5-6 September 2020, Mumbai India

PUBLICATIONS

11TH REVISION: WHO INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)

The International Classification of Diseases (ICD) is the international standard diagnostic tool for epidemiology, health management, research, and clinical purposes as well as the international standard for reporting diseases and health conditions. The inclusion of chronic pain conditions in ICD-11 will increase the recognition of chronic pain as a health problem in its own right and contribute to improved access to adequate pain treatment for patients with chronic pain worldwide. The Societal Impact of Pain (SIP) has provided a background briefing to explain the complexities of the proposals, including an ICD-11 flyer which can be downloaded at:

<https://www.sip-platform.eu/resources/details/do-you-want-to-know-more-about-the-icd-11>

The official ICD-11 website can be found at: <https://icd.who.int/en>

FURTHER EVIDENCE LINKING ORAL PENTOSAN POLYSULFATE SODIUM FOR IC/BPS TO VISION RISKS

In 1918, Dr Nieraj Jain reported that 6 patients who had been taking oral PPS for some 15 years had developed unusual changes in their macula. A new study (Prevalence of Maculopathy Associated with Pentosan Polysulfate Therapy in Kaiser Permanente Northern California), presented at the American Academy of Ophthalmology (AAO) 2019 Annual Meeting in San Francisco by Drs Vora, Patel and Melles, has uncovered additional evidence that the commonly prescribed oral bladder medication pentosan polysulfate sodium (PPS) is associated with a risk of maculopathy when taken long-term over many years. At the present time, it is suggested that annual screenings should be used to evaluate patients. Any patients who have signs of retinal damage following long-term exposure to oral PPS should consult their urologist.

In addition to the above presentation, a further study has now been published:

[PHENOTYPIC SPECTRUM OF PENTOSAN POLYSULFATE SODIUM-ASSOCIATED MACULOPATHY: A MULTICENTER STUDY.](#)

Hanif AM, Armenti ST, Taylor SC, Shah RA, Igelman AD, Jayasundera KT, Pennesi ME, Khurana RN, Foote JE, O'Keefe GA, Yang P, Hubbard GB 3rd, Hwang TS, Flaxel CJ, Stein JD, Yan J, Jain N. *JAMA Ophthalmol.* 2019 Sep 5. doi: 10.1001/jamaophthalmol.2019.3392. [Epub ahead of print] PMID: 31486843

Information about the macula:

<https://www.aao.org/eye-health/anatomy/macula-6>,

https://en.wikipedia.org/wiki/Macula_of_retina

REMINDER: A SELECTION OF ARTICLES AND EDITORIALS FROM THE 4TH INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS, 2018 JAPAN (ICICJ)

International Journal of Urology: Volume 26, Issue S1, Pages: I-iv, 1-88, June 2019 - Open Access

This is a Special [Open Access](#) Issue of the International Journal of Urology with a selection of articles and editorials from the 4th International Consultation on Interstitial Cystitis, Japan (ICICJ) and the Annual Meeting of the Society of Interstitial Cystitis of Japan (SICJ), held 17–18 April 2018, Kyoto International Conference Center, Kyoto, Japan.

To view all articles and editorial comments in full, go to:

<https://onlinelibrary.wiley.com/toc/14422042/2019/26/S1>

Or click here: [View all articles](#)

RESEARCH UPDATE

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS, BLADDER PAIN SYNDROME, HUNNER LESION, HYPERSENSITIVE BLADDER, CHRONIC (PELVIC) PAIN, ASSOCIATED DISORDERS AND KETAMINE CYSTITIS.

Most of these have a direct link to the PubMed abstract if you click on the title. An increasing number of scientific articles “In Press” or “Early View” are being published early online (on the Journal website) as “Epub ahead of print” sometimes long before they are published in the journals. While abstracts are usually available on PubMed, the pre-publication articles can only be read online if you have online access to that specific journal. However, in some cases there may be free access to the full article online. Click on the title to go to the PubMed abstract or to the full article in the case of free access.

Terminology: different published articles use different terminology, for example: interstitial cystitis, painful bladder syndrome, bladder pain syndrome, hypersensitive bladder, chronic pelvic pain (syndrome) or combinations of these. Hunner’s ulcer, Hunner lesion, Hunner IC and Classic IC are synonymous. When reviewing the article, we generally use the terminology used by the authors.

NEWS FROM THE NIH MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP) RESEARCH NETWORK

(If you would like to know more about the MAPP Research Network and its work, [click here](#) to go to the home page.)

CHANGES IN WHOLE BODY PAIN INTENSITY AND WIDESPREADNESS DURING UROLOGIC CHRONIC PELVIC PAIN SYNDROME FLARES-FINDINGS FROM ONE SITE OF THE MAPP STUDY.

Xu T, Lai HH, Pakpahan R, Vetter J, Andriole GL, Bradley C, Naliboff BD, Colditz GA, Sutcliffe S. *Neurourol Urodyn.* 2019 Nov;38(8):2333-2350. doi: 10.1002/nau.24150. Epub 2019 Sep 4. PMID: 31483064.

The purpose of this MAPP study from the USA was to investigate changes in whole body pain during urologic chronic pelvic pain syndrome (UCPPS) flares. UCPPS participants at one site of the multidisciplinary approach to the study of chronic pelvic pain research network reported their daily flare status and pain levels in 7 pelvic/genital and 42 extrapelvic body areas (scale = 0-10) for 10 days at baseline and during their first flare. Linear mixed models and conditional logistic regression were used to investigate symptom changes during flares. Analyses were stratified by chronic overlapping pain condition (COPC) status. Fifty-five out of 60 participants completed the study, 27 of whom provided information on both nonflare and flare days. Pelvic/genital pain intensity and widespreadness increased significantly during flares for all participants, whereas extrapelvic pain intensity increased significantly only among participants with COPCs. Pelvic/genital and extrapelvic pain also varied on nonflare days but symptom fluctuations were generally ≤ 1 point. Increases of ≥ 2 points in pelvic/genital pain intensity (odds ratio and ≥ 1 point in urination-related pain were independently associated with flare onset for all participants. The authors conclude that their observations of extrapelvic pain increases during flares for patients with COPCs and their independent associations between pelvic/genital/urination-related pain intensity and flare onset may provide insight into mechanisms underlying flare development (eg common biologic pathways between UCPPS phenotypes and flares), flare management (eg local vs systemic therapies by COPC status), and patient flare definitions.

A MAPP NETWORK CASE-CONTROL STUDY OF UROLOGIC CHRONIC PELVIC PAIN COMPARED WITH NON-UROLOGIC PAIN CONDITIONS.

Afari N, Buchwald D, Clauw D, Hong B, Hou X, Krieger JN, Mullins C, Stephens-Shields AJ, Gasperi M, Williams DA; MAPP Research Network. *Clin J Pain.* 2019 Sep 26. doi: 10.1097/AJP.0000000000000769. [Epub ahead of print] PMID: 31567428.

Limited research suggests commonalities between urologic chronic pelvic pain syndromes (UCPPS) and other non-urologic chronic overlapping pain conditions (COPCs) including fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. The goal of this MAPP case-control study was to examine similarities and differences between UCPPS and these other COPCs. As part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network, the authors examined 1,039 individuals with UCPPS (n=424), non-urologic COPCs (n=200), and healthy controls (n=415). Validated standardized measures were used to assess urological symptoms, non-urological pain symptoms, and psychosocial symptoms and traits. Participants with UCPPS had more urologic symptoms than non-urologic COPCs or healthy controls; non-urological COPC group also had significantly worse urological symptoms than healthy controls. Participants with non-urological COPCs reported

more widespread pain than those with UCPPS, yet both groups had similarly increased symptoms of anxiety, depression, negative affect, perceived stress, neuroticism, and lower levels of extraversion than healthy controls. Participants with UCPPS with and without COPCs reported more catastrophizing than those with non-urological COPCs. Findings are consistent with the hypothesis of common underlying biopsychosocial mechanisms and can guide the comprehensive assessment and treatment of these conditions regardless of the primary site of pain or diagnosis. Heightened catastrophizing in UCPPS should be examined to inform psychosocial interventions and improve patient care.

HUNNER LESION DISEASE

ADVANCED MANAGEMENT OF PATIENTS WITH ULCERATIVE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Crescenze IM, Gupta 2, Adams G, Oldendorf A, Stoffel JT, Romo PGB, Clemens JQ, Cameron AP.

Urology. 2019 Aug 20. pii: S0090-4295(19)30723-X. doi: 10.1016/j.urology.2019.07.036. [Epub ahead of print] PMID: 31442473

The purpose of this paper from Michigan, was to describe a stepwise management of patients with interstitial cystitis/bladder pain syndrome (IC/BPS) with Hunner lesions and present single institution long-term outcomes. This is a retrospective review of a single tertiary center experience with management of patients with Hunner lesions from January 2005 to January of 2015. Patients who met the diagnostic criteria for IC/BPS were included. Systematic approach to treatment of patients with Hunner lesions is proposed based on their results. Fifty-five patients with IC/BPS and Hunner lesions were included. Mean age was 65.0+/-12.7 years, 76.4%(42/55) were female, and median symptom duration was 2 years (IQR1,7). All patients had a biopsy to rule out malignancy with therapeutic fulguration which resulted in subjective symptom improvement in 81.8%(45/55) and median time to repeat procedures was 12 months (IQR6,21). Triamcinolone injection into the lesion was done in 35 patients and 91.4%(32/35) reported subjective improvement. Repeat injections were done for 74%(26/35) and median time between injections was 8 months (IQR 4, 13). AUA symptom scores and quality of life improved significantly with both treatment modalities. Adjunctive treatment with cyclosporine was used in 47.2%(26/55), and 7.2%(4/55) went on to have a cystectomy. The authors found that patients with Hunner lesions benefit from early progression from conservative treatments to endoscopic management. Excellent symptom control can be achieved with biopsy/fulguration and triamcinolone injections but recurrence is common and repeat treatments are needed for most patients.

LONG NONCODING RNA (MEG3) IN URINAL EXOSOMES FUNCTIONS AS A BIOMARKER FOR THE DIAGNOSIS OF HUNNER-TYPE INTERSTITIAL CYSTITIS (HIC).

Liu F, Chen Y, Liu R, Chen B, Liu C, Xing J. J Cell Biochem. 2019 Oct 8. doi: 10.1002/jcb.29356. [Epub ahead of print] PMID: 31595563

Toll-like receptor-7 (TLR7) is functionally involved in the pathogenesis of Hunner-type interstitial cystitis (HIC). In addition, maternally expressed gene 3 (MEG3) is implicated in many urethral diseases. In this study, Liu and colleagues from China aimed to verify the hypothesis that exosomal MEG3 in urine can be used as a novel diagnostic biomarker for HIC. Electron microscopy was utilized to observe the distribution of urinary exosomes between the case group and the control group. Receiver operating characteristic analysis was utilized to compare the diagnostic values of MEG3 and miR-19a-3p. Computational analysis and luciferase assay were conducted to identify the correlation between MEG3 and miR-19a-3p as well as between TLR7 and miR-19a-3p. In addition, real-time polymerase chain reaction and Western blot were performed to establish the signalling pathways implicated in the pathogenesis of HIC. When age and gender distributions are excluded, urinary exosomes were equally distributed between case and control groups. The area under the curve of MEG3 was larger than that of miR-19a-3p, indicating that MEG3 has a better value in the diagnosis of HIC. In addition, patients with HIC showed elevated MEG3 expression and inhibited miR-19a-3p expression, thus establishing a negative correlation between MEG3 and miR-19a-3p. MEG3 and TLR7 were both identified as targets of miR-19a-3p, establishing a MEG3/miR-19a-3p/TLR7 signalling pathway, in which MEG3 enhances the expression of TLR7 via inhibiting the expression of miR-19a-3p. The authors report that MEG3 level was upregulated in patients with HIC. In addition, MEG3 downregulated miR-19a-3p expression while upregulating TLR7 expression. Furthermore, MEG3 contributes to the pathogenesis of HIC. Therefore, exosomal MEG3 in urine can be used as a biomarker for HIC diagnosis.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

DEVELOPMENT OF A PHOTOGRAPHIC HANDBOOK TO IMPROVE CYSTOSCOPY FINDINGS DURING RESIDENT'S TRAINING: A RANDOMISED PROSPECTIVE STUDY.

Mantica G, Balzarini F, Dotta F, Rodriguez-Socarras M, Proietti S, Giusti G, Oneto F, Di Pierro M, Traverso P, Terrone C. Arab J Urol. 2019 Apr 24;17(3):243-248. doi: 10.1080/2090598X.2019.1596400. eCollection 2019. PMID: 31489242.

The purpose of this study from Italy was to evaluate if the use of a photographic handbook (PH) can be a useful tool to improve the detection of disorders during cystoscopy training, as several hands-on tools have been proposed to improve technical skills but very few aim to improve specificity and sensitivity. Eight junior residents (JRs) were divided into two groups: Group A, comprised four JRs with previous limited experience of performing cystoscopies; and Group B, including four inexperienced JRs who were asked to study a specific PH before performing cystoscopies. The findings of the two groups were compared using the chi-squared test. A total of 401 consecutive cystoscopies, of which 214 (53.4%) were performed by Group A and 187 (46.6%) by Group B, were considered. Group B showed superior ability in detecting uncommon findings (i.e., carcinoma in situ, bullous oedema, interstitial cystitis, etc.) with 24/46 (52.2%) detected vs eight of 32 (25%) in Group A (P = 0.016). The PH was a useful tool for improving identification of pathological conditions, which could be used to enhance hands-on simulator and practical tutored training.

PHENOTYPIC SPECTRUM OF PENTOSAN POLYSULFATE SODIUM-ASSOCIATED MACULOPATHY: A MULTICENTER STUDY.

Hanif AM, Armenti ST, Taylor SC, Shah RA, Igelman AD, Jayasundera KT, Pennesi ME, Khurana RN, Foote JE, O'Keefe GA, Yang P, Hubbard GB 3rd, Hwang TS, Flaxel CJ, Stein JD, Yan J, Jain N. JAMA Ophthalmol. 2019 Sep 5. doi: 10.1001/jamaophthalmol.2019.3392. [Epub ahead of print] PMID: 31486843

A unique pigmentary maculopathy was recently described in 6 patients with long-term exposure to pentosan polysulfate sodium (PPS), a long-standing oral therapy for interstitial cystitis. This study aimed to characterize the exposure characteristics and clinical manifestations of PPS-associated maculopathy. In this multi-institutional case series, medical records of patients who exhibited the characteristic maculopathy in the setting of prior PPS exposure were retrospectively reviewed. Data were collected from August 1, 2012, to October 1, 2018, and data were analyzed from October 2018 to January 2019. Of the 35 included patients (70 eyes), 34 (97%) were female, and the median (range) age was 60 (37-79) years. The median (range) duration of PPS intake was 15 (3-22) years, and the median (range) cumulative exposure was 1.61 (0.44-4.31) kg. The leading visual symptoms were metamorphopsia, blurred vision, and prolonged dark adaptation. Median (range) logMAR visual acuity of all eyes was 0.10 (-0.12 to 1.18). Fundus examination often revealed hyperpigmented macular spots (34 of 64 eyes [53%]) with interspersed pale-yellow deposits, although less commonly in eyes that exhibited retinal pigment epithelial atrophy (6 of 26 eyes [23%]; P < .001). Optical coherence tomography showed foci of retinal pigment epithelium elevation or thickening associated with hyperreflectance on near-infrared reflectance imaging. Fundus autofluorescence imaging typically revealed a symmetric, confluent pattern of hyperautofluorescent and hypoautofluorescent spots that involved the fovea in all eyes and extended to the retinal periphery in 24 eyes (36%). Longitudinal evaluation demonstrated dynamic changes in pigmentary abnormalities. These findings suggest that PPS-associated maculopathy is a vision-threatening condition that can manifest in the setting of long-term exposure to the drug. Multimodal imaging posits a distinctive clinical phenotype, characterized in this cohort by dynamic alterations within the retinal pigment epithelium and at the retinal pigment epithelium-photoreceptor interface. Ongoing work might explore causality and direct screening guidelines.

SEROTONIN EXERTS A DIRECT MODULATORY ROLE ON BLADDER AFFERENT FIRING IN MICE.

Konthapakdee N, Grundy L, O'Donnell T, Garcia-Caraballo S, Brierley SM, Grundy D, Daly DM. J Physiol. 2019 Nov;597(21):5247-5264. doi: 10.1111/JP278751. Epub 2019 Oct 13. PMID: 31520534.

Functional disorders (i.e. interstitial cystitis/painful bladder syndrome and irritable bowel syndrome) are associated with hyperexcitability of afferent nerves innervating the urinary tract and the bowel, respectively. Various non-5-HT₃ receptor mRNA transcripts are expressed in mouse urothelium and exert functional responses to 5-HT. Whilst 5-HT₃ receptors were not detected in mouse urothelium, 5-HT₃ receptors expressed on bladder sensory neurons plays a role in bladder afferent excitability both under normal conditions and in a mouse model of chronic visceral hypersensitivity. These data suggest that the role 5-HT₃ receptors play in bladder afferent signalling warrants further study as a potential therapeutic target for functional bladder disorders. Serotonin (5-HT) is an excitatory mediator that in the gastrointestinal (GI) tract plays a physiological

role in gut-brain signalling and is dysregulated in functional GI disorders such as irritable bowel syndrome (IBS). Patients suffering from IBS frequently suffer from urological symptoms characteristic of interstitial cystitis/painful bladder syndrome, which manifests due to cross-sensitization of shared innervation pathways between the bladder and colon. However, a direct modulatory role of 5-HT in bladder afferent signalling and its role in colon-bladder neuronal crosstalk remain elusive. The aim of this study from Thailand, Australia and the UK was to investigate the action of 5-HT on bladder afferent signalling in normal mice and mice with chronic visceral hypersensitivity (CVH) following trinitrobenzenesulfonic acid-induced colitis. Bladder afferent activity was recorded directly using ex vivo afferent nerve recordings. Expression of 14 5-HT receptor subtypes, the serotonin transporter (SERT) and 5-HT-producing enzymes was determined in the urothelium using RT-PCR. Retrograde labelling of bladder-projecting dorsal root ganglion neurons was used to investigate expression of 5-HT₃ receptors using single cell RT-PCR, while sensory neuronal and urothelial responses to 5-HT were determined by live cell calcium imaging. 5-HT elicited bladder afferent firing predominantly via 5-HT₃ receptors expressed on afferent terminals. CVH animals showed a downregulation of SERT mRNA expression in urothelium, suggesting increased 5-HT bioavailability. Granisetron, a 5-HT₃ antagonist, reversed bladder afferent hypersensitivity in CVH mice. These data suggest 5-HT exerts a direct effect on bladder afferents to enhance signalling. 5-HT₃ antagonists could therefore be a potential therapeutic target to treat functional bladder and bowel disorders.

PERSONAL CELL THERAPY FOR INTERSTITIAL CYSTITIS WITH AUTOLOGOUS STROMAL VASCULAR FRACTION STEM CELLS.

Lander EB, Berman MH, See JR. *Ther Adv Urol.* 2019 Aug 17;11:1756287219868590. doi: 10.1177/1756287219868590. eCollection 2019 Jan-Dec. PMID: 31452686

The objective of this study from the USA was to evaluate whether autologous stem-cell-based therapy may mitigate the symptoms of interstitial cystitis. Stromal vascular fraction (SVF) rich in stem cells and derived from autologous adipose tissue was deployed into 109 men and women with interstitial cystitis/painful bladder syndrome as a surgical procedure. This stem-cell-rich biologic product was injected both systemically and regionally into pelvic floor targets. Patients were queried about quality of life and symptom and bother subjective outcomes tests every 3 months for 2 years. A total of 78 patients reported a positive response at 1 year. Symptom and bother metrics were statistically improved at 1 year. There were minimal adverse events associated with the harvesting, procurement, and clinical deployment of SVF. Interstitial cystitis is a complex clinical problem that is known for its resistance to conventional therapies. SVF as an autologous personalized regenerative strategy shows good safety and efficacy and may potentially have a role in the mitigation of interstitial cystitis.

DEPRESSION AND HELPLESSNESS IMPACT INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PAIN OVER TIME.

Crawford A, Tripp DA, Nickel JC, Carr L, Moldwin R, Katz L, Muere A. *Can Urol Assoc J.* 2019 Oct;13(10):328-333. doi: 10.5489/cuaj.5703. PMID: 31364973

[Free full article, click on title.](#)

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a devastating urological chronic pelvic pain condition with an unknown etiology. Evidence-based psychological strategies are becoming more successful for symptom management as we learn more about the targets for intervention. Previous research has established an indirect relationship between depression and pain through catastrophizing, but there have yet to be studies examining the emerging role of emotion regulation in this relationship. Women with IC/BPS were recruited from tertiary care clinics in Canada and the U.S. between 2013 and 2018. Patients completed questionnaires, including demographics and scores for pain, depression, catastrophizing, and difficulties in emotion regulation at baseline, six months, and one year. Serial mediation was used to test models of pain, catastrophizing, and depression. A total of 135 women with IC/BPS completed all three time points. The only significant indirect path was from baseline depression to catastrophizing at six months to pain at one year ($b=0.10$; confidence interval. A follow-up analysis demonstrated that helplessness was the key factor of catastrophizing driving this relationship. Reducing feelings of helplessness and increasing patient feelings of control are important ways to limit the effect of low mood on patient pain experience. De-catastrophizing interventions should be part of the referral strategy for IC/BPS symptom management.

CHRONIC SCROTAL PAIN: A VARIABLE SYMPTOM OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Bosch PC, Parsons CL. *Urol Ann.* 2019 Jul-Sep;11(3):261-264. Doi: 10.4103/UA.UA_161_17. PMID: 31413503

Treatment of chronic idiopathic scrotal pain is a dilemma and challenge. Many men with this condition undergo multiple therapies and surgeries with no improvement in their symptoms. Patients with interstitial cystitis/bladder pain syndrome (IC/BPS) have a variable clinical presentation and initially complain of only one symptom of urinary urgency, frequency, or pain. Bosch and Parsons report on patients with chronic idiopathic scrotal pain treated with standard therapy for IC/BPS. Patients with chronic idiopathic scrotal content pain were evaluated, determined to have chronic idiopathic scrotal content pain, and were treated with either pentosan polysulfate sodium (PPS) or bladder instillations of alkalized lidocaine and heparin. Sixteen males were determined to have chronic idiopathic scrotal pain. Eight males received PPS and eight males received a bladder instillation of alkalized lidocaine and heparin. All patients had improvement of their scrotal pain to a self-reported acceptable level. Chronic idiopathic scrotal pain may be one of the variable presenting symptoms of IC/BPS. This scrotal pain may actually be referred pain from the bladder. Standard therapies for IC/BPS may be a treatment option for chronic idiopathic scrotal pain.

BIOINFORMATICS ANALYSIS OF THE HUB GENES AND KEY PATHWAYS OF INTERSTITIAL CYSTITIS PATHOGENESIS.

Liu J, Zhang Y, Li S, Sun F, Wang G, Wei D, Yang T, Gu S. Neurourol Urodyn. 2019 Oct 29. doi: 10.1002/nau.24196. [Epub ahead of print] PMID: 31663162

This study from China aimed to identify suitable datasets for reanalysis and then explore potential key genes and related pathways of interstitial cystitis (IC). Liu and colleagues searched the Gene Expression Omnibus database and three expression profile datasets and included 23 lesions of IC and 9 normal tissues in the analysis. Eight urine specimens of patients with IC and five urine specimens of healthy controls were also included. Then, these datasets were reanalyzed to determine the differentially expressed genes (DEGs), which were used to perform Gene Ontology and pathway enrichment analyses. These identified candidate genes were also applied to generate a protein-protein interaction (PPI) network. Forty-two common DEGs were sorted and identified from two datasets, both of which included the samples of bladder lesions. Based on their functions and signalling pathways, these 42 DEGs are mainly classified as cell-surface proteins and are involved in the immune and inflammatory responses. The PPI network included 41 nodes. In this network, the authors identified 11 genes as central nodes that are involved in the immune system and the inflammatory response. Furthermore, IC with Hunner lesions shared the same DEGs with IC without Hunner lesions. In both subgroups (IC with and without Hunner lesions), they identified some common DEGs shared between bladder lesions and urine samples. Using bioinformatics, they integrated different IC-related datasets and identified potential critical genes involved in IC that may contribute to future research on IC.

MONOACYLGLYCEROL LIPASE INHIBITION AS POTENTIAL TREATMENT FOR INTERSTITIAL CYSTITIS.

Chinnadurai A, Berger G, Burkovskiy I, Zhou J, Cox A4Lynch M, Lehmann C. Med Hypotheses. 2019 Oct;131:109321. doi: 10.1016/j.mehy.2019.109321. Epub 2019 Jul 20. PMID: 31443753

Interstitial cystitis is a chronic inflammatory condition of the urinary bladder with an unclear etiology. Currently, there are no widely accepted long-term treatment options available for patients with IC, with the European Association of Urology (EAU, 2017 guidelines), American Urology Association (AUA, 2014 guidelines), and the Royal College of Obstetricians and Gynaecologists (RCOG, 2016 guidelines) all suggesting various different conservative, pharmacological, intravesical, and surgical interventions. The endocannabinoid system represents a potential target for IC treatment and management. Activation of cannabinoid receptor 2 (CBR2) with various agonists has previously been shown to reduce leukocyte differentiation and migration, in addition to inhibiting the release of pro-inflammatory cytokines at the site of inflammation. These receptors have been identified in the detrusor and sensory nerves of the urothelium in various mammalian species, including humans. The authors from Canada hypothesize that by inhibiting the enzymes responsible for the catabolism of endogenous cannabinoids locally, bladder concentrations of CBR2 agonists will increase, particularly 2-arachidonyl glycerol, resulting in a diminished inflammatory response.

ADVERSE REACTIONS OF DIMETHYL SULFOXIDE IN HUMANS: A SYSTEMATIC REVIEW.

Kollerup Madsen B, Hilscher M, Zetner D, Rosenberg J. Version 2. F1000Res. 2018 Nov 5 [revised 2019 Aug 6];7:1746. doi: 10.12688/f1000research.16642.2. eCollection 2018. PMID: 31489176.

Free full article, [click on title.](#)

Dimethyl sulfoxide (DMSO) has been used for medical treatment and as a pharmacological agent in humans since the 1960s. Today, DMSO is used mostly for cryopreservation of stem cells, treatment of interstitial cystitis, and as a penetrating vehicle for various drugs. Many adverse reactions have been described in relation to the

use of DMSO, but according to the authors from Denmark no overview of the existing literature has been made. Their aim was to conduct a systematic review describing the adverse reactions observed in humans in relation to the use of DMSO. This systematic review was reported according to the PRISMA-harms (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines. The primary outcome was any adverse reactions occurring in humans in relation to the use of DMSO. They included all original studies that reported adverse events due to the administration of DMSO, and that had a population of five or more. They included a total of 109 studies. Gastrointestinal and skin reactions were the commonest reported adverse reactions to DMSO. Most reactions were transient without need for intervention. A relationship between the dose of DMSO given and the occurrence of adverse reactions was seen. It was concluded that DMSO may cause a variety of adverse reactions that are mostly transient and mild. The dose of DMSO plays an important role in the occurrence of adverse reactions. DMSO seems to be safe to use in small doses.

[BOTULINUM NEUROTOXIN A INTRAVESICAL INJECTIONS IN INTERSTITIAL CYSTITIS/BLADDER PAINFUL SYNDROME: A SYSTEMATIC REVIEW WITH META-ANALYSIS.](#)

Giannantoni A, Gubbiotti M, Bini V. Toxins (Basel). 2019 Aug 30;11(9). pii: E510. doi: 10.3390/toxins11090510. PMID: 31480323

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The authors from Italy aimed to point out what evidence there is regarding the effects of BoNT/A intravesically injected in patients with IC/BPS. They performed a systematic review of all randomized controlled trials (RCTs) assessing BoNT/A for IC/BPS by using Medline, EMBASE, CINAHL, CENTRAL and MetaRegister of Controlled Trials. Standardized mean differences (SMD) were extracted from the available trials and combined in a meta-analysis applying a random effect model, including heterogeneity of effects. Twelve trials were identified. Significant benefits from BoNT/A injections were detected in: Interstitial Cystitis Symptom Index and Problem Index (ICSI, ICPI); Visual Analog Scale (VAS) for pain and day-time urinary frequency. A great effect size was detected for post-void residual volume although not clinically relevant in most cases. Great heterogeneity was observed in treatments' methodologies and symptoms assessment. Overall, BoNT/A intravesical injections significantly improve some of the most relevant symptoms affecting IC/BPS patients.

[TREATMENT WITH LOW-ENERGY SHOCK WAVE ALLEVIATES PAIN IN AN ANIMAL MODEL OF UROPLAKIN 3A-INDUCED AUTOIMMUNE INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.](#)

Li H, Zhang Z, Peng J, Xin Z, Li M, Yang B, Fang D, Tang Y, Guo Y. Investig Clin Urol. 2019 Sep;60(5):359-366. doi: 10.4111/icu.2019.60.5.359. Epub 2019 Aug 30. PMID: 31501798

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The purpose of this study from China was to investigate whether treatment with low-energy shock wave (LESW) alleviates pain and bladder dysfunction in a mouse model of uroplakin 3A (UPK3A)-induced interstitial cystitis/painful bladder syndrome (IC/PBS). Forty female BALB/c mice were divided into four groups (n=10/group): Sham, Sham+LESW, UPK3A, and UPK3A+LESW. At 6 weeks of age, mice were injected with an emulsion containing water and complete Freund's adjuvant with (UPK3A and UPK3A+LESW groups) or without (Sham and Sham+LESW groups) 200 µg of UPK3A. At 10 weeks, mice received a second dose of Freund's adjuvant to booster immunization. At 12 weeks, mice underwent pain assessment and a frequency volume chart (FVC) test as the pretreatment assessment. LESW treatment and pain assessment were conducted from 13 to 15 weeks. One week after the final treatment, pain assessment and the FVC were conducted again as the post-treatment assessment. Mice were euthanized and sacrificed at 17 weeks. The presence of tactile allodynia and bladder dysfunction was significant in the UPK3A-injected mice. LESW raised the pain threshold and improved bladder function with decreased urinary frequency and increased mean urine output. Expression and secretion of local and systemic inflammatory markers, including tumor necrosis factor- α (TNF- α) and nerve growth factor (NGF), increased after UPK3A immunization. These markers were significantly decreased after LESW treatment. It was concluded that LESW treatment attenuated pain and bladder dysfunction in a UPK3A-induced model of IC/PBS. Local and systemic inflammation was partially controlled, with a reduced number of infiltrated inflammatory cells and reduced levels of TNF- α and NGF.

[URINARY DIVERSION IN THE TREATMENT OF REFRACTORY BLADDER PAIN SYNDROME.](#)

Brandt SB, Kirkeby HJ, Brandt ASV, Jensen JB. Scand J Urol. 2019 Aug 13:1-7. Doi: 10.1080/21681805.2019.1649720. [Epub ahead of print] PMID: 31407934

This study investigated the effect of urinary division in patients with bladder pain syndrome (BPS) refractory to conservative treatment. The study aimed to identify pre-operative predictive factors regarding the surgical

outcome in patients undergoing urinary diversion with or without cystectomy (CX). This study included 30 patients with BPS treated with a urinary diversion in the period from 2002-2017 at a single university hospital. The surgical procedure was selected on an individual basis, including both continent and non-continent diversions and primary procedure with or without concomitant CX. Pre- and post-operative data were registered retrospectively through medical chart review. Eight patients were treated with primary CX and eight had secondary CX within a short time following urinary diversion (1.45 years in median), mainly due to persisting pain. However, more than half the patients were successfully treated with urinary diversion alone throughout the follow-up period (estimated 58% after 12 years). Nine patients were diagnosed prior to surgery with Hunner lesions, and these had significantly greater pain relief compared to the remaining 21 patients. The higher success rate of the bladder-preserving procedure was suggested in patients older than 48 years with less pain pre-operatively, estimated by less than three opioids prior to the procedure. The authors concluded that surgical treatment with urinary diversion should be taken into consideration for refractory BPS, especially patients diagnosed with Hunner lesions. These results support a bladder-preserving strategy unless the patient is young or has severe treatment refractory pain pre-operatively.

BIOMARKERS IN THE DIAGNOSIS AND SYMPTOM ASSESSMENT OF PATIENTS WITH BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW.

Magalhaes TF, Baracat EC, Doumouchsis SK, Haddad JM. Int Urogynecol J. 2019 Aug 13. Doi: 10.1007/s00192-019-04075-9. [Epub ahead of print] PMID: 31410520

Bladder pain syndrome (BPS) is a disease of unknown etiology defined as an unpleasant sensation related to the bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of any identifiable causes. Despite its impact on quality of life (QoL) and socioeconomic burden, there are no objective methods for the diagnosis or assessment of therapeutic response. Magalhaes and colleagues from Brazil systematically reviewed biomarkers associated with BPS to update the current knowledge on this issue. A systematic review of the Cochrane Library, Embase, PubMed/MEDLINE, LILACS, SCOPUS, and ClinicalTrials.gov databases was conducted following the PRISMA statement. Original articles investigating biomarkers for the diagnosis or symptom assessment of patients with BPS were assessed; no language restrictions were applied. Animal or post-mortem studies were excluded. Of the 478 records retrieved, 11 articles were included. MIF, NGF, Etio-S, APF, and a combined methylhistamine/IL-6 model were increased in BPS urine samples versus controls. Also increased were glyceraldehyde in stool, in addition to the expression of some genes (ARID1A, ARF, CHAT, eNOS, GLI-1, iNOS, MCP-1, NGF, WNT-8A, WNT-10A), nerve density, IL-16, VCAM-1, and ICAM-1 in bladder tissue specimens. In contrast, some fecal bacteria, expression of other genes (CHT, HB-EGF, OCT-1, SMRT-1, WNT11) in the bladder urothelium, and urinary DNA methylation in CpG-sites, MCP-3, G5P1, and HB-EGF were decreased in BPS. As none of the biomarkers was studied more than once, a Forest plot could not be constructed. Only 4 articles reported the relation of biomarkers to symptom scores. The authors report that potential biomarkers for BPS in urine, stool, and bladder biopsy specimens are described. Further research is needed before their use in clinical practice.

LONG-STANDING NONULCERATIVE BLADDER PAIN SYNDROME: IMPACT OF THIELE MASSAGE ON BLADDER AND SEXUAL DOMAINS.

El-Hefnawy AS, Soliman HMM, Abd-Elbary SOM, Shereif WI. Low Urin Tract Symptoms. 2019 Oct 24. doi: 10.1111/luts.12291. [Epub ahead of print] PMID: 31647172

The purpose of this study from Egypt was to assess the efficacy of Thiele massage (TM) as monotherapy for nonulcerative interstitial cystitis/bladder pain syndrome (IC/BPS). A prospective evaluation of 40 women with IC/BPS who underwent TM was conducted. TM was initially administered by a physiotherapist and then self-administrated at home twice weekly for 16 weeks. Patients were assessed every 4 weeks on an outpatient basis. Assessment tools included 3-day voiding diaries, the Likert visual analog scale (VAS) for pain, and the Interstitial Cystitis Symptom Index (ICSI) and the Interstitial Cystitis Problem Index (ICPI) of the O'Leary-Sant questionnaire. Sexual function was assessed using the Female Sexual Function Index (FSFI). However, it was concluded that TM is not an effective option as monotreatment modality for nonulcerative IC/BPS. An attempt at physiotherapy should be integrated into a multidisciplinary treatment approach.

DIRECT CONVERSION OF FIBROBLASTS INTO UROTHELIAL CELLS THAT MAY BE RECRUITED TO REGENERATING MUCOSA OF INJURED URINARY BLADDER.

Inoue Y, Kishida T, Kotani SI, Akiyoshi M, Taga H, Seki M, Ukimura O, Mazda O. Sci Rep. 2019 Sep 25;9(1):13850. doi: 10.1038/s41598-019-50388-6. PMID: 31554870

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Urothelial cells play essential roles in protection of urine exudation and bacterial invasion at the urothelial mucosa, so that defect or damage of urothelial cells associated with urinary tract diseases may cause serious problems. If a sufficient number of functional urothelial cells are prepared in culture and transplanted into the damaged urothelial lesions, such technology may provide beneficial effects to patients with diseases of the urinary tract. Here Inoue and colleagues from Japan found that human adult dermal fibroblasts were converted into urothelial cells by transducing genes for four transcription factors, FOXA1, TP63, MYCL and KLF4 (FTLK). The directly converted urothelial cells (dUCs) formed cobblestone-like colonies and expressed urothelium-specific markers. dUCs were successfully expanded and enriched after serial passages using a specific medium that they optimized for the cells. The passaged dUCs showed similar genome-wide gene expression profiles to normal urothelial cells and had a barrier function. The FTLK-transduced fibroblasts were also converted into urothelial cells in vivo and recruited to the regenerating urothelial tissue after they were transplanted into the bladder of mice with interstitial cystitis. According to the authors, this technology may provide a promising solution for a number of patients with urinary tract disorders.

NEUROMODULATION IN UROLOGY, STATE OF THE ART.

Ammirati E, Giammò A, Manassero A, Carone R. Urologia. 2019 Nov;86(4):177-182. doi: 10.1177/0391560319866075. Epub 2019 Aug 1. PMID: 31368415

Sacral neuromodulation is an approved and validated treatment for overactive bladder syndrome, chronic non-obstructive retention, and chronic pelvic pain. Percutaneous tibial nerve stimulation is a less invasive approach of neuromodulation. Ammirati and colleagues from Italy performed a literature research to assess the current evidence available about neuromodulation. Both techniques appear to be effective and safe third-line treatments. The overall success rate ranges from 43% to 85% for sacral neuromodulation and from 40% to 79.5% for percutaneous tibial nerve stimulation. Sacral neuromodulation has a higher incidence of complications in comparison to percutaneous tibial nerve stimulation, due to the more invasive surgical technique and the presence of a permanent implant. The incidence of surgical revision ranges between 9% and 33%. The most frequent complication with sacral neuromodulation is pain at implant site (15%-42%), followed by lead migration (4%-21%), pain at lead site (5.4%-19.1%), leg pain (18%), and infection (5.7%-6.1%). The quality of the studies on sacral neuromodulation and percutaneous tibial nerve stimulation in literature is quite modest, because of the shortage of good randomized clinical trials; most of the studies are prospective observational studies with mid-term follow-up.

IMPROVING CLINICAL OUTCOMES WITH LOWER MOTOR VOLTAGE (≤ 3 V) DURING STAGE 1 SACRAL NEUROMODULATION FOR INTERSTITIAL CYSTITIS OR BLADDER PAIN SYNDROME.

Marinkovic SP. Neurourol Urodyn. 2019 Nov;38(8):2233-2241. doi: 10.1002/nau.24123. Epub 2019 Sep 12. PMID: 31512775

This study aimed to evaluate whether utilization of ≤ 3 V (new experimental approach) vs the traditional four or more volts for lead motor response during stage 1 sacral neuromodulation would lead to an improvement in voiding and pain parameters. An observational, retrospective, double cohort review was conducted of 179 female patients who experienced medically recalcitrant interstitial cystitis (IC) or bladder pain syndrome (BPS) between January 2002 and January 2013. Group A included 105 women with a motor response of ≤ 3 V; group B was comprised of 65 women with a motor response at ≥ 4 V for medically recalcitrant IC or BPS. Patients completed a 3-day pre- and postoperative voiding diary, visual analog pain (VAP) scale, pain urgency frequency (PUF), and Patient Global Impression of Improvement (PGI-I) questionnaire. The mean (standard deviation) follow-up in months was 120.1 ± 33.3 in group A and 116.3 ± 29.2 in group B ($P < .45$). A successful conversion from stage 1 to stage 2 showed statistically significant improvement for group A compared with group B. The success rate also favoured group A, with 87.6% success compared with 66.2% for group B. Group A mean postoperative VAP scores improved over group B with 3.3 ± 1.2 compared with 5.0 ± 0.8 . Group A mean postoperative PUF scores were 10.2 ± 2.7 and group B 14.7 ± 3.5 . In the ≤ 3 V patient cohort, a compelling, significant statistical improvement was noted in most clinical voiding parameters, including the VAP, PGI-I, and performance questionnaires.

EFFECT OF WATER AVOIDANCE STRESS ON SERUM AND URINARY NGF LEVELS IN RATS: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS FOR BPS/IC PATIENTS.

Dias B, Serrão P, Cruz F, Charrua A. Sci Rep. 2019 Oct 1;9(1):14113. doi: 10.1038/s41598-019-50576-4. PMID: 31575913

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Nerve growth factor (NGF) is thought to play a key role in chronic pain felt by bladder pain syndrome/interstitial cystitis (BPS/IC) patients by activating its high affinity receptor tropomyosin-related kinase subtype A (Trk A). The authors from Portugal investigated whether this pathway is also involved in the aggravation of pain sensation during stress events. The levels of plasmatic NGF were increased in rats submitted to Water Avoidance Stress test (WAS), compared to controls. The administration of the alpha1A adrenoceptors blocker silodosin prevented the increase of plasmatic NGF. Urinary NGF levels were also moderately increased in animals submitted to WAS. WAS increased pain behaviour score, lowered abdominal mechanical pain threshold and increase voiding bladder reflex activity. These changes were prevented by the administration of TrkA antagonist GW441756. These findings prompt the use of plasmatic NGF as diagnosis tool for chronic visceral painful conditions and opens therapeutic opportunities for TrkA receptors antagonist/NGF sequestration.

EFFICACY OF INSTILLATION TREATMENT WITH HYALURONIC ACID IN RELIEVING SYMPTOMS IN PATIENTS WITH BPS/IC AND UNCOMPLICATED RECURRENT URINARY TRACT INFECTIONS - LONG-TERM RESULTS OF A MULTICENTER STUDY.

Scarneciu I, Bungau S, Lupu AM, Scarneciu CC, Bratu OG, Martha O, Tit DM, Aleya L, Lupu S. Eur J Pharm Sci. 2019 Nov 1;139:105067. doi: 10.1016/j.ejps.2019.105067. Epub 2019 Sep 6. PMID: 31499170

The purpose of this study was to evaluate the efficacy of intravesical instillations with hyaluronic acid (HA) in relieving lower urinary tract irritation symptoms in patients with urinary tract infections (UTIs) and bladder pain syndrome/interstitial cystitis (BPS/IC). This research, conducted in Romania, includes 30 patients with UTIs (Group I) and 24 with BPS/IC (Group II) as defined by European Association of Urology (EAU) Diagnostic Criteria. Data were collected prospectively, using pre- and post-treatment questionnaires for pelvic pain with a symptom scale for urination and frequency as well as visual analog scale (VAS) pain quizzes. At follow-up visits, at an average of 20 months, a significant improvement in urinary bladder pain, day-time urinary frequency and quality of life was observed in Group I patients. Group II patients experienced significant improvement in urinary bladder pain, urgency, nocturia and quality of life at the 15-month follow-up visit. Eighteen patients (75%) showed a complete response to intravesical HA instillations and required no further treatment. According to the authors, this study demonstrates that intravesical HA instillations may be considered as an important treatment component, with long term positive effects in therapeutic strategy for optimal results in uncomplicated recurrent UTIs and BPS/IC, with good compliance and minimal side effects.

TERMINOLOGY REPORTS/GUIDELINES

[DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS (IC/PBS) : S2K GUIDELINE OF THE GERMAN SOCIETY OF UROLOGY]. [Article in German]

Bschleipfer T, Doggweiler R, Schultz-Lampel D, de Jong J, Gonsior A, Hensen J, Heßdörfer E, Kaftan BT, Kuhn A, Kunzendorf U, Lampel A, Landmesser A, Loch A, Moormann O, Müller B, Neuhaus J, Reich A, Roth R, Schumacher S, Stratmeyer R, Vahlensieck W, Wördehoff A, Münder-Hensen B. Urologe A. 2019 Oct 28. doi: 10.1007/s00120-019-01054-2. [Epub ahead of print]. PMID: 31659368

In this review article, the authors describe all relevant aspects of the new S2k guideline from the German Society of Urology (Deutschen Gesellschaft für Urologie, DGU) for the diagnosis and treatment of IC/PBS (interstitial cystitis/painful bladder syndrome). A list of necessary and optional examinations and the necessity of diagnosis of exclusion are summarized and evaluated. The treatment options listed (ranging from conservative, oral drug, and complementary medicine to interventional surgical procedures) also give the reader a good overview of the contents of the guideline and possible therapeutic approaches. Finally, the recommendations including consensus of the guideline group are also summarized in various information boxes.

To access the English version of this important guideline, please go to:

<https://www.awmf.org/leitlinien/detail/ll/043-050.html> then select: Diagnosis and Treatment of Interstitial Cystitis > weiterlesen.

Alternatively, go directly to:

https://www.awmf.org/fileadmin/user_upload/Leitlinien/043_D_Ges_fuer_Urologie/043-050e_S2k_Diagnosis_Treatment_Interstitial_Cystitis_2019-03.pdf

HOW CAN WE IMPROVE THE DIAGNOSIS AND MANAGEMENT OF BLADDER PAIN SYNDROME? PART 1: ICI-RS 2018.

Khullar V, Chermansky C, Tarcan T, Rahnama'i MS, Digesu A, Sahai A, Veit-Rubin N, Dmochowski R. Neurourol Urodyn. 2019 Oct 2. doi: 10.1002/nau.24166. [Epub ahead of print] PMID: 31578775

This paper summarizes the discussion in a think tank at the ICI-RS 2018 about the diagnosis of bladder pain syndrome (BPS). Its aim was to review the guidelines, investigations and subtypes of BPS based on a literature review in the light of the think tank discussion. All guidelines recommend completing history, physical examination, urine analysis, urine culture, and urine cytology to define the BPS phenotype but there are differences on further investigations. In those guidelines which recommend cystoscopy, the identification of Hunner lesions (HLs) is recommended as this changes the treatment plan and outcome. The authors propose that the differentiation of Hunner's ulcers is an important step in the assessment of these patients. Further suggestions for research are put forward.

GUIDELINE OF GUIDELINES: SOCIAL MEDIA IN UROLOGY.

Taylor J, Loeb S. BJU Int. 2019 Oct 20. doi: 10.1111/bju.14931. [Epub ahead of print] PMID: 31631471

Global usage of the social media (SoME) has increased exponentially. Facebook has close to 2.4 billion users, Twitter 330 million, YouTube 2 billion viewers each month, Instagram 1 billion active users, and LinkedIn 310 million users. This represents increases of 75%, 16%, 90%, 500%, and 19% respectively for these platforms over the past five years.

KETAMINE CYSTITIS

EPIGENETIC REGULATION OF COX-2 EXPRESSION BY DNA HYPOMETHYLATION VIA NF-KB ACTIVATION IN KETAMINE-INDUCED ULCERATIVE CYSTITIS.

Chuang SM, Lu JH, Lin KL, Long CY, Lee YC, Hsiao HP, Tsai CC, Wu WJ, Yang HJ, Juan YS. Int J Mol Med. 2019 Sep;44(3):797-812. Doi: 10.3892/ijmm.2019.4252. Epub 2019 Jun 21. PMID: 31257475

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This study from Taiwan investigated the methylation of CpG sites in the cyclooxygenase (COX)-2 promoter via nuclear factor (NF)-κB transcriptional regulation and elucidated its effect on the COX-2 transcriptional expression in a ketamine-induced ulcerative cystitis (KIC) animal model. The results revealed that ketamine treatment induced NF-κB p65 translocation to nuclei and activated COX-2 expression and prostaglandin (PGE)₂ production in bladder tissue, whereas COX-2 inhibitor suppressed the inflammatory effect. Moreover, DNA hypomethylation of the COX-2 promoter region located from -1,522 to -829 bp might contribute to transcriptional regulation of COX-2 expression and induce a pro-inflammatory response in KIC. Ketamine treatment increased the binding of NF-κB and permissive histone H3 lysine-4 (H3K4)m₃, but caused a decrease in the repressive histone H3K27m₃ and H3K36m₃ on the COX-2 promoter ranging from -1,522 to -1,331 bp as determined by a chromatin immunoprecipitation assay. Moreover, in the ketamine group, the level of Ten-Eleven-Translocation methylcytosine dioxygenase for demethylation as determined by reverse transcription-quantitative PCR assay was increased in comparison with the control group, but that was not the case for the level of DNA methyltransferases for methylation. The present findings revealed that there was a hypomethylation pattern of the COX-2 promoter in association with the level of COX-2 transcription in KIC.

BA-WEI-DIE-HUANG-WAN (HACHIMI-JIO-GAN) CAN AMELIORATE KETAMINE-INDUCED CYSTITIS BY MODULATING NEURORECEPTORS, INFLAMMATORY MEDIATORS, AND FIBROGENESIS IN A RAT MODEL.

Lee WC, Tain YL, Chuang YC, Tsai CN, Yu CC, Su CH. Neurourol Urodyn. 2019 Nov;38(8):2159-2169. doi: 10.1002/nau.24165. Epub 2019 Sep 20. PMID: 31541501.

Lee and colleagues from Taiwan investigated the effects of Ba-Wei-Die-Huang-Wan (BWDHW) on ketamine-induced cystitis (KIC) in a rat model. Female Sprague-Dawley rats were distributed into three groups: control (saline), ketamine (25 mg/kg/day for 28 days), or ketamine (25 mg/kg/day for 28 days) plus BWDHW (90 mg/kg/day, started from day 14). Functional magnetic resonance imaging (fMRI), metabolic cage study, and cystometry were evaluated. Bladder histology was evaluated. Western blots of the bladder proteins were carried out. Compared with controls, ketamine-treated rats showed stronger fMRI intensity in the periaqueductal gray area and bladder overactivity in the bladder functional study, but the ketamine/BWDHW-treated rats did not. Furthermore, ketamine breached the uroplakin III membrane at the apical surface of the urothelium, enhanced substance P spread over the urothelium, induced suburothelial hemorrhage and monocyte/macrophage infiltration, and caused interstitial fibrosis deposition. By contrast, the BWDHW-treated rats exhibited less substance P spread, lower suburothelial monocyte/macrophage infiltration, and lower interstitial fibrosis deposition. The ketamine group showed significant overexpression of neuroreceptors in the bladder mucosa (the transient receptor potential vanilloid 1 and M2 - and M3 -muscarinic receptors) and detrusor (M2 - and M3 -muscarinic receptors); inflammatory mediators in the detrusor (interleukin-1β [IL-1β], IL-6, tumor necrosis

factor- α , nuclear factor- κ B, cyclooxygenase-2, and intercellular adhesion molecule-1); and fibrogenesis molecules in the detrusor (transforming growth factor- β 1, collagen I, collagen III, and fibronectin). However, no significant changes were noted between the ketamine/BWDHW and control groups. It was concluded that BWDHW could exert therapeutic effects by inhibiting the upregulation of neuroreceptors, modulating inflammatory mediators, suppressing fibrogenesis, and ameliorating bladder overactivity in rats with KIC.

MICROBIOME IN UROLOGY

THE UTILITY OF DNA NEXT GENERATION SEQUENCING AND EXPANDED QUANTITATIVE URINE CULTURE IN THE DIAGNOSIS AND MANAGEMENT OF CHRONIC OR PERSISTENT LOWER URINARY TRACT SYMPTOMS.

Gasiorek M, Hsieh MH, Forster CS. *J Clin Microbiol.* 2019 Oct 16. pii: JCM.00204-19. doi: 10.1128/JCM.00204-19. [Epub ahead of print] PMID: 3161953

Many patients suffer from chronic, irritative lower urinary tract symptoms (LUTS). The evaluation and management of these patients has proven difficult with the use of standard diagnostic tools, including urinalysis and urine culture. The growing body of literature on the urinary microbiome has looked at the possible implications of the bladder microbiome and dysbiosis, or perturbations in the microbiome, in conditions associated with chronic LUTS. Disorders such as recurrent urinary tract infections (UTI) and interstitial cystitis have been studied utilizing 16S ribosomal RNA rapid next-generation gene sequencing (NGS) and expanded quantitative urine culture (EQUC). In this paper, the authors from the USA first present a brief review of the literature describing the current understanding of the urinary microbiome, and the features and applications of NGS and EQUC. Next, they discuss the conditions most commonly associated with chronic, persistent LUTS, and present the limitations of current diagnostic practices utilized in this patient population. They then review the limited data available surrounding treatment efficacy and clinical outcomes in patients who have been managed based on results provided by these two recently established diagnostic tools (DNA NGS and/or EQUC). Finally, they propose a variety of clinical scenarios in which the use of these two techniques may affect patients' clinical outcomes.

MICROBIOME AND FIBROMYALGIA

ALTERED MICROBIOME COMPOSITION IN INDIVIDUALS WITH FIBROMYALGIA.

Minerbi A, Gonzalez E, Brereton NJB, Anjarkouchian A, Dewar K, Fitzcharles MA, Chevalier S, Shir Y. *Pain.* 2019 Nov;160(11):2589-2602. doi: 10.1097/j.pain.0000000000001640. PMID: 31219947

Fibromyalgia (FM) is a prevalent syndrome, characterised by chronic widespread pain, fatigue, and impaired sleep, that is challenging to diagnose and difficult to treat. The authors from Canada compared microbiomes of 77 women with FM and that of 79 control participants using 16S rRNA gene amplification and whole-genome sequencing. When comparing FM patients with unrelated controls using differential abundance analysis, significant differences were revealed in several bacterial taxa. Variance in the composition of the microbiomes was explained by FM-related variables more than by any other innate or environmental variable and correlated with clinical indices of FM. In line with observed alteration in butyrate-metabolising species, targeted serum metabolite analysis verified differences in the serum levels of butyrate and propionate in FM patients. Using machine-learning algorithms, the microbiome composition alone allowed for the classification of patients and controls (receiver operating characteristic area under the curve 87.8%). The authors report that to the best of their knowledge this is the first demonstration of gut microbiome alteration in nonvisceral pain. This observation paves the way for further studies, elucidating the pathophysiology of FM, developing diagnostic aids and possibly allowing for new treatment modalities to be explored.

GUT MICROBIOME AND SERUM METABOLOME ANALYSES IDENTIFY MOLECULAR BIOMARKERS AND ALTERED GLUTAMATE METABOLISM IN FIBROMYALGIA.

Clos-Garcia M, Andrés-Marin N, Fernández-Eulate G, Abecia L, Lavín JL, van Liempd S, Cabrera D, Royo F, Valero A, Errazquin N, Vega MCG, Govillard L, Tackett MR, Tejada G, González E, Anguita J, Bujanda L, Orcasitas AMC, Aransay AM, Maíz O, López de Munain A, Falcón-Pérez JM. *EBioMedicine.* 2019 Aug;46:499-511. doi: 10.1016/j.ebiom.2019.07.031. Epub 2019 Jul 18. PMID: 31327695.

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Fibromyalgia is a complex, relatively unknown disease characterised by chronic, widespread musculoskeletal pain. The gut-brain axis connects the gut microbiome with the brain through the enteric nervous system (ENS); its disruption has been associated with psychiatric and gastrointestinal disorders. To gain an insight into the

pathogenesis of fibromyalgia and identify diagnostic biomarkers, this multi-centre team from Spain combined different omics techniques to analyse microbiome and serum composition. They collected faeces and blood samples to study the microbiome, the serum metabolome and circulating cytokines and miRNAs from a cohort of 105 fibromyalgia patients and 54 age- and environment-matched healthy individuals. They sequenced the V3 and V4 regions of the 16S rDNA gene from faeces samples. UPLC-MS metabolomics and custom multiplex cytokine and miRNA analysis (FirePlex™ technology) were used to examine sera samples. Finally, they combined the different data types to search for potential biomarkers. They found that the diversity of bacteria is reduced in fibromyalgia patients. The abundance of the Bifidobacterium and Eubacterium genera (bacteria participating in the metabolism of neurotransmitters in the host) in these patients was significantly reduced. The serum metabolome analysis revealed altered levels of glutamate and serine, suggesting changes in neurotransmitter metabolism. The combined serum metabolomics and gut microbiome datasets showed a certain degree of correlation, reflecting the effect of the microbiome on metabolic activity. They also examined the microbiome and serum metabolites, cytokines and miRNAs as potential sources of molecular biomarkers of fibromyalgia. Their results show that the microbiome analysis provides more significant biomarkers than the other techniques employed in the work. Gut microbiome analysis combined with serum metabolomics can shed new light onto the pathogenesis of fibromyalgia. They provide a list of bacteria whose abundance changes in this disease and propose several molecules as potential biomarkers that can be used to evaluate the current diagnostic criteria.

MICROBIOME AND SJÖGREN'S SYNDROME

[SALIVA MICROBIOME IN PRIMARY SJOGREN'S SYNDROME REVEALS DISTINCT SET OF DISEASE ASSOCIATED MICROBES.](#)

Sharma D, Sandhya P, Vellarikkal SK, Surin AK, Jayarajan R, Verma A, Kumar A, Ravi R, Danda D, Sivasubbu S, Vinod S. Oral Dis. 2019 Sep 12. doi: 10.1111/odi.13191. [Epub ahead of print] PMID: 31514257.

This study from India systematically aimed to evaluate the salivary microbiome in patients with primary Sjögren's syndrome (pSS) using 16S rRNA sequencing approach. DNA isolation and 16S rRNA sequencing was performed on saliva of 37 pSS and 35 control (CC) samples on HiSeq 2500 platform. 16S rRNA sequence analysis was performed independently using two popular computational pipelines, QIIME and LoTuS. There were no significant changes in the alpha diversity between saliva of patients and controls. However, four genera including Bifidobacterium, Lactobacillus, Dialister and Leptotrichia were found to be differential between the two sets, and common between both QIIME and LoTuS analysis pipelines (Fold change of 2 and $p < 0.05$). Bifidobacterium, Dialister and Lactobacillus were found to be enriched, while Leptotrichia was significantly depleted in pSS compared to the controls. Exploration of microbial diversity measures (Chao, Observed Species and Shannon Index) revealed a significant increase in the diversity in patients with renal tubular acidosis. An opposite trend was noted, with depletion of diversity in patients with steroids. According to the authors, their analysis suggests that while no significant changes in the diversity of the salivary microbiome could be observed in Sjögren's syndrome compared to the controls, a set of four genera were significantly and consistently differential in the saliva of patients with pSS. Additionally, a difference in alpha diversity in patients with renal tubular acidosis and those on steroids was observed.

MICROBIOME AND IRRITABLE BOWEL SYNDROME

[NO DISTINCT MICROBIOME SIGNATURE OF IRRITABLE BOWEL SYNDROME FOUND IN A SWEDISH RANDOM POPULATION.](#)

Hugerth LW, Andreasson A, Talley NJ, Forsberg AM, Kjellström L, Schmidt PT, Agreus L, Engstrand L. Gut. 2019 Oct 10. pii: gutjnl-2019-318717. doi: 10.1136/gutjnl-2019-318717. [Epub ahead of print] PMID: 31601615.

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The etiopathogenesis of irritable bowel syndrome (IBS) is unknown. While a link to the gut microbiome is postulated, the heterogeneity of the healthy gut makes it difficult to draw definitive conclusions. The authors from Sweden aimed to describe the faecal and mucosa-associated microbiome (MAM) and health correlates on a community cohort of healthy and IBS individuals with no colonoscopic findings. The PopCol study recruited a random sample of 3556 adults; 745 underwent colonoscopy. IBS was defined by Rome IV criteria and organic disease excluded. 16S rRNA gene sequencing was conducted on sigmoid biopsy samples from 376 representative individuals (63 IBS cases) and faecal samples from 185 individuals (32 IBS cases). While sigmoid MAM was dominated by Lachnospiraceae, faeces presented a higher relative abundance of Ruminococcaceae. Microbial richness in MAM was linearly correlated to that in faeces from the same individual as was diversity. MAM diversity decreased with increasing body mass index and poorer self-rated health, but no other health correlates.

Faecal microbiome diversity was correlated to stool consistency. Several taxonomic groups were correlated to age, BMI, depression and self-reported health, including *Coprococcus catus* associated with lower levels of depression. The degree of heterogeneity observed between IBS patients is higher than that observed between healthy individuals. No distinct microbial signature was observed in IBS. Individuals presenting with low self-rated health or high BMI have lower gut microbiome richness.

VISCERAL PAIN

PAINFUL INTERACTIONS: MICROBIAL COMPOUNDS AND VISCERAL PAIN.

van Thiel IAM, Botschuijver S, de Jonge WJ, Seppen J. Biochim Biophys Acta Mol Basis Dis. 2019 Oct 18:165534. doi: 10.1016/j.bbadis.2019.165534. [Epub ahead of print] PMID: 31634534

Visceral pain, characterized by abdominal discomfort, originates from organs in the abdominal cavity and is a characteristic symptom in patients suffering from irritable bowel syndrome, vulvodynia or interstitial cystitis. Most organs in which visceral pain originates are in contact with the external milieu and continuously exposed to microbes. In order to maintain homeostasis and prevent infections, the immune- and nervous system in these organs cooperate to sense and eliminate (harmful) microbes. Recognition of microbial components or products by receptors expressed on cells from the immune and nervous systems can activate immune responses but may also cause pain. Van Thiel and colleagues from Amsterdam review the microbial compounds and their receptors that could be involved in visceral pain development.

SYSTEMIC LUPUS ERYTHEMATOSUS – LUPUS CYSTITIS

SYSTEMIC LUPUS ERYTHEMATOSUS OF THE URINARY TRACT: FOCUS ON LUPUS CYSTITIS.

Liberski S, Marczak D, Mazur E, Miętkiewicz K, Leis K, Gałzka P. Reumatologia. 2018;56(4):255-258. doi: 10.5114/reum.2018.77978. Epub 2018 Aug 31. PMID: 30237631

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Systemic lupus erythematosus (SLE) frequently manifests as urinary tract disease, most commonly in the form of lupus nephritis. Bladder involvement in the disease course takes a subclinical form and may affect both children and adults. Lupus cystitis can precede SLE diagnosis and may present with very unspecific urinary and digestive tract symptoms or no symptoms at all. The exact mechanism of bladder inflammation in lupus is not fully understood; however, histopathological studies suggest a possible role of immune complex-mediated small vessel vasculitis. Lupus cystitis is a rare SLE manifestation, but poses a challenge for physicians, due to its complex diagnostics and treatment.

CHRONIC PELVIC PAIN

EVALUATING DISABILITY-RELATED QUALITY OF LIFE IN WOMEN WITH CHRONIC PELVIC PAIN.

Ye AL, Adams W, Westbay LC, Fitzgerald CM. Female Pelvic Med Reconstr Surg. 2019 Aug 15. doi: 10.1097/SPV.0000000000000771. [Epub ahead of print] PMID: 31425373

The primary aim of this USA study was to describe quality of life (QOL) in women with chronic pelvic pain using the Pain Disability Index (PDI). A secondary goal was to assess the measurement properties and validity of the PDI for this population. This study was a cross-sectional retrospective chart review. In the setting of an outpatient female pelvic pain clinic, the authors included data from an initial evaluation of patients 16 years and older with chronic pelvic pain (N = 317) from 2012 to 2017. Quality of life was measured using the PDI and previously validated measures for depression and anxiety. The mean PDI score across all patients was similar to previously reported means for similar chronic pain populations. Patients experienced the most disability in their sexual activities. The most common cause of chronic pelvic pain was pelvic floor myofascial pain. Common diagnostic categories covered gynecologic, urologic, gastrointestinal, musculoskeletal, and neurological causes. The PDI was unable to discriminate between diagnoses. On average, patients qualified for mild depression and anxiety diagnoses. Results from a confirmatory factor analysis revealed the original factor structure for the PDI fits this population. The PDI shows promise as a questionnaire for QOL and could be a valuable clinician tool for tracking QOL in the chronic pelvic pain population. Additional research should be focused on assessing its ability to measure minimum clinically significant change over time.

VULVODYNIA AND LOWER URINARY TRACT SYMPTOMS

THE ASSOCIATION OF VULVAR PAIN AND UROLOGICAL URGENCY AND FREQUENCY: FINDINGS FROM A COMMUNITY-BASED CASE-CONTROL STUDY.

Sun Y, Harlow BL. *Int Urogynecol J.* 2019 Aug 2. doi: 10.1007/s00192-019-04052-2. [Epub ahead of print] PMID: 31375872

Vulvodynia is chronic debilitating burning vulvar pain or pain on contact. Although women who suffer from vulvodynia are more likely than others to experience co-morbid interstitial cystitis (IC) and urinary tract infections (UTIs), few studies have explored whether women with vulvodynia experience adverse urinary symptoms (lower urinary tract symptoms [LUTS]) in the absence of urological pain. In this study from the USA, 211 participants with and 226 participants without clinically confirmed vulvodynia completed the Pelvic Pain and Urgency/Frequency (PUF) questionnaire and were scored using all questions, and then a subset of questions relating only to their current frequency and bother of urination during day and night, and the frequency, severity and bother of urgency after voiding. Total, symptom, and bother scores were compared in women with and without vulvodynia, and regression models estimated adjusted odds ratios and 95% confidence intervals for the various LUTS symptoms. As expected, 40% of women with vulvodynia met the criteria for IC (PUF > 12) compared with 2% without vulvodynia. After excluding questions related to bladder or vulvovaginal pain, women with vulvodynia, compared with those without, were skewed toward higher PUF scores, including being 2.4 times more likely to report usually or always bothered by night-time voiding (95% CI 1.22-4.74), and 18 times more likely to report moderate/severe urgency after urination (95% CI 5.48-64.12). The authors concluded that women with vulvodynia are substantially more likely to report voiding dysfunction and symptoms of urgency than women with no history of vulvar pain. These findings are independent of comorbid interstitial cystitis or history of UTIs.

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