

International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization focused on interstitial cystitis/bladder pain syndrome/hypersensitive bladder/Hunner lesion
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RESEARCH UPDATE - May 2023

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

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 open 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 open access. We also include several so-called "Preprints". These are preliminary reports of work that have not been certified by peer review. They should therefore not be relied on to guide clinical practice or health-related behaviour. (See <https://www.medrxiv.org/content/about-medrxiv> for further information).

Terminology: different published articles use different terminology, for example: interstitial cystitis, painful bladder syndrome, (primary) 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.

HUNNER LESION

[STUDY PROTOCOL OF A MULTICENTRE DOUBLE-BLIND RCT, COMPARING A TRADITIONAL RCT WITH AN AGGREGATED N-OF-1 TRIAL: GAG THERAPY EFFICACY TRIAL SOLUTION FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS \(GETSBI STUDY\)](#)

Charlotte van Ginkel, Cléo Baars, John Heesakkers, Frank Martens, Dick Janssen. BMJ Open. 2023 Apr 12;13(4):e068546. doi: 10.1136/bmjopen-2022-068546. PMID: 37045569.

Obtaining level 1 evidence on efficacy of glycosaminoglycan (GAG) therapy is difficult, due to low incidence of bladder pain syndrome/interstitial cystitis (BPS/IC) and heterogeneous symptoms experienced by patients with BPS/IC. Currently, because of a lack of high-grade evidence, the recommendation for applying GAG therapy in most guidelines is 'low grade'. An aggregated N-of-1 trial is a multicrossover design that yields similar level 1 evidence as a traditional randomised controlled trial (RCT), while requiring far less patients. The goal of this study from the Netherlands is to investigate the efficacy of intravesical GAG therapy (Ialuril) for patients with BPS/IC with Hunner lesions using a dual RCT and aggregated N-of-1 trial design to obtain level 1 evidence. The GETSBI study is a double-blind multidesign multicentre randomised placebo-controlled study to assess the short-term and long-term efficacy of hyaluronic acid (1.6%) + chondroitin sulfate (2%) therapy (Ialuril Prefill, IBSA, Goodlife) in patients with symptomatic BPS/IC with Hunner lesions. It starts as a standard RCT (n=80), but continues as an aggregated N-of-1 trial. There are three parallel arms, receiving blinded treatment for three periods (1 x/week for 6 weeks, ratio placebo to intervention in periods of 2:1). Followed by an open prospective part for the long-term efficacy. The primary study

outcome is the maximum bladder pain experienced in the last 3 days measured using the visual analogue pain scale (0-10). This study is a collaboration with the Dutch government and will deliver evidence for the decision to reimburse the therapy. Furthermore, this multidesign study will allow comparison of the two main methods to evaluate applicability for future study designs for BPS/IC research.

[DEEP LEARNING MODELS FOR CYSTOSCOPIC RECOGNITION OF HUNNER LESION IN INTERSTITIAL CYSTITIS](#)

Takuya Iwaki, Yoshiyuki Akiyama, Hirokazu Nosato, Manami Kinjo, Aya Niimi, Satoru Taguchi, Yuta Yamada, Yusuke Sato, Taketo Kawai, Daisuke Yamada, Hidenori Sakanashi, Haruki Kume, Yukio Homma, Hiroshi Fukuhara. Eur Urol Open Sci. 2023 Jan 26;49:44-50. doi:

10.1016/j.euros.2022.12.012. eCollection 2023 Mar. PMID: 36874607 PMCID: PMC9975003

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Accurate cystoscopic recognition of Hunner lesions (HLs) is indispensable for better treatment prognosis in managing patients with Hunner-type interstitial cystitis (HIC), but frequently challenging due to its varying appearance. The purpose of this study from Japan was to develop a deep learning (DL) system for cystoscopic recognition of a HL using artificial intelligence (AI). A total of 626 cystoscopic images collected from January 8, 2019 to December 24, 2020, consisting of 360 images of HLs from 41 patients with HIC and 266 images of flat reddish mucosal lesions resembling HLs from 41 control patients including those with bladder cancer and other chronic cystitis, were used to create a dataset with an 8:2 ratio of training images and test images for transfer learning and external validation, respectively. AI-based five DL models were constructed, using a pretrained convolutional neural network model that was retrained to output 1 for a HL and 0 for control. A five-fold cross-validation method was applied for internal validation. True- and false-positive rates were plotted as a receiver operating curve when the threshold changed from 0 to 1. Accuracy, sensitivity, and specificity were evaluated at a threshold of 0.5. Diagnostic performance of the models was compared with that of urologists as a reader study. The mean area under the curve of the models reached 0.919, with mean sensitivity of 81.9% and specificity of 85.2% in the test dataset. In the reader study, the mean accuracy, sensitivity, and specificity were, respectively, 83.0%, 80.4%, and 85.6% for the models, and 62.4%, 79.6%, and 45.2% for expert urologists. Limitations include the diagnostic nature of a HL as warranted assertibility. The authors constructed the first DL system that recognizes HLs with accuracy exceeding that of humans. This AI-driven system assists physicians with proper cystoscopic recognition of a HL.

Patient summary: In this diagnostic study, the authors developed a deep learning system for cystoscopic recognition of Hunner lesions in patients with interstitial cystitis. The mean area under the curve of the constructed system reached 0.919 with mean sensitivity of 81.9% and specificity of 85.2%, demonstrating diagnostic accuracy exceeding that of human expert urologists in detecting Hunner lesions. This deep learning system assists physicians with proper diagnosis of a Hunner lesion.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: BASIC SCIENCE, DIAGNOSIS AND TREATMENT

[STIMULATED WHOLE-BLOOD CYTOKINE/CHEMOKINE RESPONSES ARE ASSOCIATED WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PHENOTYPES AND FEATURES OF NOCIPLASTIC PAIN: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN RESEARCH NETWORK STUDY](#)

Andrew Schrepf, Chelsea Kaplan, Richard E Harris, David A Williams, Daniel J Clauw, Sawsan As-Sanie, Sara Till, J Quentin Clemens, Larissa V Rodriguez, Adrie Van Bokhoven, Richard Landis, Robert Gallop, Catherine Bradley, Bruce Naliboff, Mike Pontari, Michael O'Donnell, Yi Luo, Karl Kreder, Susan

K Lutgendorf, Steven E Harte. *Pain*. 2023 May 1;164(5):1148-1157. doi: 10.1097/j.pain.0000000000002813. PMID: 36279178.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a common and debilitating disease with poor treatment outcomes. Studies from the multidisciplinary approach to the study of chronic pelvic pain research network established that IC/BPS patients with chronic overlapping pain conditions (COPCs) experience poorer quality of life and more severe symptoms, yet the neurobiological correlates of this subtype are largely unknown. The authors (USA) previously showed that ex vivo toll-like receptor 4 (TLR4) cytokine/chemokine release is associated with the presence of COPCs, as well as widespread pain and experimental pain sensitivity women with IC/BPS. Here, they attempt to confirm these findings in the multisite multidisciplinary approach to the study of chronic pelvic pain Symptom Patterns Study using TLR4-stimulated whole blood (female IC/BPS patients with COPC n = 99; without n = 36). Samples were collected in tubes preloaded with TLR4 agonist, incubated for 24 hours, and resulting supernatant assayed for 7 cytokines/chemokines. These were subject to a principal components analysis and the resulting components used as dependent variables in general linear models. Controlling for patient age, body mass index, and site of collection, they found that greater ex vivo TLR4-stimulated cytokine/chemokine release was associated with the presence of COPCs ($P < 0.01$), extent of widespread pain ($P < 0.05$), but not experimental pain sensitivity ($P > 0.05$). However, a second component of anti-inflammatory, regulatory, and chemotactic activity was associated with reduced pain sensitivity ($P < 0.01$). These results confirm that the IC/BPS + COPCs subtype show higher levels of ex vivo TLR4 cytokine/chemokine release and support a link between immune priming and nociplastic pain in IC/BPS.

[INTEGRATED MICROBIOME AND METABOLOME ANALYSIS REVEALS NOVEL URINARY MICROENVIRONMENTAL SIGNATURES IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS](#)

Zhenming Zheng, Jintao Hu, Wenshuang Li, Kaiqun Ma 1, Caixia Zhang, Kuiqing Li, Yousheng Yao. *J Transl Med*. 2023 Apr 19;21(1):266. doi: 10.1186/s12967-023-04115-5. PMID: 37076836 PMCID: PMC10114403.

The pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS) has not been elucidated, but urinary microorganisms and metabolites have been shown to be closely associated with the inflammatory response of IC/BPS. Nevertheless, the exact mechanisms related to this response have not been clarified. In this study from China, 16S rRNA sequencing and untargeted metabolomics techniques were used to analyse the urinary microbial and metabolite profiles of 30 IC/BPS patients and 30 healthy controls, and correlation analyses were performed to explore the mechanisms by which they might be involved in the inflammatory response of IC/BPS. Twenty-eight differential genera, such as *Lactobacillus* and *Sphingomonas*, were identified. A total of 44 differential metabolites such as 1,3,7-trimethyluric acid and theophylline were screened. The abundance of *Lactobacillus* and *Escherichia-Shigella* was significantly higher in the urine of female IC/BPS patients and healthy controls compared to males, while *Bacteroides* and *Acinetobacter* were lower than in males. The results of the Pearson correlation analysis suggested that differential microorganisms may influence the composition of metabolites. The *Lactobacillus* genus may be a protective bacterium against IC/BPS, whereas *Sphingomonas* may be a pathogenic factor. The differential metabolite theophylline, as an anti-inflammatory substance, may downregulate the inflammatory response of IC/BPS. This study revealed microbial and metabolite profiles in the urine of IC/BPS patients versus healthy controls in both males and females. The authors also found some microorganisms and metabolites closely related to the inflammatory response of IC/BPS, which provided directions for future aetiological and therapeutic research.

[EARLY AND RECENT EXPOSURE TO ADVERSITY, TLR-4 STIMULATED INFLAMMATION, AND DIURNAL CORTISOL IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A MAPP RESEARCH NETWORK STUDY](#)

Susan K Lutgendorf, Sharaf Zia, Yi Luo, Michael O'Donnell, Adrie van Bokhoven, Catherine S Bradley, Robert Gallup, Jennifer Pierce, Bayley J Taple, Bruce D Naliboff, J Quentin Clemens, Karl J Kreder, Andrew Schrepf. Brain Behav Immun. 2023 Mar 29;111:116-123. doi: 10.1016/j.bbi.2023.03.024. Online ahead of print. PMID: 37001828.

Both early (ELA) and recent life adversity (RLA) have been linked with chronic pain conditions and persistent alterations of neuroendocrine and inflammatory responses. Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a chronic urologic disorder characterized by bladder and/or pelvic pain, and excessive urinary frequency and/or urgency. IC/BPS has been associated with high levels of ELA as well as a distinct inflammatory signature. However, associations between ELA and RLA with inflammatory mechanisms in IC/BPS that might underlie the link between adversity and symptoms have not been examined. Here the authors from the USA investigated ELA and RLA in women with IC/BPS as potential risk factors for inflammatory processes and hypothalamic-pituitary-adrenal (HPA) abnormalities using data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. Women with IC/BPS and healthy controls (n = 154 and 32, respectively) completed surveys, collected salivary cortisol at awakening and bedtime for 3 days, and gave a blood sample which was analyzed for 7 LPS-stimulated cytokines and chemokines (IL-6, TNF α , IL-1 β , MIP1 α , MCP1, IL-8, and IL-10). Two cytokine/chemokine composites were identified using principal components analysis. Patients with greater exposure to RLA or cumulative ELA and RLA of at least moderate severity showed elevated levels of a composite of all cytokines, adjusting for age, body mass index, and study site. Furthermore, there was a trending relationship between ELA and the pro-inflammatory composite score. Nocturnal cortisol and cortisol slope were not associated with ELA, RLA, or inflammation. The present findings support the importance of adverse events in IC/BPS via a biological mechanism and suggest that ELA and RLA should be assessed as risk factors for inflammation as part of a clinical workup for IC/BPS.

[WIDESPREAD PAIN PHENOTYPES IMPACT TREATMENT EFFICACY RESULTS IN RANDOMIZED CLINICAL TRIALS FOR INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME: A MAPP NETWORK STUDY](#)

John Farrar, Kenneth Locke, J Clemens, James Griffith, Steven Harte, Ziya Kirkali, Karl Kreder, John Krieger, H Henry Lai, Robert Moldwin, Chris Mullins, Bruce Naliboff, Michel Pontari, Larissa Rodriguez, Anthony Schaeffer, Alisa Stephens-Shields, Siobhan Sutcliffe, Bayley Taple, David Williams, J Landis. Res Sq. 2023 Feb 23;rs.3.rs-2441086. doi: 10.21203/rs.3.rs-2441086/v1. Preprint PMID: 36865104 PMCID: PMC9980200

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Clinical trials of pain are notoriously difficult and inefficient in demonstrating efficacy even for known efficacious treatments. Determining the appropriate pain phenotype to study can be problematic. Recent work has identified the extent of widespread pain as an important factor in the likelihood of response to therapy but has not been tested in clinical trials. Using data from three previously published negative studies of the treatment of interstitial cystitis/ bladder pain with data on the extent of widespread pain, this MAPP team examined the response of patients to different therapies based on the amount of pain beyond the pelvis. Participants with predominately local but not widespread pain responded to therapy targeting local symptoms. Participants with widespread and local pain responded to therapy targeting widespread pain. Differentiating patients with and without widespread pain phenotypes may be a key feature of designing future pain clinical trials to demonstrate treatments that are effective versus not.

[PLATELET LYSATE THERAPY ATTENUATES HYPOXIA INDUCED APOPTOSIS IN HUMAN UROEPITHELIAL SV-HUC-1 CELLS THROUGH REGULATING THE OXIDATIVE STRESS AND MITOCHONDRIAL-MEDIATED INTRINSIC APOPTOTIC PATHWAY](#)

Zong-Sheng Wu, Hou-Lun Luo, Yao-Chi Chuang, Wei-Chia Lee, Hung-Jen Wang, Michael B Chancellor. *Biomedicines*. 2023 Mar 17;11(3):935. doi: 10.3390/biomedicines11030935. PMID: 36979913 PMCID: PMC10045666.

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Ischemia/hypoxia plays an important role in interstitial cystitis/bladder pain syndrome (IC/BPS). Platelet-rich plasma (PRP) has been shown to relieve symptoms of IC/BPS by regulating new inflammatory processes and promoting tissue repair. However, the mechanism of action of PRP on the IC/BPS bladder remains unclear. The authors from Taiwan and the USA hypothesize that PRP might protect the urothelium during ischemia/hypoxia by decreasing apoptosis. SV-HUC-1 cells were cultured under hypoxia for 3 h and treated with or without 2% PLTGold® human platelet lysate (PL). Cell viability assays using trypan blue cell counts were examined. Molecules involved in the mitochondrial-mediated intrinsic apoptosis pathway, HIF1 α , and PCNA were assessed by Western blot analysis. The detection of apoptotic cells and CM-H₂DCFDA, an indicator of reactive oxygen species (ROS) in cells, was analyzed by flow cytometry. After 3 h of hypoxia, the viability of SV-HUC-1 cells and expression of PCNA were significantly decreased, and the expression of ROS, HIF1 α , Bax, cytochrome c, caspase 3, and early apoptosis rate were significantly increased, all of which were attenuated by PL treatment. The addition of the antioxidant N-acetyl-L-cysteine (NAC) suppressed the levels of ROS induced by hypoxia, leading to inhibition of late apoptosis. PL treatment could potentially protect the urothelium from apoptosis during ischemia/hypoxia by a mechanism that modulates the expression of HIF1 α , the mitochondria-mediated intrinsic apoptotic pathway, and reduces ROS.

[HYALURONAN NANOPATELETS EXERT AN INTRINSIC ANTI-INFLAMMATORY ACTIVITY IN A RAT MODEL OF BLADDER PAINFUL SYNDROME/INTERSTITIAL CYSTITIS](#)

Raul Diaz-Salmeron, Catherine Cailleau, Stéphanie Denis, Gilles Ponchel, Kawthar Bouchemal. *J Control Release*. 2023 Apr;356:434-447. doi: 10.1016/j.jconrel.2023.03.014. Epub 2023 Mar 14. PMID: 36921722.

Glycosaminoglycan (GAG) replenishment therapy consists of the instillation of GAG solutions directly in the bladder to alleviate Bladder Painful Syndrome/Interstitial Cystitis (BPS/IC). However, several issues were reported with this strategy because the GAG solutions are rapidly eliminated from the bladder by spontaneous voiding, and GAG have low bioadhesive behaviors. In this study from France, GAG nanomaterials with typical flattened morphology were obtained by a self-assembly process. The formation mechanism of those nanomaterials, denoted as nanoplatelets, involves the interaction of α -cyclodextrin cavity and alkyl chains covalently grafted on the GAG. Three GAG were used in this investigation, hyaluronan (HA), chondroitin sulfate (CS), and heparin (HEP). HA NP showed the best anti-inflammatory activity in an LPS-induced in vitro inflammation model of macrophages. They also exhibited the best therapeutic efficacy in a BPS/IC rat inflammation model. Histological examinations of the bladders revealed that HA NP significantly reduced bladder inflammation and regenerated the bladder mucosa. This investigation could open new perspectives to alleviate BPS/IC through GAG replenishment therapy.

[DETERMINATION OF THE ROLES OF CADPR AND NAADP AS INTRACELLULAR CALCIUM MOBILIZING MESSENGERS IN S1P-INDUCED CONTRACTIONS IN RAT BLADDERS HAVING IC/PBS](#)

Denizalti Merve, Anjum Irfan, Durlu-Kandilci Nezahat Tugba, Sahin-Erdemli Inci. *Life Sci*. 2023 Apr 4;121651. doi: 10.1016/j.lfs.2023.121651. Online ahead of print. PMID: 37023954

Interstitial cystitis/painful bladder syndrome (IC/PBS) is characterized by lower abdominal pain and increased frequency and urgency of urine. Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid that plays role in calcium homeostasis in smooth muscle. The intracellular calcium mobilizing secondary messengers are also involved in smooth muscle contraction. The role of intracellular calcium storing depots in S1P-induced contraction was investigated in permeabilized detrusor smooth muscle having cystitis. In this study from Turkey, IC/PBS was induced by cyclophosphamide

injection. The detrusor smooth muscle strips isolated from rats were permeabilized with β -escin. S1P-induced contraction was increased in cystitis. S1P-induced enhanced contraction was inhibited by cyclopiazonic acid, ryanodine and heparin showing involvement of sarcoplasmic reticulum (SR) calcium stores. Inhibition of S1P-induced contraction by bafilomycin and NAADP suggested the participation of lysosome-related organelles. IC/PBS triggers S1P-induced increase in intracellular calcium from SR and lysosome-related organelles in permeabilized detrusor smooth muscle.

IMMUNOGENIC CELL DEATH ASSOCIATED MOLECULAR PATTERNS AND THE DUAL ROLE OF IL17RA IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Wei Zhang, Xiaodong Liu, Jiawen Wang, Xinhao Wang, Yaoguang Zhang. *Biomolecules*. 2023 Feb 23;13(3):421. doi: 10.3390/biom13030421. PMID: 36979355 PMCID: PMC10046465.

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The unclear etiology and pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS) are responsible for the lack of effective treatment and the poor patient prognosis. Various studies show that chronic inflammation and immune responses are important factors contributing to the pathogenesis of IC/BPS. The process of immunogenic cell death (ICD) involves both the immune response and inflammatory process, and the involvement of ICD in IC/BPS pathogenesis has not been explored. In this study from Beijing, China, Two IC/BPS transcriptome datasets collected from the Gene Expression Omnibus (GEO) database were used to identify distinct ICD-associated molecular patterns (IAMPs). IAMPs and IC/BPS subtypes were found to be related. The inflammatory immune microenvironments (IIME) in different IAMPs were studied. The potential mechanism by which the interleukin 17 receptor A (IL17RA) influences IC/BPS was examined using in vitro assays. The expression of ICD-related genes (IRGs) was upregulated in IC/BPS bladders, compared with normal bladders. Disease prediction models, based on differentially expressed IRGs, could accurately predict IC/BPS. The IC/BPS patients had two distinct IAMPs, each with its own subtype and clinical features and association with remodelling IIME. IL17RA, a well-established IC/BPS bladder biomarker, mediates both the inflammatory insult and the protective responses. In summary, the current study identified different IAMPs in IC/BPS, which may be involved in the pathogenesis of IC/BPS by remodelling the IIME. The chronic inflammatory process in IC/BPS may be prolonged by IL17RA, which could mediate both pro- and anti-inflammatory responses. The IL17RA-associated pathway may play a significant role in the development of IC/BPS and can be used as a therapeutic target.

LncRNA MEG3 ALLEVIATES INTERSTITIAL CYSTITIS IN RATS BY UPREGULATING NRF2 AND INHIBITING THE P38/NF-KB PATHWAY

Min Wang, Xudong Li, Zengyue Yang, Yong Chen, Tao Shu, Yi Huang. *Cytokine*. 2023 May;165:156169. doi: 10.1016/j.cyto.2023.156169. Epub 2023 Mar 16. PMID: 36933397

Interstitial cystitis (IC), a chronic pain syndrome characterized by urinary frequency, urgency, and bladder or pelvic floor pain, severely affects the quality of life of patients. The aim of this study from Shaanxi, China was to investigate the role and mechanism of long noncoding RNA Maternally Expressed Gene3 (lncRNA MEG3) in IC. In this study, an IC rat model was established by intraperitoneal injection of cyclophosphamide combined with bladder perfusion of fisetin and tumor necrosis factor- α (TNF- α) to mimic IC. An in vitro model was established using TNF- α -induced rat bladder epithelium cells. H&E staining was used to assess bladder tissue damage and ELISA was used to measure inflammatory cytokine levels. Western blot analysis was used to examine Nrf2, Bax, Bcl-2, cleaved caspase-3, p-p38, p38, p-NF- κ B and NF- κ B protein expression levels. RNA immunoprecipitation and RNA pull-down assays were used to examine the interaction between MEG3 and Nrf2. MEG3 levels were upregulated in IC tissues and bladder epithelial cells, whereas Nrf2 expression was found to be downregulated. Knockdown of MEG3 reduced bladder tissue injury, inflammation, oxidative stress and apoptosis. MEG3 was negatively correlated with Nrf2. Downregulation of MEG3 alleviated IC inflammation and injury by upregulating Nrf2 and inhibiting

the p38/NF- κ B pathway. Downregulation of MEG3 alleviated inflammation and injury in IC rats by upregulating Nrf2 and inhibiting the p38/NF- κ B pathway.

MOLECULAR PROFILING OF INFLAMMATORY PROCESSES IN A MOUSE MODEL OF IC/BPS: FROM THE COMPLETE TRANSCRIPTOME TO MAJOR SEX-RELATED HISTOLOGICAL FEATURES OF THE URINARY BLADDER

Dominika Peskar, Tadeja Kuret, Katja Lakota, Andreja Erman. Int J Mol Sci. 2023 Mar 17;24(6):5758. doi: 10.3390/ijms24065758. PMID: 36982831 PMCID: PMC10058956.

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Animal models are invaluable in the research of the pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS), a chronic aseptic urinary bladder disease of unknown etiology that primarily affects women. In this study from Slovenia, a mouse model of IC/BPS was induced with multiple low-dose cyclophosphamide (CYP) applications and thoroughly characterized by RNA sequencing, qPCR, Western blot, and immunolabeling to elucidate key inflammatory processes and sex-dependent differences in the bladder inflammatory response. CYP treatment resulted in the upregulation of inflammatory transcripts such as Ccl8, Eda2r, and Vegfd, which are predominantly involved in innate immunity pathways, recapitulating the crucial findings in the bladder transcriptome of IC/BPS patients. The JAK/STAT signalling pathway was analyzed in detail, and the JAK3/STAT3 interaction was found to be most activated in cells of the bladder urothelium and lamina propria. Sex-based data analysis revealed that cell proliferation was more pronounced in male bladders, while innate immunity and tissue remodelling processes were the most distinctive responses of female bladders to CYP treatment. These processes were also reflected in prominent histological changes in the bladder. The study provides an invaluable reference dataset for preclinical research on IC/BPS and an insight into the sex-specific mechanisms involved in the development of IC/BPS pathology, which may explain the more frequent occurrence of this disease in women.

MENDELIAN DISORDERS IN AN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME COHORT

Elicia Estrella, Shira Rockowitz, Marielle Thorne, Pressley Smith, Jeanette Petit, Veronica Zehnder, Richard N Yu, Stuart Bauer, Charles Berde, Pankaj B Agrawal, Alan H Beggs, Ali G Gharavi, Louis Kunkel, Catherine A Brownstein. Adv Genet (Hoboken). 2022 Nov 27;4(1):2200013. doi: 10.1002/ggn2.202200013. eCollection 2023 Mar. PMID: 36910591 PMCID: PMC10000272

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain disorder causing symptoms of urinary frequency, urgency, and bladder discomfort or pain. Although this condition affects a large population, little is known about its etiology. Genetic analyses of whole exome sequencing are performed on 109 individuals with IC/BPS. One family has a previously reported SIX5 variant (ENST00000317578.6:c.472G>A, p.Ala158Thr), consistent with Branchiootorenal syndrome 2 (BOR2). A likely pathogenic heterozygous variant in ATP2A2 (ENST00000539276.2:c.235G>A, p.Glu79Lys) is identified in two unrelated probands, indicating possible Darier-White disease. Two private heterozygous variants are identified in ATP2C1 (ENST00000393221.4:c.2358A>T, p.Glu786Asp (VUS/Likely Pathogenic) and ENST00000393221.4:c.989C>G, p.Thr330Ser (likely pathogenic)), indicative of Hailey-Hailey Disease. Sequence kernel association test analysis finds an increased burden of rare ATP2C1 variants in the IC/BPS cases versus a control cohort ($p = 0.03$, OR = 6.76), though does not survive Bonferroni correction. The data suggest that some individuals with IC/BPS may have unrecognized Mendelian syndromes. Comprehensive phenotyping and genotyping aid in understanding the range of diagnoses in the population-based IC/BPS cohort. Conversely, ATP2C1, ATP2A2, and SIX5 may be candidate genes for IC/BPS. Further evaluation with larger numbers is needed. Genetically screening individuals with IC/BPS may help diagnose and treat this painful disorder due to its heterogeneous nature.

SAFETY AND EFFICACY OF INTRAVESICAL INSTILLATION OF RESINIFERATOXIN IN HEALTHY CATS: A PRELIMINARY STUDY

Michele Barletta, Julie Gordon, André Escobar, Krista Mitchell, H Nicole Trenholme, Janet A Grimes, Juan M Jiménez-Andrade, Alexis Nahama, Alvaro Cisternas. *Front Vet Sci.* 2023 Jan 12;9:922305. doi: 10.3389/fvets.2022.922305. eCollection 2022. PMID: 36713852 PMCID: PMC9878299

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The purpose of this study from the USA and Mexico was to evaluate the safety of intravesical application of resiniferatoxin (RTX) in healthy cats and its effects on calcitonin gene-related peptide (CGRP) and substance P (SP) produced by C-fibers. Seven adult female cats received either 25 mL of saline (control; n = 1), or intravesical RTX at 5, 25, or 50 µg in 25 mL of saline to a final concentration of 0.2 µg/mL (318 nM), 1 µg/mL (1,591 nM), and 2 µg/mL (3,181 nM) (n = 2 per group). The treatment was instilled into the urinary bladder for 20 min. Plasma concentrations of RTX were measured at 0, 0.5, 1, and 4 h. Physical exam, complete blood count, and serum biochemical analysis were performed on day 0, 7, and 14. After 14 days, the sacral dorsal root ganglia (DRG) and the urinary bladder were harvested for histological and immunofluorescence analysis. Intravesical RTX was well tolerated and plasma concentrations were below the quantifiable limits except for one cat receiving 1 µg/mL. Mild to moderate histopathological changes, including epithelial changes, edema, and blood vessel proliferation, were observed at lower doses (0.2 and 1 µg/mL), and were more severe at the higher dose (2 µg/mL). C-fiber ablation was observed in the urinary bladder tissue at all doses, as shown by an apparent reduction of both CGRP and SP immunoreactive axons. A dose of 25 µg (1 µg/mL) of RTX instilled in the urinary bladder of healthy cats appeared to decrease the density of SP and CGRP nerve axons innervating bladder and induced moderate changes in the bladder tissue.

DIAGNOSTIC AND THERAPEUTIC CYSTOSCOPY IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: SYSTEMATIC REVIEW OF LITERATURE AND CONSENSUS ON METHODOLOGY

Rajesh Taneja, Sanjay Pandey, Shivam Priyadarshi, Apul Goel, Amita Jain, Ranjana Sharma, Navita Purohit, Vidya Bandukwalla, Tanvir, Meera Ragavan, Amit Agrawal, Amit Shah, Zeenie Girn, Vikky Ajwani, Uttam Mete. *Int Urogynecol J.* 2023 Jan 28. doi: 10.1007/s00192-023-05449-w. Online ahead of print. PMID: 36708406.

Cystoscopy has been routinely performed in patients suspected to be suffering from bladder pain syndrome/interstitial cystitis (BPS/IC) across the globe. The methodology reported by various guidelines appears to have differences in the techniques and hence there is a need for a review of all those techniques in order to arrive at a consensus. The aim of this study from India was to review the literature describing the prevalent techniques of cystoscopy for patients of BPS/IC and try to evolve a consensus. The Global Interstitial Cystitis, Bladder Pain Society (GIBS) has worked collectively to systematically review the literature using the key words, "Cystoscopy in Hunner's lesions, bladder pain syndrome, painful bladder syndrome and interstitial cystitis" in the PubMed, COCHRANE, and SCOPUS databases. A total of 3,857 abstracts were studied and 96 articles referring to some part of technique of cystoscopy were short-listed for review as full-length articles. Finally, six articles with a description of a technique of cystoscopy were included for final tabulation and comparison. The group went on to arrive at a consensus for a stepwise technique of diagnostic and therapeutic cystoscopy in cases of BPS/IC. This technique has been compared with the previously described techniques and may serve to be a useful practical guide for treating physicians. It was concluded that it is important to have a uniform standardized technique for performing a diagnostic and therapeutic cystoscopy in patients with BPS/IC. Consensus on one such a technique has been arrived at and described in the present article.

PERIOPERATIVE SAFETY OF BLADDER HYDRODISTENTION IN PATIENTS ON ANTITHROMBOTIC THERAPY

Liao Peng, Wei Wang, Xiao-Shuai Gao, De-Yi Luo. Urogynecology (Phila). 2022 Dec 23. doi: 10.1097/SPV.0000000000001300. Online ahead of print. PMID: 36944055.

Bladder hydrodistention (BH) is commonly used to diagnose and treat patients with interstitial cystitis/bladder pain syndrome (IC/BPS), but the overall assessment of bleeding complications for patients taking antithrombotics is lacking. This study from Sichuan, China aimed to investigate if perioperative complications were more common in patients with IC/BPS receiving antithrombotic therapy after BH. The authors retrospectively reviewed patients with IC/BPS who underwent hydrodistention during January 2010 and May 2021. Patients with and without antithrombotic drugs were identified and grouped, and their medical records were reviewed. Perioperative data and symptom scores were assessed. The rates of complications in the 2 groups were recorded at 3 months and at the last visit postoperatively. A total of 387 patients were eventually included. Among them, 29 (7.5%) patients were receiving systemic antithrombotic therapy and 358 (92.5%) were not. Compared with the non-antithrombotic group, patients receiving antithrombotic therapy demonstrated a longer hospital stay ($P = 0.033$) and a longer catheterization time ($P = 0.034$). Moreover, the patients with antithrombotic drugs had increased odds of bladder tamponade (odds ratio, 6.76; $P = 0.019$) and urinary retention (odds ratio, 5.79; $P = 0.033$) both 3 months postoperatively and last follow-up, but this is not statistically different between patients with and without Hunner lesions. No thromboembolic events were identified during the study period. Although a small number of patients with IC/BPS needed anticoagulants, longer hospital stays, longer catheterization time, and increased odds of bladder tamponade and urinary retention were observed in patients receiving antithrombotic therapy. Still, a comprehensive management scheme to balance bleeding complications and antithrombotic agents is needed for individuals.

SEXUAL DYSFUNCTION IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: DO ONABOTULINUM TOXIN-A INJECTIONS IMPROVE SEXUAL FUNCTION?

Murat Topcuoglu, Murat Can Karaburun, Arif İbiş, Mehmet İlker Gokce, Evren Süer, Omer Gülpinar. Neurourol Urodyn. 2023 Jan 28. doi: 10.1002/nau.25139. Online ahead of print. PMID: 36708358.

Interstitial cystitis/bladder pain syndrome (IC/BPS) has a negative impact on female sexual function. The authors from Turkey aimed to evaluate the effect of intravesical botulinum toxin-A (BTX-A) injection on the improvement of sexual dysfunction and urinary symptoms using the multi-domain female sexual function Index (FSFI), interstitial cystitis symptom index (ICSI), and interstitial cystitis problem index (ICPI). The data of the 23 patients (study group) who received intravesical BTX-A with the diagnosis of IC/BPS were reviewed. Twenty-three age-matched healthy, sexually active women were determined as the control group. Patients received 100 U BTX-A submucosally injections, including the trigone. One hundred units of BTX-A were diluted to 20 cc 0.9% saline, and 1 cc was then applied submucosally on 20 different points of the bladder wall (5 U/1 mL per site). The study group was asked to fill out FSFI, ICSI, and ICPI, as well as the visual analog scale (VAS) and bladder diary before and 3 months after the treatment. Patients in the control group completed the same questionnaires once. The pre- and post-treatment questionnaire scores were compared in the study group. The study group's data were also compared to the control group. Compared to the pretreatment period, the study group showed statistically significant improvement in the total FSFI score and each domain of the FSFI after BTX-A injection. The mean total FSFI score and three domains of FSFI (desire, lubrication, pain) reached to the score of the control group following BTX-A injection. Statistically significant improvements were also shown in scores of ICSI, ICPI, and VAS. ($p < 0.05$). It was concluded that IC/BPS is associated with a very high incidence of sexual dysfunction. Intravesical BTX-A injection may provide significant improvement in sexual dysfunction in women with IC/BPS.

BOTULINUM TOXIN THERAPY FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Rahnama'i MS, Marand AJB, Janssen D, Mostafaei H, Gatsos S, Hajebrahimi S, Apostolidis A, Taneja R. Curr Bladder Dysfunct Rep 18, 147–153 (2023). <https://doi.org/10.1007/s11884-023-00695-6>

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Bladder pain syndrome (BPS)/interstitial cystitis (IC) can also be classified as either non-ulcerative or ulcerative, corresponding to the characteristic cystoscopic findings under hydrodistention. Promising therapeutic effects, including decreased bladder pain, have been reported from recent clinical trials using botulinum toxin A (BoNTA) for the treatment of BPS/IC. This review summarizes the current state of the literature on the underlying mechanisms of BoNTA therapy in BPS/IC as well as new forms of its application. BoNTA has its effect in the central nervous system in the afferent nerves as well as in the bladder wall. Besides the well-known effects of BoNTA in the nervous system, pain control as well as reduction of urinary urgency in BPS patients could be achieved by mast cell stabilization effecting histamine release as well as modulation of TRPV and PGE2 pathways, among other systems. In addition, new forms of BoNTA administration have focused on intravesical instillation of the drug in order to circumvent bladder wall injections. Hyperthermia, intravesical hydrogel, and lysosomes have been studied as new ways of BoNTA application in BPS/IC patients. From the available studies, bladder instillation of BoNTA in combination with EMDA is the most promising and effective novel approach. The most promising novel application methods for BoNTA in patient with BPS/IC are bladder instillations. Future research needs to point out if bladder instillations with BoNTA with some form of bladder absorption enhancement such as hyperthermia or EMDA would be able to replace BoNTA injections in patients with BPS/IC.

[THE CLINICAL APPLICATION OF INTRAVESICAL BOTULINUM TOXIN A INJECTION IN PATIENTS WITH OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS](#)

Yuan-Hong Jiang, Jia-Fong Jhang, Hann-Chorng Kuo. Tzu Chi Med J. 2022 Mar 11;35(1):31-37. doi: 10.4103/tcmj.tcmj_313_21. eCollection 2023 Jan-Mar. PMID: 36866354 PMCID: PMC9972932

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Botulinum toxin A (BoNT-A) has been widely used in several urological functional disorders including neurogenic detrusor overactivity (NDO), overactive bladder (OAB), lower urinary tract dysfunction, and interstitial cystitis/bladder pain syndrome (IC/BPS). Chronic inflammation is found in a large proportion of patients with OAB and IC/BPS. The chronic inflammation activates sensory afferents which resulting in central sensitization and bladder storage symptoms. Because BoNT-A can inhibit the sensory peptides released from the vesicles in sensory nerve terminals, the inflammation can be reduced and symptom subsided. Previous studies have demonstrated that the quality of life improved after BoNT-A injections, both in neurogenic and non-NDO. Although the use of BoNT-A in treatment of IC/BPS has not been approved by FDA, intravesical BoNT-A injection has been included in the AUA guideline as the fourth line therapy. Generally, intravesical injections of BoNT-A are well tolerated, though transient hematuria and urinary tract infection can occur after the procedure. In order to prevent these adverse events, experimental trials have been conducted to test if BoNT-A can be delivered into the bladder wall without intravesical injection under anesthesia such as using liposomes encapsulated BoNT-A or application of low energy shock wave on the bladder to facilitate BoNT-A penetrating across the urothelium and treat OAB or IC/BPS. This article from Hualien, Taiwan reviews current clinical and basic research into BoNT-A in OAB and IC/BPS.

[COMPARISON OF THE CLINICAL EFFICACY AND ADVERSE EVENTS BETWEEN INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA AND BOTULINUM TOXIN A FOR THE TREATMENT OF INTERSTITIAL CYSTITIS REFRACTORY TO CONVENTIONAL TREATMENT](#)

Jia-Fong Jhang, Wan-Ru Yu, Hann-Chorng Kuo. Toxins (Basel). 2023 Feb 2;15(2):121. doi: 10.3390/toxins15020121. PMID: 36828435 PMCID: PMC9961286

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Intravesical injection of Botulinum toxin A (BoNT-A) and platelet-rich plasma (PRP) have been reported to alleviate bladder pain and decrease nocturia in patients with refractory interstitial cystitis/bladder pain syndrome (IC/BPS). Both treatments are novel and there has no comparison between them. This study from Taiwan compared the therapeutic effects and adverse events

between IC/BPS patients receiving PRP or BoNT-A injections. This study retrospectively analyzed female patients with IC/BPS who were refractory to conventional treatment and received BoNT-A (n = 26) or PRP (n = 30) injections within the previous two years. Patients were arbitrarily treated with four monthly injections of PRP or a single injection of 100 U of BoNT-A. All injections were followed by cystoscopic hydrodistention. The primary endpoint was the global response assessment (GRA), and secondary endpoints were changes in the O'Leary-Sant IC symptom score, visual analog score (VAS) of bladder pain, voiding diary, and uroflow measures from baseline to six months after the first injection day. The baseline demographics revealed no significant difference between groups. The GRA at one, three, and six months was similar between groups. A significant improvement in IC symptom scores was noted in both groups. Although VAS was significantly improved in overall patients, no significant difference was noted between the PRP and BoNT-A groups at 6 months. Only half of the study cohort had a GRA ≥ 2 at six months. An increase in the post-void residual was noted one month after the BoNT-A injection, but there was no difference between groups at three and six months. More patients reported dysuria (19.2% vs. 3.3%, $p = 0.086$) and urinary tract infection (UTI, 15.4% vs. 0%, $p = 0.041$) after BoNT-A injection than after the PRP injections. The time from the first injection to receiving alternative treatment was similar between groups. Both intravesical PRP and BoNT-A injections have similar efficacy in IC symptom improvement. However, only half of the study cohort had a GRA of ≥ 2 at the six-month follow-up. BoNT-A injection carries a potential risk of UTI after treatment.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION FOR PELVIC PAIN: A SCOPING REVIEW OF TREATMENT PROTOCOLS, PRACTICAL INDICATIONS, AND CAVEATS

Stefano Terzoni, Cristina Mora, Constantina Cloconi, Giorgia Gaia, Maria C Sighinolfi, Serena Maruccia, Bernardo Rocco, Barbara Pinna, Paolo Ferrara, Mauro Parozzi, Anne Destrebecq. NeuroUrol Urodyn. 2023 Mar;42(3):631-640. doi: 10.1002/nau.25137. Epub 2023 Jan 26. PMID: 36701176

Neuromodulation (NM) is a family of therapies based on electrical stimulation to target specific nerves that control LUTS (Lower Urinary Tract Symptoms) and pain. The aim of this study from Italy and Cyprus was to modulate what is happening within the nervous system to achieve therapeutic effects. A particular type of neuromodulation, called TENS (Transcutaneous Electrical Nerve Stimulation), has proven effective for treating pelvic pain. The available evidence provides indications regarding the many aspects of TENS that influence therapeutic effects, but a comprehensive review has yet to be conducted. Scoping review on Pubmed, CINAHL, Embase, Scopus, and Web of Science, including clinical trials, reviews, case studies or series, and other descriptive studies, according to the Joanna Briggs and PRISMA methodology. The 31 papers retrieved allowed the formulation of precise indications about the DOs and DON'Ts of electrode placement, waveform, pulse duration, pulse frequency, amplitude, session duration, and frequency of sessions. This paper also discusses the biochemical and neuro urological mechanisms of TENS. TENS effectiveness is influenced by many factors, some self-evident, others subtle, which this paper elucidates. Pelvic pain requires a multimodal approach, of which TENS is just a part. TENS should therefore be viewed as one of the components of the rehabilitation program in the frame of thorough and continuous patient assessment.

SACRAL NEUROMODULATION IN THE MANAGEMENT OF CHRONIC PELVIC PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Julian Greig, Quentin Mak, Marc A Furrer, Arun Sahai, Nicholas Raison. NeuroUrol Urodyn. 2023 Mar 6. doi: 10.1002/nau.25167. Online ahead of print. PMID: 36877182.

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Sacral neuromodulation (SNM) is a treatment approved for use in several conditions including refractory overactive bladder (OAB) and voiding dysfunction. Chronic pelvic pain (CPP) is a debilitating condition for which treatment is often challenging. SNM shows promising effect in

patients with refractory CPP. However, there is a lack of clear evidence, especially in long-term outcomes. This systematic review will assess outcomes of SNM for treating CPP. In this study from the United Kingdom and Switzerland, a systematic search of MEDLINE, Embase, Cochrane Central and clinical trial databases was completed from database inception until January 14, 2022. Studies using original data investigating SNM in an adult population with CPP which recorded pre and posttreatment pain scores were selected. Primary outcome was numerical change in pain score. Secondary outcomes were quality of life assessment and change in medication use and all-time complications of SNM. Risk of bias was assessed using the Newcastle Ottawa Tool for cohort studies. Twenty-six of 1026 identified articles were selected evaluating 853 patients with CPP. The implantation rate after test-phase success was 64.3%. Significant improvement of pain scores was reported in 13 studies; three studies reported no significant change. WMD in pain scores on a 10-point scale was -4.64 (95% confidence interval [CI] = -5.32 to -3.95, $p < 0.00001$) across 20 studies which were quantitatively synthesized: effects were maintained at long-term follow-up. Mean follow-up was 42.5 months (0-59). Quality of life was measured by RAND SF-36 and EQ-5D questionnaires and all studies reported improvement in quality of life. One hundred and eighty-nine complications were reported in 1555 patients (Clavien-Dindo Grade I-IIIb). Risk of bias ranged from low to high risk. Studies were case series and bias stemmed from selection bias and loss to follow-up. It was concluded that Sacral Neuromodulation is a reasonably effective treatment of Chronic Pelvic Pain and significantly reduces pain and increases patients' quality of life with immediate to long-term effects.

[SACRAL NEUROMODULATION TREATMENT FOR URINARY VOIDING DYSFUNCTIONS: RESULTS OF TREATMENT WITH THE LARGEST SINGLE-CENTER SERIES IN A TERTIARY REFERRAL CENTER IN TURKEY.](#)

Mehmet Umut Kütükoğlu, Türker Altuntaş, Bahadır Şahin, Ahmet Rahmi Onur. Turk J Med Sci. 2023 Feb;53(1):206-210. doi: 10.55730/1300-0144.5575. Epub 2023 Feb 22. PMID: 36945940

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Sacral neuromodulation (SNM) is a minimally invasive treatment that modulates spinal reflexes to regulate bladder, urinary sphincter, and pelvic floor and has successfully been used in the treatment of refractory voiding dysfunctions. The aim of this study from Turkey was to present experience with SNM in a tertiary referral centre with the largest number of patients and review the safety and efficacy of the procedure. A total of 42 patients with refractory lower urinary tract symptoms were included in the study. After an initial test period, patients who showed more than 50% improvement in their symptoms underwent the second stage of SNM. Twelve patients had overactive bladder (OAB), bladder pain syndrome/interstitial cystitis (BPS/IC) and 17 had urinary retention. The clinical success was examined during follow-up by voiding diary, urodynamics, and global response assessment. Between February 2015 and December 2020, a total of 29 patients underwent stages I&II SNM procedures. The mean ages of patients in OAB/BPS group and retention group were 40 (37-57 years) and 35 (27-44 years), respectively. Mean follow-up time was at least 1 year. Overall, 58.5% success rate was observed in OAB, BPS/IC, and urinary retention groups. Global response assessment score in both groups increased significantly ($p = 0.001$). No statistically significant difference was found between success or failure rates when sex and age were variable parameters ($p > 0.05$). SNM appears to be an effective and safe treatment option in restoring voiding dysfunctions in patients with refractory idiopathic and neurogenic voiding dysfunctions. The authors report that their initial series revealed favourable results; however, further studies with larger series and longer follow-up are needed.

[DIMETHYL SULFOXIDE ENHANCES ACETYLCHOLINE-INDUCED CONTRACTIONS IN RAT URINARY BLADDER SMOOTH MUSCLE BY INHIBITING ACETYLCHOLINESTERASE ACTIVITIES](#)

Keisuke Obara, Yuka Matsuoka, Naoya Iwata, Yukako Abe, Yohei Ikegami, Ayano Fujii, Kento Yoshioka, Yoshio Tanaka. Biol Pharm Bull. 2023;46(2):354-358. doi: 10.1248/bpb.b22-00791. PMID: 36724965.

Dimethyl sulfoxide (DMSO) has been used not only as an experimental solvent, but also as a therapeutic agent for interstitial cystitis. The therapeutic effects of DMSO on interstitial cystitis are presumed to involve anti-inflammatory and analgesic effects. However, the effects of DMSO on urinary bladder smooth muscle (UBSM) have not been fully investigated. Thus, in this study from Japan, the authors investigated the effects of DMSO on rat UBSM contractions, and these effects were compared with those of acetone, which has a structure in which the sulfur of DMSO is replaced with carbon. DMSO (0.5-5%) enhanced acetylcholine (ACh)-induced contractions, whereas acetone (3 and 5%) suppressed them. Additionally, DMSO (5%) suppressed carbachol-induced contractions. DMSO/acetone (0.5-5%) inhibited 80 mM KCl-induced contractions in a concentration-dependent manner; however, the inhibitory effects of DMSO were weaker than those of acetone. The enhancing/suppressing effects of DMSO and acetone were almost completely abolished by wash out. DMSO and acetone (0.5-5%) inhibited recombinant human acetylcholinesterase (rhAChE) activity in a concentration-dependent manner. At 0.5 and 1%, the inhibitory effects of DMSO on rhAChE activity were more potent than those of acetone. These findings suggest that DMSO can enhance ACh-induced UBSM contractions and promote urinary bladder motility by inhibiting acetylcholinesterase (AChE), although DMSO also inhibits Ca²⁺ influx-mediated UBSM contractions. In addition, the sulfur atom in DMSO might play an important role in its enhancing effect on ACh-induced contractions by inhibiting AChE, as acetone did not enhance these contractions.

[A PROSPECTIVE, RANDOMIZED TRIAL COMPARING INTRAVESICAL DIMETHYL SULFOXIDE \(DMSO\) TO BUPIVACAINE, TRIAMCINOLONE, AND HEPARIN \(BTH\), FOR NEWLY DIAGNOSED INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME \(IC/PBS\)](#)

Nani P Moss, Henry H Chill, Peter K Sand, Cecilia Chang, Roger P Goldberg, Adam Gafni-Kane. Neurourol Urodyn. 2023 Feb 6. doi: 10.1002/nau.25142. Online ahead of print. PMID: 36747494.

The primary aim of this study from the USA was to compare the effect of bladder instillations using dimethyl sulfoxide (DMSO) with triamcinolone versus bupivacaine, triamcinolone, and heparin (BTH) in women with newly diagnosed interstitial cystitis/painful bladder syndrome. The primary outcome was improvement in symptoms measured using the O'Leary-Sant Interstitial Cystitis Symptoms Index (ICSI) score. Secondary comparisons included changes in urinary frequency, nocturia, and bladder capacity. This was a prospective, randomized study. Patients with a recent diagnosis of interstitial cystitis/painful bladder syndrome (IC/PBS) were randomized 1:1 to treatment with either 6 weekly bladder instillations of DMSO with triamcinolone or BTH. During follow-up visits, patients completed the ICSI questionnaire, and bladder capacity was determined through the retrograde filling of the bladder. The χ^2 test or Student's t test were used for data analysis. A total of 83 patients were randomized, and final analysis included 70 participants who completed the 6 weekly instillations (42 DMSO, 28 BTH). The groups were similar in baseline demographics and clinical characteristics, except for cystometric maximum capacity (DMSO 338.62 ± 139.44 mL, BTH 447.43 ± 180.38 mL, $p = 0.01$). In the DMSO group, 63% of patients had a greater than 29.5% reduction in total ICSI score versus 43% in the BTH group ($p = 0.15$). Nocturia and pain were significantly reduced in the DMSO group. There was a significant increase from baseline in bladder capacity for both groups. It was concluded that in women with newly diagnosed IC/PBS, bladder instillations with DMSO and triamcinolone provide greater improvement in pain and nocturia compared to BTH.

[CANNABIDIOL AS A PROMISING THERAPEUTIC OPTION IN IC/BPS: IN VITRO EVALUATION OF ITS PROTECTIVE EFFECTS AGAINST INFLAMMATION AND OXIDATIVE STRESS](#)

Tadeja Kuret, Mateja Erdani Kreft, Rok Romih, Peter Veranič. Int J Mol Sci. 2023 Mar 6;24(5):5055. doi: 10.3390/ijms24055055. PMID: 36902479 PMCID: PMC10003465.

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Several animal studies have described the potential effect of cannabidiol (CBD) in alleviating the symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS), a chronic inflammatory disease of the urinary bladder. However, the effects of CBD, its mechanism of action, and modulation of downstream signaling pathways in urothelial cells, the main effector cells in IC/BPS, have not been fully elucidated yet. In this study from Ljubljana, Slovenia, the authors investigated the effect of CBD against inflammation and oxidative stress in an in vitro model of IC/BPS comprised of TNF α -stimulated human urothelial cells SV-HUC1. Their results show that CBD treatment of urothelial cells significantly decreased TNF α -upregulated mRNA and protein expression of IL1 α , IL8, CXCL1, and CXCL10, as well as attenuated NF κ B phosphorylation. In addition, CBD treatment also diminished TNF α -driven cellular reactive oxygen species generation (ROS), by increasing the expression of the redox-sensitive transcription factor Nrf2, the antioxidant enzymes superoxide dismutase 1 and 2, and hem oxygenase 1. CBD-mediated effects in urothelial cells may occur by the activation of the PPAR γ receptor since inhibition of PPAR γ resulted in significantly diminished anti-inflammatory and antioxidant effects of CBD. These observations provide new insights into the therapeutic potential of CBD through modulation of PPAR γ /Nrf2/NF κ B signaling pathways, which could be further exploited in the treatment of IC/BPS.

[A GYNECOLOGICAL PERSPECTIVE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME MAY OFFER CURE IN SELECTED CASES](#)

Peter Petros. Cent European J Urol. 2022;75(4):395-398. doi: 10.5173/ceju.2022.106. Epub 2022 Dec 3. PMID: 36794030

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Recent publications of interstitial cystitis (IC)/bladder pain syndrome cure by a gynecological prolapse protocol, run counter to traditional treatments such as bladder instillations which do not offer such cure. The prolapse protocol, uterosacral ligament (USL) repair, is based on the 'Posterior Fornix Syndrome' (PFS). PFS was described in the 1993 iteration of the Integral Theory. PFS comprises predictably co-occurring symptoms of frequency, urgency, nocturia, chronic pelvic pain, abnormal emptying and post-void residual urine, caused by USL laxity and cured or improved by repair thereof. This study from Australia concerned analysis and interpretation of published data showing cure of IC by USL repair. In many women, USL pathogenesis of IC can be explained by the effect of weak or loose USLs weakening two pelvic muscles which contract against them, levator plate (LP) and conjoint longitudinal muscle of the anus (LMA). The now weakened pelvic muscles cannot stretch the vagina sufficiently to prevent afferent impulses from urothelial stretch receptors 'N' reaching the micturition centre where they are interpreted as urge. The same unsupported USLs cannot support the visceral sympathetic/parasympathetic visceral autonomic nerve plexuses (VP). A gynecological schema cannot explain all IC phenotypes, especially male IC. However, for those women who obtain relief from the predictive speculum test, there is a significant possibility of cure of both the pain and the urge by uterosacral ligament repair. In this context, it may well be in such female patients' interests, at least in the exploratory diagnostic phase, for ICS/BPS to be subsumed into the PFS disease category. It would give such women a significant chance of cure, something denied to them for now.

[FOOD SENSITIVITIES IN A DIVERSE NATIONWIDE COHORT OF VETERANS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Aubrey Jarman, Jessica L Janes, Barbara Shorter, Robert Moldwin, Amanda M De Hoedt, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger. J Urol. 2023 Jan;209(1):216-224. doi: 10.1097/JU.0000000000002938. Epub 2022 Aug 24. PMID: 36001744.

Prior studies suggest that certain foods exacerbate interstitial cystitis/bladder pain syndrome symptoms. However, these studies were limited in size and demographics. The authors from the USA assessed the presence of diet sensitivities among patients with interstitial cystitis/bladder pain syndrome and compared them with patients with other pelvic pain conditions and healthy controls.

They identified Veterans Affairs patients nationwide by querying ICD-9/10 codes for interstitial cystitis/bladder pain syndrome. Patients were assigned to interstitial cystitis, other pelvic pain, or healthy control cohorts after chart review. They mailed all patients the Shorter-Moldwin Food Sensitivity Questionnaire to evaluate the self-perceived effects of specific foods/beverages on urinary symptoms and/or bladder pain. In the IC/BPS cohort, 70% had ≥ 1 food sensitivity vs 37% of the other pelvic pain cohort and 32% of healthy controls ($P < .001$). The average number of sensitivities were similar between other pelvic pain conditions and healthy control cohorts, which were significantly less than in interstitial cystitis/bladder pain syndrome patients. IC/BPS patients were more sensitive to acidic, spicy foods, and certain beverages vs other cohorts (all $P < .001$). Within the interstitial cystitis/bladder pain syndrome cohort, Black patients had significantly higher sensitivity to alcoholic and noncaffeinated beverages than Whites. Black patients did report significantly worsened urinary urgency than Whites ($P < .05$). In a diverse population of veterans, IC/BPS patients had significantly more food sensitivities than those without IC/BPS. This suggests that food sensitivities could be suggestive of IC/BPS, which could make the Shorter-Moldwin Food Sensitivity Questionnaire a helpful diagnostic tool and aid in distinguishing IC/BPS from conditions often confused with IC/BPS.

VALIDATION OF A CHRONIC PELVIC PAIN MAP: A NEW SELF-ASSESSMENT TOOL FOR PAIN LOCALIZATION

Kelli Aibel, Robert Moldwin. BJU Int. 2023 Feb 1. doi: 10.1111/bju.15979. Online ahead of print. PMID: 36722397.

The purpose of this study from the USA was to develop and validate a Chronic Pelvic Pain Map in order to fill a gap in the need for a localized body map of the pelvic region. The Chronic Pelvic Pain Map incorporated input from 12 chronic pelvic pain experts across the United States as well as patient feedback to assess face validity. Finalized diagrams are single, front-facing images of the male and female pelvis that incorporate both abdominal and perineal views. Assessment of test-retest reliability and construct (convergent and discriminant) validity was carried out on a retrospective cohort of Chronic Pelvic Pain Syndrome (CPPS) patients who completed the maps from January 2022 to May 2022. Other validated measures completed consisted of the male and female forms of the Genitourinary Pain Index (GUPI) and the short form of the Pain Catastrophizing Scale (PCS-6). Test-retest for individual map zones demonstrated moderate to excellent reliability (Cohen's Kappa Coefficients ranging from 0.28 to 0.64) and for total map zones demonstrated excellent reliability (Intraclass Correlation Coefficient = 0.90). Convergent validity for individual map zones with location descriptors from the GUPI was strong (Phi Coefficients ranging from 0.26 to 0.79) and for total map zones was moderate (Spearman's Correlation Coefficient = 0.56). Discriminant validity for total map zones with separated, but related constructs from the GUPI and PCS was weakly positive (Spearman's Coefficients ranging from 0.27 to 0.32). This study suggests that the Chronic Pelvic Pain Map is a valid and reliable tool for assessing location of pain in patients with chronic pelvic pain. Their findings highlight the potential utility of this map in guiding treatment selection and monitoring response to treatment in patients with chronic pelvic pain.

PELVIC MAPPING TO EXPLORE PATTERNS OF CHRONIC PELVIC PAIN

Kelli Aibel, Sharon Choi, Robert Moldwin. Neurourol Urodyn. 2023 Feb 25. doi: 10.1002/nau.25145. Online ahead of print. PMID: 36840909.

Chronic pelvic pain syndromes (CPPS) are commonly encountered by urologists and urogynecologists and pose diagnostic and therapeutic challenges. Body maps have been helpful adjuncts to verbal descriptions of pain and may serve a role in phenotyping what is known to be a heterogeneous patient population. The aim of this study from the USA was to assess whether patterns of pain as marked on a body map of the pelvis exist among common CPPS diagnoses. The secondary aim was to investigate the association between the total number of pain locations marked on the map and clinical indices in patients with 1 to 3 CPPS diagnoses. Data was collected on patients who visited the

Northwell Health Pelvic Pain Treatment Center (PPTC) from January to May 2022 and were diagnosed with at least one of four major CPPS diagnoses: interstitial cystitis/bladder pain syndrome (IC/BPS), pelvic floor myalgia (PFM), chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and vulvodynia. Demographic data as well as survey data from pelvic pain maps, Genitourinary Pain Index (GUPI) forms, and the short form-6 of the Pain Catastrophizing Scale (PCS-6) were recorded. Descriptive statistics among CPPS groups and Pearson correlations among the number of CPPS diagnoses were computed. One hundred seventy females and 125 males with CPPS were included in the study. Significant cross-over in mapping patterns was notable between IC/BPS and PFM groups, both most commonly marking "abdomen" and "genital" regions. The most distinct pattern of pain was seen in patients with CP/CPPS and in patients with vulvodynia. Among the total sample, as the mean number of pain locations marked within the pelvis increased, GUPI and PCS scores increased ($p < 0.05$). As the number of CPPS diagnoses increased, the strength of the relationship independently increased. Pelvic body mapping demonstrated that different forms of CPPS displayed different distributions of pain, but mapping was not predictive of any diagnostic group. Nevertheless, the pelvic body map proved useful in identifying precise locations of pain and may help uncover regions of pain that cannot be easily communicated. The total number of pain sites marked appeared to correlate with worse clinical features.

CLINICALLY IMPORTANT DIFFERENCES FOR PAIN AND URINARY SYMPTOMS IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME: A MAPP NETWORK STUDY

Alisa J Stephens-Shields, H Henry Lai, J Richard Landis, Karl Kreder, Larissa V Rodriguez, Bruce D Naliboff, Niloofar Afari, Siobhan Sutcliffe, Robert Moldwin, James W Griffith, J Quentin Clemens, Catherine S Bradley, Susan Quallich, Priyanka Gupta, Steven E Harte, John T Farrar. J Urol. 2023 Feb 27;101097JU0000000000003394. doi: 10.1097/JU.0000000000003394. Online ahead of print. PMID: 36848118.

Symptom heterogeneity in interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, collectively termed urologic chronic pelvic pain syndrome (UCPPS), has resulted in difficulty in defining appropriate clinical trial endpoints. In this study from the USA, the authors determined clinically important differences (CIDs) for 2 primary symptom measures, Pelvic Pain Severity (PPS) and Urinary Symptom Severity (USS), and evaluated subgroup differences. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain Symptom Patterns Study enrolled individuals with UCPPS. They defined CIDs by associating changes in PPS and USS over 3 to 6 months with marked improvement on a global response assessment using regression and receiver operating characteristic curves. They evaluated CIDs for absolute and percent change and examined differences in CIDs by sex-diagnosis, presence of Hunner lesions, pain type, pain widespreadness, and baseline symptom severity. An absolute change of -4 was clinically important in PPS among all patients, but CID estimates differed by pain type, presence of Hunner lesions, and baseline severity. PPS CID estimates for percent change were more consistent across subgroups and ranged from 30 to 57 percent. The absolute change USS CID was -3 for female participants and -2 for male participants with CP/CPPS only. Patients with greater baseline severity required larger decreases in symptoms to feel improved. Estimated CIDs had lower accuracy among participants with low baseline symptoms. A reduction of 30-50% in PSS is a clinically meaningful endpoint for future therapeutic trials in UCPPS. USS CIDs are more appropriately defined separately for male and female participants.

A BIBLIOMETRIC ANALYSIS OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME FROM 2000 TO 2022

Jie Wang, Bin Cao, Sihao Lin, Yong Wang, Qifa Zhang, Yang Jiang, Wei Li, Yingjian Zhu. J Pain Res. 2023 Apr 10;16:1225-1241. doi: 10.2147/JPR.S396009. eCollection 2023. PMID: 37064957 PMCID: PMC10103784.

Urologic chronic pelvic pain syndrome has attracted a lot of attention in the new century, and an increasing number of relevant studies have been published. Therefore, the authors from Shanghai, China performed a bibliometric analysis of these publications, hoping to show the current research

hotspots and future research trends. The articles on were selected from the Web of Science Core Collection. Countries, authors, references and keywords in the field were visualized and analyzed using CiteSpace and VOSViewer software. A total of 1014 articles on urologic chronic pelvic pain syndrome were identified, with "chronic pelvic pain syndrome" being the most common keyword, with a strong association with "interstitial cystitis" and "chronic prostatitis". The hotspot of urologic chronic pelvic pain syndrome research has gradually shifted from chronic prostatitis / urologic chronic pelvic pain syndrome to interstitial cystitis/bladder pain syndrome over the past few years. Future research tends to focus on urologic chronic pelvic pain syndrome etiology, including oxidative stress and inflammation. Research into urologic chronic pelvic pain syndrome is steadily growing. The United States has made the most prominent contribution in this area, and the share of China's contribution is expected to grow further. The etiology of urologic chronic pelvic pain syndrome, including inflammation and oxidative stress, has been the focus of current research and developmental trends in the future research.

CURRENT STATUS OF PATIENT-REPORTED OUTCOME MEASURES AND OTHER SUBJECTIVE ASSESSMENT GRADING TOOLS IN BLADDER PAIN SYNDROME

Sabine Uguzova, Patrick Juliebø-Jones, Christopher Beisland, Ahsanul Haq. Int Urogynecol J. 2023 May 2. doi: 10.1007/s00192-023-05551-z. Online ahead of print. PMID: 37129626.

Bladder pain syndrome (BPS) is characterised by chronic pain in the bladder area accompanied by urgency and/or frequency without the presence of other confusable diseases. Owing to a lack of gold standard diagnostic tests and definitive cure it is paramount to define treatment goals and validated measurements of outcomes. Patient-reported outcome measures (PROMs) are validated questionnaires completed by patients that can help to reduce ambiguity in the BPS patient treatment pathway, but they are currently underutilised. The authors from Norway and UK present to their knowledge the first summary and analysis of all available PROMs in BPS patients. This study was a review and critical evaluation of all relevant BPS guidelines presented in English language and a systematic search for PubMed database articles relating to PROMs and subjective assessment grading tools in BPS, interstitial cystitis and chronic pelvic pain syndrome. The ideal PROMs for BPS should assess urinary symptoms, pain, quality of life and sexual health. There are five PROMs designed specifically for BPS patients. The most universally used and quoted is the O'Leary-Sant questionnaire followed by the Pelvic Pain and Urgency Score and the Wisconsin Interstitial Cystitis scale. However, there is no single PROM for BPS that is ideal, and for comprehensive assessment several questionnaires are often used simultaneously. Patient-reported outcome measures are a valuable tool for use in the long-term management of patients burdened with BPS. There are now several disease-specific PROMs in use that have their respective advantages and disadvantages. Their use should be encouraged in future research as well as continued efforts to develop new PROMs that can address current shortcomings.

QUALITY, VALUE, AND EFFICACY OF COMPLEMENTARY AND ALTERNATIVE MEDICINE IN THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Béatrice Bouchard, Lysanne Campeau. Curr Bladder Dysfunct Rep 18, 51–58 (2023). <https://doi.org/10.1007/s11884-022-00683-2>

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a difficult condition to treat, and few treatments have been demonstrated to be effective. Patients are therefore often willing to try treatments that traditional medicine does not offer, such as complementary and alternative medicine (CAM). The purpose of this paper from Canada is to review the current CAM treatments for IC/BPS. Several modalities have been explored in the treatment of IC/BPS. Dietary modification with the elimination of arylalkylamine-containing foods has been shown to reduce symptom flares. Different nutraceuticals have also been studied. Promising results were shown for calcium glycerophosphate taken before the ingestion of foods responsible for symptom flares. The glycosaminoglycan layer appears to be damaged in this condition, and therefore intravesical and oral

therapies targeting this layer have the potential of improving symptoms. Mind–body interventions including yoga, mindfulness-based stress reduction, and hypnosis can improve symptoms, relaxation, and help patients in feeling more empowered. Manipulative approaches such as myofascial physical therapy, transvaginal biofeedback, and intravaginal Thiele massage can improve pelvic floor hypertonicity. Pulsed electromagnetic field therapy and acupuncture with or without moxibustion are associated with a reduction in pain. Different areas of complementary and alternative medicine have been studied for the treatment of IC/BPS, including biologically based therapies, mind-body interventions, manipulative and body-based approaches, and whole medical systems. These therapies have shown promising results. However, most of them have a small number of participants and do not provide high-quality evidence regarding their effectiveness. Randomized, placebo-controlled studies should be conducted to establish the efficacy of CAMs.

BLADDER PAIN SYNDROME

[Article in Danish]

Hanne Kobberø, Karin Andersen, Rie Seifert, Charlotte Graugaard-Jensen. *Ugeskr Laeger*. 2023 Mar 20;185(12):V10220614. PMID: 36999301

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Bladder pain syndrome is rare and leads to increased morbidity and decreased quality of life. The patients are a heterogenous group with different clinical presentations, and little is known of the different aspects of the syndrome. A thorough patient history and specialised diagnostics are required to offer these patients the best possible treatment. This review suggests an algorithm to manage these patients at all levels of the Danish health-care system. It is recommended that final diagnosis and multidisciplinary treatment should be centered at large regional hospitals.

[INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)]

[Article in German]

Winfried Vahlensieck. *Urologie*. 2023 Apr 28. doi: 10.1007/s00120-023-02080-x. Online ahead of print. PMID: 37115301. Abstract in English, German

In this review by W. Vahlensieck from Germany, aspects of interstitial cystitis/bladder pain syndrome (IC/BPS) are presented against the background of the German S2k guideline on this disease. Quite often this disease, characterized by bladder or lower abdominal pain (permanent or intermittent) and pollakisuria without pathogenic bacteria in the urine culture, is diagnosed much too late. The debate on disease definition, aspects on pathophysiology and epidemiology are presented here. For diagnosis, disease severity must be determined and relevant differential diagnoses like bladder cancer must be excluded. Conservative measures (clothing, food, sexuality, sport, bladder training, sufficient fluid intake, prevention of hypothermia) are effective especially in early stages of the disease. Combination drug therapy with mucosa stabilizing, anti-inflammatory, psychotropic, and pain-reducing drugs should be adjusted individually. Inpatient rehabilitation, hydrodistension, laser- and electrocoagulation, neuromodulation (sacral or pudendal) or hyperbaric oxygen therapy may help after pharmacotherapy failure. Cystectomy and urinary diversion are used in irreversible shrunken urinary bladder. If all treatment modalities are consequently used, many patients may reach a state that is more bearable. With a high level of suffering in many patients with IC/BPS, all available treatment modalities should be known and used.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: WHAT TODAY'S UROLOGIST SHOULD KNOW

Ifeoluwa Adelugba, Sana Siddiqui, Asef Aziz, Elise J. B. De, Gillian Wolff. *Curr Bladder Dysfunct Rep* 18, 16–28 (2023). <https://doi.org/10.1007/s11884-022-00676-1>

Interstitial cystitis/bladder pain syndrome is one of the more complicated pelvic pain conditions to diagnose and treat. This is confounded by its history of reclassification and redefinition within the literature over time. IC-BPS is conceptualized to exist as a local, organ-specific entity but is also expressed along a continuum of chronic pain, inflammatory and neurologic/psychiatric

pathophysiology. Patients with IC-BPS often present with co-morbidities such as fibromyalgia, migraine, depression/anxiety, irritable bowel syndrome, vulvodynia, and endometriosis. In this review from the USA, the authors highlight recent insights on approach, therapeutic optimization, and the most important strategies for the urologist to apply when caring for the IC-BPS patient. Current literature is focused on delineating IC-BPS into subgroups based on organ-localizing features such as Hunner lesions, biomarkers, and consideration of overlapping pain conditions. Guidelines and recent reviews of medication efficacy are presented. The benefits of a multidisciplinary approach are highlighted. Patient education and engagement is promoted as a means by which to improve efficiency and optimize care. Interstitial cystitis/bladder pain syndrome is a treatable condition. This article explores recent publications on pathophysiology and concludes with tools that urologists and collaborators can use in a multifaceted, multidisciplinary approach.

THE EFFECT OF THE PANDEMIC PERIOD ON BLADDER PAIN SYNDROME PATIENTS UNDER AMITRIPTYLINE TREATMENT

Mehmet Fatih Şahin, Ridvan Özcan, Arzu Malak, Çağrı Doğan, Cenk Murat Yazıcı, Müge Özcan, Murat Akgül. Neurourol Urodyn. 2023 May 8. doi: 10.1002/nau.25199. Online ahead of print. PMID: 37155258.

COVID-19 is a disease that may cause anxiety, depression, and stress. Bladder pain syndrome (BPS) is a disease in which stress and psychological factors might negatively affect its course. In this study from Turkey, Sahin and colleagues aimed to examine the possible clinical aggregation of the pandemic period on BPS patients. A total of 35 BPS patients diagnosed between 2010 and 2018 were included. All patients were using medical treatment, and the follow-up period was at least 6 months. According to their clinical follow-up protocol, the BPS patients were given the King's Health Questionnaire (KHQ), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Overactive Bladder Form V8 (OAB-V8), and Visual Analog Score (VAS) at every visit. In the sixth month of the pandemic, the clinical course of the patients was questioned by telephone or video interview, and their treatment continuities were questioned. Information was received about the delays in their follow-up and the difficulties in accessing healthcare opportunities. The same questionnaires were filled out and compared with pre-pandemic scores. The mean age of the patients included in the study was 50.2 ± 13.32 (min:20, max:74), 11 were males and 24 were females. The mean follow-up periods were 71.8 ± 35.6 months. All questionnaire scores showed an increase compared to the pre-pandemic period. A statistically significant increase was detected during the pandemic in all sub-units of the KHQ. The VAS and OAB-V8 scores of 16 patients who requested hospital admission were significantly higher than before the pandemic. However, there was no statistically significant difference in the increase in VAS and OAB-V8 scores of the 19 patients who refused to come to the hospital. BPS patients have been negatively affected by the emotional effects of the COVID-19 pandemic. Due to the fear, stress, anxiety, and depression, the symptoms of BPS patients exacerbated, and the patients could not receive the necessary support due to a lack of regular follow-ups.

UROLOGIC CHRONIC PELVIC PAIN SYNDROME - MALE

PREDICTORS OF MALE SEXUAL DYSFUNCTION IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS), OTHER CHRONIC PAIN SYNDROMES, AND HEALTHY CONTROLS IN THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP) RESEARCH NETWORK

Jeffrey C Loh-Doyle, Alisa J Stephens-Shields, Renee Rolston, Craig Newcomb, Bayley Taple, Siobhan Sutcliffe, Claire C Yang, Henry Lai, Larissa V Rodriguez. J Sex Med. 2022 Dec 1;19(12):1804-1812. doi: 10.1016/j.jsxm.2022.08.196. PMID: 37057400.

Sexual dysfunction (SD), including erectile (ED) and ejaculatory dysfunction, is associated with diminished quality of life (QoL) in men with UCPPS (chronic prostatitis/chronic pelvic pain syndrome

(CP/CPPS) and/or interstitial cystitis/bladder pain syndrome (IC/BPS)). This MAPP team sought to compare SD among male patients with UCPPS, other chronic pain conditions (positive controls, PC), and healthy controls (HC) without chronic pain, and to evaluate the association of comorbidities, psychosocial factors, and urologic factors of SD in all 3 groups. Baseline data from male UCPPS participants, PC (irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia) and HC enrolled in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Epidemiology and Phenotyping Study were included in the analysis. Sexual function was assessed using the International Index of Erectile Function-Erectile Function Domain (IIEFEF) and Ejaculatory Function Scale (EFS). Male ED was defined as a composite IIEF-EF score <21. Higher EFS score indicated worse sexual dysfunction; no threshold to define SD was identified for the EFS. Multivariable logistic and linear regression was used to investigate associations of comorbidities, psychosocial factors, and urologic factors with ED and ejaculatory, respectively. Comorbidities, genital pain, and psychosocial factors are associated with SD across the study population and male patients with UCPPS had a high prevalence of ED and greater ejaculatory dysfunction. There were 191 males with UCPPS; 44 PC; and 182 HC. Males with UCPPS had worse SD compared to PC and HC including lower mean IIEF-EF scores, greater degree of ejaculatory dysfunction, and lower quality of sexual relationships. Among all 3 cohorts, depression, stress, and pain were associated with ED in univariable and multivariable analysis, as was diabetes mellitus. Pain in the genitalia, severity of urinary symptoms, depression, stress, and history of childhood sexual trauma were associated with ejaculatory dysfunction in univariable and multivariable analysis. This was a multidisciplinary approach that addressed the identified risk factors for SD may improve overall QoL in males with UCPPS. This study is strengthened by its use of validated, patient-reported questionnaires and inclusion of healthy and positive controls. The authors note that their understanding of the role of IC in this study is limited because only 1 patient in the study had IC/BPS as a sole diagnosis. When compared to healthy controls and patients with other chronic pain conditions, males with UCPPS experience higher degrees of SD, including erectile and ejaculatory dysfunction.

CROSS SENSITIZATION

ANTINOCICEPTIVE EFFECTS OF AN ANTI-CGRP ANTIBODY IN RAT MODELS OF COLON-BLADDER CROSS ORGAN SENSITIZATION

Ehsan Noor-Mohammadi, Casey O Ligon, Kimberly D Mackenzie, Jennifer Stratton, Sara J Shnider, Beverley Greenwood-Van Meerveld. J Pharmacol Exp Ther. 2023 May 10;JPET-AR-2022-001480. doi: 10.1124/jpet.122.001480. Online ahead of print. PMID: 37164371.

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Irritable bowel syndrome (IBS) and bladder pain syndrome/interstitial cystitis (BPS/IC) are comorbid visceral pain disorders seen commonly in women with unknown etiology, limited treatment options and can involve visceral organ cross-sensitization. Calcitonin gene-related peptide (CGRP) is a mediator of nociceptive processing and may serve as a target for therapy. In three rodent models, the authors from the USA employed a monoclonal anti-CGRP F(ab')₂ to investigate the hypothesis that visceral organ cross-sensitization is mediated by abnormal CGRP signalling. Visceral organ cross-sensitization was induced in adult female rats via transurethral infusion of protamine sulfate (PS) into the urinary bladder or infusion into the colon of trinitrobenzene sulfonic acid (TNBS). Colonic sensitivity was assessed via the visceromotor response (VMR) to colorectal distension (CRD). Bladder sensitivity was assessed as the frequency of abdominal withdrawal responses (AWR) to von Frey filaments applied to the suprapubic region. PS- or TNBS-induced changes in colonic and bladder permeability were investigated in vitro via quantification of transepithelial electrical resistance (TEER). Peripheral administration of an anti-CGRP F(ab')₂ inhibited PS-induced visceral pain behaviours and colon hyperpermeability. Similarly, TNBS-induced pain behaviours and colon and bladder hyperpermeability were attenuated by anti-CGRP F(ab')₂ treatment. PS into the bladder or TNBS into the colon significantly increased the VMR to CRD and AWR to suprapubic stimulation and decreased bladder and colon TEER. These findings suggest an important role of peripheral CGRP in

visceral nociception and organ cross-sensitization and support the evaluation of CGRP as a therapeutic target for visceral pain in patients with IBS and/or BPS/IC. A monoclonal antibody against calcitonin gene-related peptide (CGRP) was found to reduce concomitant colonic and bladder hypersensitivity and hyperpermeability. The results of this study suggest that CGRP-targeting antibodies, in addition to migraine prevention, may provide a novel treatment strategy for multi-organ abdominopelvic pain following injury or inflammation.

CHRONIC PELVIC & GENITOURINARY PAIN

CLINICAL PROFILING OF SPECIFIC DIAGNOSTIC SUBGROUPS OF WOMEN WITH CHRONIC PELVIC PAIN.

Lysia Demetriou, Michal Krassowski, Pedro Abreu Mendes, Kurtis Garbutt, Allison F. Vitonis, Elizabeth Wilkins, Lydia Coxon, Lars Arendt-Nielsen, Qasim Aziz, Judy Birch, Andrew W Horne, Anja Hoffman, Lone Hummelshoj, Claire E Lunde, Jane Meijlink, Danielle Perro, Nilufer Rahmioglu, Kathryn L. Terry, Esther Pogatzki-Zahn, Christine B Sieberg, Rolf-Detlef Treede, Christian M Becker, Francisco Cruz, Stacey A Missmer, Krina T Zondervan, Jens Nagel, Katy Vincent. doi: <https://doi.org/10.1101/2022.10.03.22280515>. medRxiv

This article is a preprint.

Chronic pelvic pain (CPP) is a common condition affecting up to 26.6% of women, with many suffering for several years before diagnosis and/or treatment. Its clinical presentation is varied and there are frequently comorbid conditions both within and outside the pelvis. The authors aim to explore whether specific subgroups of women with CPP report different clinical symptoms and differing impact of pain on their quality of life (QoL). The study is part of the Translational Research in Pelvic Pain (TRiPP) project which is a cross-sectional observational cohort study. The study includes 769 female participants of reproductive age who completed an extensive set of questions derived from standardised WERF EPHeCT questionnaires. Within this population, the authors defined a control group (reporting no pelvic pain, no bladder pain syndrome, and no endometriosis diagnosis, N=230) and four pain groups: endometriosis-associated pain (EAP, N=237), interstitial cystitis/bladder pain syndrome (BPS, N=72), comorbid endometriosis-associated pain and BPS (EABP, N=120), and pelvic pain only (PP, N=127). Clinical profiles of women with CPP (13-50 years old) show variability of clinical symptoms. The EAP and EABP groups scored higher than the PP group ($p<0.001$) on the pain intensity scales for non-cyclical pelvic pain and higher than both the BPS and PP groups ($p<0.001$) on the dysmenorrhoea scale. The EABP group also had significantly higher scores for dyspareunia ($p<0.001$), even though more than 50% of sexually active participants in each pain group reported interrupting and/or avoiding sexual intercourse due to pain in the last 12 months. Scores for the QoL questionnaire (SF-36) reveal that CPP patients had significantly lower QoL across all SF-36 subscales ($p<0.001$). Significant effects were also observed between the pain groups for pain interference with their work ($p<0.001$) and daily lives ($p<0.001$), with the EABP suffering more compared to the EAP and PP groups ($p<0.001$). Their results demonstrate the negative impact that chronic pain has on CPP patients' QoL and reveal an increased negative impact of pain on the comorbid EABP group. Furthermore, it demonstrates the importance of dyspareunia in women with CPP. Overall, the results demonstrate the need for further exploration of interventions targeting QoL more broadly and suggest that novel approaches to classifying women with CPP are needed.

MYOFASCIAL FREQUENCY SYNDROME: A NOVEL SYNDROME OF BOTHERSOME LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH MYOFASCIAL PELVIC FLOOR DYSFUNCTION

A Lenore Ackerman, Nicholas J Jackson, Ashley T Caron, Melissa R Kaufman, Jonathan C Routh, Jerry L Lowder. medRxiv. 2023 Apr 17;2023.04.14.23288590. doi: [10.1101/2023.04.14.23288590](https://doi.org/10.1101/2023.04.14.23288590). PMID: 37131628 PMCID: PMC10153318.

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This article is a preprint.

Patients presenting with lower urinary tract symptoms (LUTS) are historically classified to several symptom clusters, primarily overactive bladder (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS). Accurate diagnosis, however, is challenging due to overlapping symptomatic features, and many patients do not readily fit into these categories. To enhance diagnostic accuracy, the authors previously described an algorithm differentiating OAB from IC/BPS. Herein, the authors from the USA sought to validate the utility of this algorithm for identifying and classifying a real-world population of individuals presenting with OAB and IC/BPS and characterize patient subgroups outside the traditional LUTS diagnostic paradigm. An Exploratory cohort of 551 consecutive female subjects with LUTS evaluated in 2017 were administered 5 validated genitourinary symptom questionnaires. Application of the LUTS diagnostic algorithm classified subjects into controls, IC/BPS, and OAB, with identification of a novel group of highly bothered subjects lacking pain or incontinence. Symptomatic features of this group were characterized by statistically significant differences from the OAB, IC/BPS and control groups on questionnaires, comprehensive review of discriminate pelvic exam, and thematic analysis of patient histories. In a Reassessment cohort of 215 subjects with known etiologies of their symptoms (OAB, IC/BPS, asymptomatic microscopic hematuria, or myofascial dysfunction confirmed with electromyography), significant associations with myofascial dysfunction were identified in a multivariable regression model. Pre-referral and specialist diagnoses for subjects with myofascial dysfunction were catalogued. Application of a diagnostic algorithm to an unselected group of 551 subjects presenting for urologic care identified OAB and IC/BPS in 137 and 96 subjects, respectively. An additional 110 patients (20%) with bothersome urinary symptoms lacked either bladder pain or urgency characteristic of IC/BPS and OAB, respectively. In addition to urinary frequency, this population exhibited a distinctive symptom constellation suggestive of myofascial dysfunction characterized as "persistency" : bothersome urinary frequency resulting from bladder discomfort/pelvic pressure conveying a sensation of bladder fullness and a desire to urinate. On examination, 97% of persistency patients demonstrated pelvic floor hypertonicity with either global tenderness or myofascial trigger points, and 92% displayed evidence of impaired muscular relaxation, hallmarks of myofascial dysfunction. They therefore classified this symptom complex "myofascial frequency syndrome". To confirm this symptom pattern was attributable to the pelvic floor, they confirmed the presence of "persistency" in 68 patients established to have pelvic floor myofascial dysfunction through comprehensive evaluation corroborated by symptom improvement with pelvic floor myofascial release. These symptoms distinguish subjects with myofascial dysfunction from subjects with OAB, IC/BPS, and asymptomatic controls, confirming that myofascial frequency syndrome is a distinct LUTS symptom complex. This study describes a novel, distinct phenotype of LUTS they classified as myofascial frequency syndrome in approximately one-third of individuals with urinary frequency. Common symptomatic features encompass elements in other urinary syndromes, such as bladder discomfort, urinary frequency and urge, pelvic pressure, and a sensation of incomplete emptying, causing significant diagnostic confusion for providers. Inadequate recognition of myofascial frequency syndrome may partially explain suboptimal overall treatment outcomes for women with LUTS. Recognition of the distinct symptom features of MFS (persistency) should prompt referral to pelvic floor physical therapy. To improve understanding and management of this as-yet understudied condition, future studies will need to develop consensus diagnostic criteria and objective tools to assess pelvic floor muscle fitness, ultimately leading to corresponding diagnostic codes.

RETROPERITONEAL CAUSES OF GENITOURINARY PAIN SYNDROMES: SYSTEMATIC APPROACH TO EVALUATION AND MANAGEMENT

Tarek Khalife, Amy M Hagen, Jessica E C Alm. Sex Med Rev. 2022 Oct 1;10(4):529-542. doi: 10.1016/j.sxmr.2022.06.009. PMID: 37051972.

Women with pelvic pain commonly report pain in their ovaries, vagina, uterus, or bladder. These symptoms may be caused by visceral genitourinary pain syndromes but also may be caused by musculoskeletal disorders of the abdomen and pelvis. Understanding neuroanatomical and

musculoskeletal factors that may contribute to genitourinary pain is important for evaluation and management. This review aimed to (i) highlight the importance of clinical knowledge of pelvic neuroanatomy and sensory dermatomal distribution of the lower abdomen, pelvis, and lower extremities, exemplified in a clinical case; (ii) review common neuropathic and musculoskeletal causes of acute and chronic pelvic pain that may be challenging to diagnose and manage; and (iii) discuss female genitourinary pain syndromes with a focus on retroperitoneal causes and treatment options. A comprehensive review of the literature was performed by searching the PubMed, Ovid Embase, MEDLINE, and Scopus databases using the keywords "chronic pelvic pain," "neuropathy," "neuropathic pain," "retroperitoneal schwannoma," "pudendal neuralgia," and "entrapment syndromes." Retroperitoneal causes of genitourinary pain syndromes have substantial overlap with common conditions treated in a primary care setting. Thus, a comprehensive and systematic history and physical examination, with focused attention to the pelvic neuroanatomy, is key to establishing the correct diagnosis. In the clinical case, such a comprehensive approach led to the unexpected finding of a large retroperitoneal schwannoma. This case highlights the intricacy of pelvic pain syndromes and the complex nature of their possible overlapping causes, which ultimately affects treatment planning. Knowledge of the neuroanatomy and neurodermatomes of the abdomen and pelvis, in addition to understanding pain pathophysiology, is critical when evaluating patients with pelvic pain. Failure to apply proper evaluation and implement proper multidisciplinary management strategies contributes to unnecessary patient distress, decreased quality of life, and increased use of health care services.

INTERVENTIONAL PAIN MANAGEMENT IN THE TREATMENT OF CHRONIC PELVIC PAIN

Jake Huntzinger, Meron Selassie. Curr Urol Rep. Curr Urol Rep. 2023 Apr;24(4):165-171. doi: 10.1007/s11934-022-01141-6. Epub 2023 Jan 31. PMID: 36719535.

Chronic pelvic pain syndrome (CPPS) is a common yet complex disease in the field of urology, gynecology, and pain management. This review article from the USA summarizes the anatomy and physiology of CPP with an in-depth discussion of established and emerging interventional treatment options. Though psychosocial variables play a significant role in the development and propagation of CPPS, interventional treatment strategies are available to ameliorate symptoms. Sympathetic and peripheral nerve blocks along with chemical and radiofrequency denervation are conventional, evidence-based treatments. Recent advances in spinal cord stimulation and dorsal root ganglion stimulation offer novel and effective therapeutic options to treat CPPS. A biopsychosocial model should be employed for effective management of CPPS with advances in neuromodulation offering newfound hope in alleviating symptoms and restoring function.

INFLAMMATORY BLADDER DISEASE

DESTROYED BLADDERS: CHARACTERIZATION OF PROGRESSIVE INFLAMMATORY CYSTITIS

Anna Faris, Giulia I Lane, Rohit Mehra, Vipulkumar Dadhania, Iryna Crescenze, J Quentin Clemens, Paholo Barboglio Romo, John Stoffel, Bahaa Malaeb, Yooni Blair, Meidee Goh, Priyanka Gupta, Anne P Cameron. PMID: 37126389.

Faris and colleagues from the USA identified a subset of patients with noninfectious cystitis who develop refractory symptoms marked by diffuse inflammatory changes, reduced bladder capacity, and vesicoureteral reflux (VUR), termed here as "progressive inflammatory cystitis" (PIC). Their objective was to describe the phenotype, disease outcomes, and pathologic findings of PIC. A single institution retrospective cohort study of patients with PIC. Patients with a history of pelvic radiation, urologic malignancy, or neurogenic bladder were excluded. The authors describe cohort characteristics and use bivariate analyses to compare subgroups. Kaplan-Meier methods estimate time to urinary diversion. From 2008 to 2020, 46 patients with PIC were identified. The median age of symptom onset was 63 years old (interquartile range [IQR]: 56, 70) and the most common presenting symptoms were urinary urgency/frequency (54%) and incontinence (48%). Urodynamics

showed a median maximum bladder capacity of 80 mL (IQR: 34, 152), commonly with VUR (68%) and hydronephrosis (59%). Ultimately 36 patients (78%) underwent urinary diversion at a median of 4.5 years (IQR: 2, 6.5) after symptom onset. Significant pathologic findings include presence of ulceration (52%), acute and chronic inflammation (68%), including eosinophils (80%), lymphoid follicles (56%), and mast cells in both lamina and muscularis propria (76%). PIC is a newly defined entity characterized by significantly diminished bladder capacity, upper tract changes, and relatively quick progression to urinary diversion. Larger prospective cohort studies are required to further characterize this severe phenotype of chronic non-infectious cystitis, aid earlier diagnosis, and guide management decisions.

LOWER URINARY TRACT

[AN ANALYSIS OF STATED INSURANCE COVERAGE AND ESTIMATED PATIENT-INCURRED COSTS OF TREATMENTS FOR LOWER URINARY TRACT SYMPTOMS](#)

Nuha Khalfay, Eric Lo, Tamara Grisales, A Lenore Ackerman. *Urogynecology (Hagerstown)*. 2023 Feb 1;29(2):287-294. doi: 10.1097/SPV.0000000000001307. PMID: 36735446.

Lower urinary tract symptoms (LUTSs) affect more than half of all adults, yet clinical care remains poor. Anecdotally, patients and health care providers express frustration over obstacles from insurance providers to obtaining LUTS treatment; however, little information concerning actual patient-incurred costs for these medications is available. This study from the USA aimed to analyze coverage by 5 major insurance companies and patient costs for LUTS pharmacotherapy. For each of 5 major nationwide insurance providers (Aetna, Blue Cross/Blue Shield, Cigna, Humana, United HealthCare), formulary coverage of medications for overactive bladder, interstitial cystitis/bladder pain syndrome, and genitourinary syndrome of menopause were reviewed for low- and high-cost plans. When not covered, the best preinsurance cash price of medications was determined from GoodRx. This qualitative analysis demonstrates that no guideline-directed therapy was universally covered by all insurance providers at low cost, regardless of the availability of generic alternatives. Medication prices ranged from \$3 to \$900 per month across plans. Inconsistencies in coverage and medication prices were common across insurance providers, between similar medications used for treatment of a given condition, and between a provider's low- and high-cost plans. Even medications that are U.S. Food and Drug Administration-approved and indicated by guidelines can have patient costs that are prohibitive. Because lack of care for LUTSs profoundly affects quality of life, the ability to live independently, and overall morbidity, improved price transparency is required to understand the health implications of limited coverage on LUTS care.

FUNCTIONAL BLADDER DISORDERS

[THE INNOVATIVE APPROACH IN FUNCTIONAL BLADDER DISORDERS: THE COMMUNICATION BETWEEN BLADDER AND BRAIN-GUT AXIS](#)

Jiwon Jung, Aram Kim, Seung-Hoon Yang. *Int Neurourol J*. 2023 Mar;27(1):15-22. doi: 10.5213/inj.2346036.018. Epub 2023 Mar 31. PMID: 37015721 PMCID: PMC10072998

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Functional bladder disorders including overactive bladder and interstitial cystitis may induce problems in many other parts of our body such as brain and gut. In fact, diagnosis is often less accurate owing to their complex symptoms. To have correct diagnosis of these diseases, it is necessary to understand the pathophysiology behind overlapping clinical presentation. First, the authors from Seoul, Korea focused on reviewing literature that has reported a link between the bladder and brain, as patients with bladder disorders frequently experience mood disorders such as depression and anxiety. Second, they reviewed literature that has described the relationship between the bladder and gut. Much evidence exists of patients who suffer from both bladder and intestinal diseases, such as irritable bowel syndrome and inflammatory bowel disease. Furthermore,

the interaction between brain and gut, well-known as brain-gut axis, might be a key factor that could change the activity of the bladder and vice versa. For example, the affective disorders could alter the activity of efferent nerves or the autonomic nervous system that modulate the gut itself and its microbiota, which might eventually cause the destruction of homeostasis in the bladder. In this way, communication between the bladder and brain-gut axis might affect permeability, inflammation, as well as infectious etiology and dysbiosis in bladder diseases. In this review, the authors aimed to find an innovative insight into the pathophysiology in functional bladder disorders and provide a new understanding of the overlapping clinical presentation by elucidating the pathophysiology of functional bladder disorders.

URINARY OXIDATIVE STRESS BIOMARKER LEVELS MIGHT BE USEFUL IN IDENTIFYING FUNCTIONAL BLADDER DISORDERS IN WOMEN WITH FREQUENCY AND URGENCY SYNDROME

Yuan-Hong Jiang, Jia-Fong Jhang, Hann-Chorng Kuo. *J Clin Med.* 2023 Mar 17;12(6):2336. doi: 10.3390/jcm12062336. PMID: 36983336 PMCID: PMC10057901.

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Lower urinary tract dysfunctions (LUTDs) are difficult to diagnose based on symptoms. This study from Hualien, Taiwan used a cluster of urinary biomarkers, including inflammatory cytokines, neurogenic proteins, and oxidative stress biomarkers, to identify LUTDs in women with frequency and urgency symptoms. In total, 253 women with video urodynamics (VUDS)- and cystoscopy-confirmed detrusor overactivity (DO), interstitial cystitis/bladder pain syndrome (IC/BPS), dysfunctional voiding (DV), and hypersensitive bladder (HSB), and normal controls were included. Before diagnosis and treatment, urine samples were collected for analysis of biomarkers. The urine levels of biomarkers were compared between groups with bladder dysfunctions and controls and were combined to test the sensitivity in identifying total pathological bladder diseases and specific bladder diseases. After video urodynamic study, VUDS, and urological examinations, bladder dysfunctions were classified into DO (n = 31), IC/BPS (n = 114), DV (n = 45), HSB (n = 29), and control (n = 34) groups. By using a cystometric bladder capacity of ≤ 350 mL, 186/219 (84.9%) of the patients with DO, IC/BPS, DV, and HSB can be discriminated from the controls. Among these urine biomarkers, oxidative stress biomarkers 8-isoprostane, 8-hydroxydeoxyguanosine (8-OHdG), or total antioxidant capacity (TAC) are useful for identifying pathological bladder dysfunction (DO, IC/BPS, and DV) and HSB. With elevated IL-1 β and lower IL-2, and elevated TNF- α levels, most patients with DV can be identified. Between DO and IC/BPS, a higher NGF level can identify 58.3% of IC/BPS cases, whereas a lower NGF level can identify 75.0% of DO cases. By using a cluster of urine biomarkers, DO, IC/BPS, and DV cases can be identified based on elevated levels of urine oxidative stress biomarkers 8-isoprostane, TAC, or 8-OHdG, and HSB cases with a low TAC. These urine biomarkers are useful for identifying specific LUTDs in women with frequency and urgency symptoms.

OVERACTIVE BLADDER COMPARED TO IC/BPS

OVERACTIVE BLADDER WITH URODYNAMIC STUDY-INDUCED BLADDER PAIN: AN OVERACTIVE BLADDER SUBTYPE WITH SYMPTOMS SIMILAR TO THOSE OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Hsueh-Yu Mu, Ming-Ping Wu, I-Te Wang, Jeng-Cheng Wu, Hung-Yen Chin. *Medicine (Baltimore).* 2023 Feb 10;102(6):e32790. doi: 10.1097/MD.00000000000032790. PMID: 36820564 PMCID: PMC9907989.

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Overactive bladder (OAB) and interstitial cystitis/painful bladder syndrome (IC/PBS) are 2 lower urinary tract disorders with urgency and bladder pain for diagnosis and with several other shared symptoms. Because of their overlapping symptoms, precise differential diagnosis of OAB and IC/PBS remains difficult. Thus, the authors from Taiwan characterized a subgroup of OAB with bladder pain (OAB-BP) that can be differentiated from OAB alone by urodynamic study (UDS) findings. They also

further examined the clinical presentations and urodynamic parameters of OAB alone, OAB-BP, and IC/PBS. Data were collected between September 2018 and April 2019. Patients were categorized into 3 groups, OAB-alone (no bladder pain during UDS, n = 39), OAB-BP (with bladder pain during UDS, n = 35), and IC/PBS (the comparator, n = 39). Chi-square tests were used to compare OAB alone, OAB-BP, and IC/PBS with respect to their clinical presentations and urodynamic parameters. Factors with $P < .05$ were further analyzed through post hoc comparisons with Bonferroni adjustment. A unique subgroup of OAB patients was identified (i.e., OAB-BP), bladder pain can only be induced at maximal cytometric capacity during UDS. They also identified that the case histories and UDS parameters (e.g., low first desire, normal desire, and maximum cytometric capacity) of the OAB-BP group were more similar to those of the IC/PBS group than to those of the OAB-alone group. The OAB-BP group and the IC/PBS group reported more intrusive, longer-lasting symptoms before their final diagnoses, more extensive family history of urinary tract disorder, and more associated comorbidities (e.g., irritable bowel syndrome, and myofascial pain) than the OAB-alone group. The UDS assessment induced bladder pain in the OAB-BP group to reveal their hidden symptoms. Careful attention to patient history and sophisticated UDS evaluation may help to identify this unique OAB group.

ASSESSMENT OF BLADDER PRESSURE AND DISCOMFORT SYMPTOMS: HOW DO OVERACTIVE BLADDER DIFFER FROM INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS?

Angelica Gousse, Joel Vetter, H Henry Lai. *BMC Urol.* 2023 Mar 30;23(1):53. doi: 10.1186/s12894-022-01164-8. PMID: 36997906 PMCID: PMC10061968.

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The purpose of this study from the USA was to better understand the sensation of bladder "pressure" and "discomfort", and how they are similar or distinct from the "pain" and "urgency" symptoms in IC/BPS and OAB. IC/BPS and OAB patients rated their bladder pain, pressure, discomfort, and urinary urgency on separate 0-10 numeric rating scales (NRS). Their NRS ratings were compared between IC/BPS and OAB, and Pearson correlations were performed. Among IC/BPS patients (n = 27), their mean numeric ratings of pain, pressure, discomfort, and urinary urgency were almost identical (6.6 ± 2.1 , 6.0 ± 2.5 , 6.5 ± 2.2 , and 6.0 ± 2.8 respectively). The three-way correlations between pain, pressure, or discomfort were very strong (all > 0.77). Among OAB patients (n = 51), their mean numeric ratings of pain, pressure, and discomfort (2.0 ± 2.6 , 3.4 ± 2.9 , 3.4 ± 2.9) were significantly lower than urgency (6.1 ± 2.6 , $p < 0.001$). The correlations between urgency and pain, and between urgency and pressure were weak in OAB (0.21 and 0.26). The correlation between urgency and discomfort was moderate in OAB (0.45). The most bothersome symptom of IC/BPS was bladder/pubis pain, while the most bothersome symptom of OAB was urinary urgency and daytime frequency. IC/BPS patients interpreted bladder pain, pressure, or discomfort as similar concepts and rated their intensity similarly. It is unclear whether pressure or discomfort provide additional information beyond pain in IC/BPS. Discomfort may also be confused with urgency in OAB. We should re-examine the descriptors pressure or discomfort in the IC/BPS case definition.

MICROBIOME

MICROBIOME IN LOWER URINARY TRACT SYMPTOMS (LUTSS): MAPPING THE STATE OF THE ART WITH BIBLIOMETRIC ANALYSIS

Hadi Mostafaei, Hanieh Salehi-Pourmehr, Mohammad Sajjad Rahnema'i, Helia Mostafaei, Shahrokh F Shariat, Sakineh Hajebrahimi. *Life (Basel).* 2023 Feb 16;13(2):552. doi: 10.3390/life13020552. PMID: 36836909 PMCID: PMC9964026.

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The main objective of this study from Austria, Iran and the Netherlands was to provide the first characterization of the current research field of the clinical microbiome in LUTS. First-of-its-kind scientometric insight into the historical development and structural state of the discipline is

provided by a field analysis, mapping, and sub-analysis of articles for future research. On 22 December 2022, the entire Scopus database was searched without language or date restrictions. Search terms included "Chronic prostatitis", OR "Interstitial cystitis", OR "Lower urinary tract symptoms", OR "Lower urinary tract dysfunction", OR "Overactive bladder", OR "Incontinence", OR "Urolithiasis", OR "Urothelium", OR "Urine", OR "Urology", OR "urinary disorder", OR "Pathophysiology", OR "Benign prostatic hyperplasia", OR "Benign prostatic enlargement", AND "Microbiota", OR "Microbiome", OR "Urobio-ma", OR "Urobiota; microflora". The author and institutional data were transformed using the analytical tool Biblioshiny (a Shiny app for Bibliometrix), which took into account variations in author spelling as well as institutional naming and subgroups. The specified search strategy was able to locate 529 documents from 267 sources published from 1981 to 2022. The average number of years from publication was 4.59 years. The authors with the most publications were Wolfe AJ and Brubaker I. The top three most collaborative networks were Loyola University Chicago, Loyola University Medical Center, and the University of California San Diego. The most frequently occurring words among the 50 nodes were: human, humans, nonhuman, female, adult, article, microbiology, microflora, microbiota, and controlled study. *Frontiers in Cellular and Infection Microbiology* and the *International Urogynecology Journal*, followed by *Nature Reviews Urology*, were the top three most relevant sources in microbiome research in urology. One of the most crucial requirements for developing research policies and anticipating the scientific requirements of researchers is paying attention to the evolution of various scientific fields. Understanding research gaps and future needs in microbiome research in urology can be effectively understood by paying attention to the models, maps, and visualizations used in this research, which are the results of systematic analysis of scientific products in the most esteemed scientific journals in the world.

MENOPAUSAL CHANGES IN THE MICROBIOME-A REVIEW FOCUSED ON THE GENITOURINARY MICROBIOME

Min Gu Park, Seok Cho, Mi Mi Oh. Diagnostics (Basel). 2023 Mar 21;13(6):1193. doi: 10.3390/diagnostics13061193. PMID: 36980501 PMCID: PMC10047399

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The authors from Korea note that balanced interaction between the host and its microbiome is crucial to health. Research regarding the significance of the gut and vaginal microbiomes in female health is substantial. However, fewer data regarding the urinary microbiome are available. Interactions between the gut, vaginal, and urinary microbiomes are also currently being researched. Hormone-induced dysbiosis after menopause is believed to have effects on physical changes and health consequences. Postmenopausal changes in the gut microbiome are associated with increased short-chain fatty acids and hydrogen sulfide levels. Increased vaginal pH caused by reduced estrogen alters the vaginal microbiome, resulting in reduced levels of *Lactobacillus*. Such changes influence the vaginal structure and functions, contributing to the onset of genitourinary syndrome of menopause. A dysbiosis of the urinary microbiome is associated with urgency and urinary incontinence and also related to interstitial cystitis/bladder pain syndrome and neuropathic bladder. As these diseases commonly affect postmenopausal women, hormone-induced changes in the microbiome may play a role. Menopause increases the alpha diversity of the urinary microbiome and lowers the percentage of *Lactobacillus* in urine, and such changes precede recurrent cystitis. More research regarding the effects of changes in the urinary microbiome due to menopause on urinary tract diseases is needed.

KETAMINE CYSTITIS

CURRENT APPROACHES FOR THE TREATMENT OF KETAMINE-INDUCED CYSTITIS

Juan Zhou, Cassidy Scott, Ziba Rovei Miab, Christian Lehmann. Neurourol Urodyn. 2023 Mar;42(3):680-689. doi: 10.1002/nau.25148. Epub 2023 Feb 13. PMID: 36780131

Ketamine is a dissociative anesthetic, historically used in a clinical setting for the induction and maintenance of anesthesia. Ketamine usage can produce undesirable psychological manifestations including hallucinations and long-term psychotomimetic effects. As a result of its fast onset and short period of action, ketamine is widely used as a recreational drug. Chronic abuse of ketamine can lead to significant urinary system complications including ketamine-induced cystitis (KIC). Common side effects of chronic ketamine abuse are urinary pain and discomfort and decreased bladder compliance and voiding pressure. Cessation of ketamine use is associated with improvement of symptoms however the exact pathophysiology of KIC remains unknown, complicating the ability of clinicians to treat this condition. The authors from Canada performed a literature search using the National Center for Biotechnology Information (NCBI) Pubmed database up to May 2021. Animal models of KIC are necessary to further understanding of KIC pathophysiology and explore potential treatment options. In all cases, cessation of ketamine use is the first line of treatment and is most effective in managing KIC. In addition to cessation, treatment plans must be tailored to the individual, based on the severity of symptoms and disease progression, and include options such as: oral anti-inflammatories, intravesical treatment and in the most severe cases, surgical intervention. KIC is a painful condition that currently lacks standardized treatment methods. Both animal models of KIC and clinical trials to further elucidate the mechanism of KIC pathophysiology must be explored to create targeted treatment plans.

RELATIONSHIP BETWEEN SEXUAL AND BLADDER DYSFUNCTION IN WOMEN CONSUMING KETAMINE

Bor-En Jong, Shang-Jen Chang, Chia-Hua Li, Stephen Shei-Dei Yang. J Sex Med. 2023 Mar 31;20(4):467-474. doi: 10.1093/jsxmed/qdac052. PMID: 36806738.

Although ketamine has become the second most popular recreational drug in Taiwan, there have been very few reported studies that investigated female sexual dysfunction (FSD) in ketamine abusers (KAs). The authors from Taiwan sought to compare the difference between street and hospital KAs and explored the risk factors for FSD and lower urinary tract symptoms (LUTS) in KAs. In this cross-sectional study, female KAs aged 18 years or older were invited to complete anonymous questionnaires during an educational course provided by the departments of substance control and prevention of the local government or under the instruction of medical providers at a urology clinic. Data were reported as median (IQR) and OR and analyzed with commercial statistical software. Key outcome measurements were illicit drug use history, FSD symptoms, and LUTS severity. They included 139 women (104 street and 35 hospital KAs) with a median age of 27.08 years. FSD was reported in 76% of all the participants (street vs hospital KAs, 68% vs 97%, $P < 0.001$). LUTS (Interstitial Cystitis Symptom Index [ICSI] + Interstitial Cystitis Problem Index [ICPI] ≥ 12) was found to be a significant risk factor for FSD in KAs. More hospital KAs (71%) reported experiencing LUTS (ICSI + ICPI ≥ 12) than street KAs (8%, $P < 0.001$). Longer duration of ketamine use (≥ 36 months) and mild to severe psychological symptoms (5-item Brief Symptom Rating Scale [BSRS-5] ≥ 6) were significant risk factors for LUTS. Sexual problems among KAs should not be overlooked since more severe sexual dysfunction was observed in patients reporting LUTS. According to the authors and to the best of their knowledge, the present study is the largest study using validated and reliable questionnaires to examine FSD in KAs and also the first study to include street KAs. The main limitation of this study is using self-report questionnaires as they are subjective and susceptible to human errors and recall biases. Women who abused ketamine and reported experiencing LUTS were found to be more likely to have FSD.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

CHARACTERIZATION OF PENTOSAN POLYSULFATE PATIENTS FOR DEVELOPMENT OF AN ALERT AND SCREENING SYSTEM FOR OPHTHALMIC MONITORING

Grant L Hom, Blanche L Kuo, James H Ross, Graham C Chapman, Neha Sharma, Resya Sastry, Justin C Muste, Tyler E Greenlee, Thais F Conti, Rishi P Singh, Sumit Sharma. Can J Ophthalmol. 2023 Mar 3;S0008-4182(23)00041-8. doi: 10.1016/j.jcjo.2023.01.019. Online ahead of print. PMID: 36878265

Pentosan polysulfate (PPS; ELMIRON, Janssen Pharmaceuticals, Titusville, NJ) is a U.S. Food and Drug Administration-approved oral medication for interstitial cystitis. Numerous reports have been published detailing retinal toxicity with the use of PPS. Studies characterizing this condition are primarily retrospective, and consequently, alert and screening systems need to be developed to actively screen for this disease. The goal of this study was to characterize ophthalmic monitoring trends of a PPS-using patient sample to construct an alert and screening system for monitoring this condition. A single-institution retrospective chart review was conducted between January 2005 and November 2020 to characterize PPS use. An electronic medical record (EMR) alert was constructed to trigger based on new PPS prescriptions and renewals offering ophthalmology referral. A total of 1407 PPS users over 15 years was available for characterization, with 1220 (86.7%) being female, the average duration of exposure being 71.2 ± 62.6 months, and the average medication cumulative exposure being 669.7 ± 569.2 g. A total of 151 patients (10.7%) had a recorded visit with an ophthalmologist, with 71 patients (5.0%) having optical coherence tomography imaging. The EMR alert fired for 88 patients over 1 year, with 34 patients (38.6%) either already being screened by an ophthalmologist or having been referred for screening. It was concluded that an EMR support tool can improve referral rates of PPS maculopathy screening with an ophthalmologist and may serve as an efficient method for longitudinal screening of this condition with the added benefit of informing pentosan polysulfate prescribers about this condition. Effective screening and detection may help determine which patients are at high risk for this condition.

NOCTURIA AND SLEEP DISORDERS

SLEEP DISORDERS, COMORBIDITIES, ACTIONS, LOWER URINARY TRACT DYSFUNCTION, AND MEDICATIONS ("SLEEP C.A.L.M.") IN THE EVALUATION AND MANAGEMENT OF NOCTURIA: A SIMPLE APPROACH TO A COMPLEX DIAGNOSIS

Thomas F Monaghan, Jeffrey P Weiss, Alan J Wein, Syed N Rahman, Jason M Lazar, Donald L Bliwise, Karel Everaert, Gary E Lemack, Jean-Nicolas Cornu, Marcus J Drake, Christopher R Chapple, Hashim Hashim, Jerry G Blaivas, Roger R Dmochowski. Neurourol Urodyn. 2023 Mar;42(3):562-572. doi: 10.1002/nau.25128. Epub 2023 Jan 19. PMID: 36655726.

Nocturia arises from a fundamental mismatch between nocturnal urine production, storage capacity, and sleep architecture, which may be driven by abnormalities of the genitourinary tract, but also by sleep disorders, medical diseases, patient actions/lifestyle factors, or medications. This article from the USA, France, Belgium and the United Kingdom introduces a novel system for organizing the complex differential diagnosis for nocturia, as proposed by an international collective of practicing urologists, physician specialists, and sleep experts: "Sleep CALM"-Sleep Disorders, Comorbidities, Actions, Lower Urinary Tract Dysfunction, and Medications. This is a narrative review of current evidence regarding the relevance of each "Sleep CALM" factor to nocturia pathogenesis, evaluation, and management. Nocturia and sleep disorders are highly intertwined and often bidirectional, such that nocturnal awakenings for reasons other than a sensation of bladder fullness should not be used as grounds for exclusion from nocturia treatment, but rather leveraged to broaden therapeutic options for nocturia. Nocturia is an important potential harbinger of several serious medical conditions beyond the genitourinary tract. Urologists should have a low threshold for primary care and medical specialty referral for medical optimization, which carries the potential to significantly improve nocturnal voiding frequency in addition to overall health status. Adverse patient actions/lifestyle factors, lower urinary tract dysfunction, and medication use commonly coexist with disordered sleep and comorbid medical conditions and may be the primary mediators of nocturia severity and treatment response, or further exacerbate nocturia severity and complicate treatment. "Sleep CALM" provides a memorable and clinically relevant means by which to structure the initial

patient history, physical exam, and clinical testing in accordance with current best-practice guidelines for nocturia. Although not intended as an all-encompassing diagnostic tool, the "Sleep CALM" schema may also be useful in guiding individualized ancillary testing, identifying the need for specialty referral and multidisciplinary care, and uncovering first-line treatment targets.

VULVODYNIA, VULVAR/VESTIBULAR PAIN

[SAFETY AND EFFICACY OF FRACTIONAL CO2 LASER TREATMENT TO THE VESTIBULE: A RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED, PROSPECTIVE 3-SITE CLINICAL STUDY IN WOMEN WITH VESTIBULAR PAIN](#)

Sue W Goldstein, Irwin Goldstein, Noel N Kim, Susan Kellogg-Spadt, Filippo Murina. J Sex Med. 2023 Feb 13; qdac053. doi: 10.1093/jsxmed/qdac053. Online ahead of print. PMID: 36779572.

The authors from the USA and Italy note that data are limited regarding fractional CO2 laser as a nonhormonal treatment for vestibular pain. Here they sought to perform what is, to their knowledge, the first multisite prospective randomized, double-blind, sham-controlled clinical trial to assess the safety and efficacy of fractional CO2 laser treatment to the vestibule in women with vestibular pain. Subjects (n = 70) meeting inclusion/exclusion criteria at each of 3 sites were randomized 2:1 to active or sham (zero energy) fractional CO2 laser treatment using the vestibular probe (SmartXide2 V2LR - MonaLisa Touch, DEKA, Florence, Italy). Subjects in each treatment arm received 3 treatments 4 weeks apart. At the initial follow-up (week 12), subjects were unblinded and those initially assigned to sham started active treatment. Outcome measures included changes from baseline in sexual activity diaries and scores for the Vulvosopic Genital Tissue Appearance Scale (VGTA), vestibular cotton-tipped swab testing, McGill Pain Questionnaire, Female Sexual Function Index (FSFI), Female Sexual Distress Scale-Revised (FSDS-R), and the O'Leary-Sant voiding and pain indices, the Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI). After active treatment, VGTA scores significantly improved in 5 parameters. Pain associated with cotton-tipped swab testing was significantly reduced at weeks 4 through 16 (mean change from baseline -0.64 [95% CI, -0.79 to -0.50] and -1.31 [95% CI, -1.46 to -1.16], respectively). FSFI pain domain scores improved significantly at weeks 12 and 16 (mean change from baseline 0.925 [95% CI, 0.10-1.75] and 1.22 [95% CI, 0.40-2.05], respectively). FSFI total scores increased significantly at weeks 12 and 16 (mean change from baseline 6.24 [95% CI, 2.64-9.85] and 4.96 [95% CI, 1.36-8.57], respectively). FSDS-R scores decreased significantly at weeks 12 and 16 (mean change from baseline -5.84 [95% CI, -8.80 to -2.87] and -9.15 [95% CI, -12.11 to -6.18], respectively). ICSI scores decreased significantly at weeks 12 and 16 (mean change from baseline -0.91 [95% CI, -1.65 to -0.18] and -0.754 [95% CI, -1.49 to -0.02], respectively). ICPI scores decreased significantly at week 16 (mean change from baseline -0.99 [95% CI, -1.63 to -0.34]). In contrast, there were no significant changes in outcomes in the sham arm. No serious adverse events occurred. Fractional CO2 laser treatment in women with vestibular pain resulted in improvement from baseline in multiple key outcome measures of vestibular health. Strengths of the study were that it was a multisite prospective randomized double-blind, sham-controlled clinical trial that included multiple measures related to vestibular pain and sexual function. Limitations were the nonvalidated primary outcome measure and limited study cohort. It was concluded that fractional CO2 laser therapy is a safe and effective nonhormonal treatment for vestibular pain.

GUIDELINES & CLASSIFICATIONS

[TOWARDS HARMONIZING THE CONCEPTS AND DEFINITIONS OF PAIN IN THE WORLD HEALTH ORGANIZATION'S FAMILY OF INTERNATIONAL CLASSIFICATIONS](#)

Michiel F Reneman, Melissa Selb, Beatrice Korwisi, Antonia Barke, Reuben S Escorpizo, Samson W Tu, Rolf-Detlef Treede. Pain. 2022 Dec 22. doi: 10.1097/j.pain.0000000000002854. Online ahead of print. PMID: 36728950 DOI: 10.1097/j.pain.0000000000002854

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Consistency of language is essential to facilitate high-quality care and patient education, high-quality and generalizable research, and high-quality education for the general public and students of healthcare professions in all stages of academic and professional training. A uniform language that is universally accepted and understood is key to enhancing communication and targeted delivery of care. The World Health Organization (WHO) has developed a “family” of 3 reference classifications to define and describe diseases, functioning, and interventions: the International Statistical Classification of Diseases and Related Health Problems (ICD), the International Classification of Functioning, Disability and Health (ICF), and the International Classification of Health Interventions (ICHI). The ICD enables the categorical classification of disease, disorders, and reasons for encounter with the health system, while the ICF provides a framework for documenting functioning and health. The ICHI is a tool for reporting and analyzing health interventions. All these classifications are intended for use at the individual and population level.

See video: https://cdn-links.lww.com/permalink/pain/b/pain_2023_02_02_reneman_pain-d-22-00623_sdc1.mp4

STATPEARLS (BOOKS) <https://www.ncbi.nlm.nih.gov/books/NBK430685/>

AMITRIPTYLINE

Amit Thour, Raman Marwaha.

In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.

2023 Feb 16. PMID: 30725910 Bookshelf ID: NBK537225

Free Books & Documents

Amitriptyline is FDA approved medication to treat depression in adults. The Non-FDA approved indications are anxiety, post-traumatic stress disorder, insomnia, chronic pain (diabetic neuropathy, fibromyalgia), irritable bowel syndrome, interstitial cystitis (bladder pain syndrome), migraine prophylaxis, postherpetic neuralgia, and sialorrhea. This activity reviews the indications, contraindications, activity, adverse events, and other key elements of amitriptyline in the clinical setting related to the essential points needed by members of an interprofessional team managing the care of patients that can benefit from amitriptyline therapy.

INTERSTITIAL CYSTITIS

Yizhe Lim, Seanan O'Rourke.

In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. 2023 Feb 8. PMID:

34033350 Bookshelf ID: NBK570588

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Interstitial cystitis is a condition that affects the urinary bladder, characterized by chronic inflammation. It is not secondary to an infection. In many cases, because it remains a diagnosis of exclusion, the condition is often diagnosed late in the patient's journey. Patients often describe pain in the bladder region (suprapubic), with a strong sensation to want to urinate (urgency). This sensation is worsened by filling the bladder and is often relieved by passing urine more often (frequency). This may be during the daytime and/or during the night (nocturia). There may also be other symptoms such as pain or discomfort on passing urine (dysuria) and pain or discomfort during sexual intercourse, known as dyspareunia. Due to these symptoms, there is a profound impact on the emotional, psychological and social well-being of the patient.

DYSURIA

Parth Mehta, Stephen W. Leslie, Anil Kumar Reddy Reddivari. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. 2023 Mar 6. PMID: 31751108 Bookshelf ID: NBK549918

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Dysuria is defined as the sensation of pain and/or burning, stinging, or itching of the urethra or urethral meatus associated with urination. It is a very common urinary symptom experienced by

most people at least once over their lifetime. Dysuria typically occurs when urine comes in contact with the inflamed or irritated urethral mucosal lining. This is exacerbated by and associated with detrusor muscle contraction and urethral peristalsis, which then stimulates the submucosal pain receptors resulting in pain or a burning sensation during urination. Several conditions can cause dysuria via different mechanisms. True dysuria requires differentiation from other symptoms, which can also occur due to pelvic discomfort from various bladder conditions such as interstitial cystitis, prostatitis, and suprapubic or retropubic pain.

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