

International Painful Bladder Foundation

The IPBF is a voluntary non-profit organization focused on interstitial cystitis/bladder pain syndrome/hypersensitive bladder/Hunner lesion
<https://www.painful-bladder.org/>

RESEARCH UPDATE

May 2022

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 free access to the full article online. Click on the title to go to the PubMed abstract or to the full article in the case of free access.

Terminology: different published articles use different terminology, for example: interstitial cystitis, painful bladder syndrome, (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. When reviewing the article, we use the terminology used by the authors.

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

IMMUNE CELL PROFILES OF PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Robert M Moldwin, Vishaan Nursey, Oksana Yaskiv, Siddhartha Dalvi, Eric J Macdonald, Michael Funaro, Chengliang Zhang, William DeGouveia, Marina Ruzimovsky, Horacio R Rilo, Edmund J Miller, Souhel Najjar, Inna Tabansky, Joel N H Stern. *J Transl Med.* 2022 Feb 21;20(1):97. doi: 10.1186/s12967-022-03236-7. PMID: 35193610 DOI: 10.1186/s12967-022-03236-7

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a disorder characterized by bladder pain upon filling which severely affects quality of life. Clinical presentation can vary. Local inflammatory events typify the clinical presentation of IC/BPS patients with Hunner lesions (IC/BPS-HL). It has previously been proposed that B cells are more prevalent in HL, but understanding their exact role in this environment requires a more complete immunological profile of HL. Moldwin and colleagues from the USA characterized immunological dysfunction specifically in HL using immunohistochemistry. They detected significantly more plasma cells (50× increase, $p < 0.0001$), B cells (28× increase, $p < 0.0001$), T cells (3× increase, $p < 0.0001$), monocytes/macrophages (6× increase, $p < 0.0001$), granulocytes (4× increase, $p < 0.0001$), and natural killer cells (2× increase, $p = 0.0249$) in IC/BPS patients with HL than in unaffected controls (UC). Patients with IC/BPS-HL also had significantly elevated urinary levels of IL-6 ($p = 0.0054$), TNF- α ($p = 0.0064$) and IL-13 ($p = 0.0304$) compared to patients with IC/BPS without HL (IC/BPS-NHL). In contrast, IL-12p70 levels were significantly lower in the patients with HL than in those without these lesions ($p = 0.0422$). Different cytokines were elevated in the urine of IC/BPS patients with and without HL, indicating that different disease processes are active in IC/BPS patients with and without HL. Elevated levels of CD138+, CD20+, and CD3+ cells in HL are consistent B and T-cell involvement in disease processes within HL.

SMALL FIBER POLYNEUROPATHY MAY BE A NEXUS BETWEEN AUTONOMIC NERVOUS SYSTEM DYSREGULATION AND PAIN IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Dylan T Wolff, Stephen J Walker. *Front Pain Res (Lausanne).* 2022 Jan 4;2:810809. doi: 10.3389/fpain.2021.810809. eCollection 2021. PMID: 35295485 PMCID: PMC8915770.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a highly heterogeneous chronic and debilitating condition which affects millions of women and men in the United States. While primarily defined by urinary symptoms and pain perceived to be emanating from the bladder, IC/BPS patients frequently have co-occurring conditions

and symptoms, many of which affect diverse body systems related to autonomic nervous system function. The impact on the autonomic system appears to stem from increased sympathetic innervation of the urinary tract, along with increased systemic sympathetic tone and decreased parasympathetic tone. Concurrent with these findings is evidence for destruction of peripheral sympathetic innervation to the sweat glands which may relate to small fiber polyneuropathy. It is unknown to what degree the wider alterations in autonomic function are also related to destruction/alterations in the small fibers carrying autonomic innervation. This potential nexus is an important point of investigation to better understand the unclarified pathophysiology of interstitial cystitis/bladder pain syndrome, the numerous co-occurring symptoms and syndromes, and for the identification of novel targeted therapeutic strategies.

CHANGES IN THE ULTRASTRUCTURE OF THE BLADDER UROTHELIUM IN PATIENTS WITH INTERSTITIAL CYSTITIS AFTER INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA

Yu-Khun Lee, Yuan-Hong Jiang, Jia-Fong Jhang, Han-Chen Ho, Hann-Chorng Kuo. Biomedicines. 2022 May 20;10(5):1182. doi: 10.3390/biomedicines10051182. PMID: 35625918.

Urothelial dysfunction is considered a key pathological mechanism of interstitial cystitis/bladder pain syndrome (IC/BPS). Intravesical platelet-rich plasma (PRP) injections might be effective for treating IC/BPS. This prospective study from Taiwan investigated the changes in electron microscopic findings among IC/BPS patients after intravesical PRP injections. Twenty-six patients with refractory non-ulcer IC/BPS underwent monthly intravesical PRP injections for 4 months. Changes in clinical symptom scores and video urodynamic study parameters were assessed from baseline to after the PRP injections. A post-treatment Global Response Assessment (GRA) score ≥ 2 was considered a successful outcome. The mean GRA score was significantly higher after 4 PRP injections than at baseline. Approximately 42% of patients experienced successful outcomes after PRP treatment. Urothelial ultrastructural defects showed no significant differences between baseline and after the PRP injections. However, patients showed variable improvements in different urothelial defects (grade improvements: urothelium cell layers, 31%; umbrella cell integrity, 42%; umbrella cell surface uroplakin plaque, 54%; tight junctions between adjacent umbrella cells, 46%; lysed organelles, 58%; inflammatory cell infiltration, 31%). Patients with successful treatment outcomes showed significant improvements in urothelial tight junction defects. Repeated intravesical PRP injections are effective for improving IC/BPS symptoms as they promote urothelial ultrastructural defect recovery.

ACTIVATION OF CXCL13/CXCR5 AXIS AGGRAVATES EXPERIMENTAL AUTOIMMUNE CYSTITIS AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Jiang Zhao, Shan Chen, Chengfei Yang, Mi Zhou, Teng Yang, Bishao Sun, Jingzheng Zhu, Hengshuai Zhang, Qudong Lu, Longkun Li, Zhenxing Yang, Bo Song, Wenhao Shen, Shanhong Yi, Shuangshuang Dai. Biochem Pharmacol. 2022 Jun;200:115047. doi: 10.1016/j.bcp.2022.115047. Epub 2022 Apr 19. PMID: 35452631.

The abnormal CXCL13/CXCR5 axis is involved in many inflammatory diseases and its selective inhibitor, TAK-799 has exhibited strong anti-inflammatory potency. The sequencing of clinical specimens from interstitial cystitis/bladder pain syndrome (IC/BPS) has shown that CXCL13 and CXCR5 are highly expressed, but the role of CXCL13/CXCR5 axis in IC/BPS has not been rarely reported. Therefore, in this study from Chongqing, China, the authors analyzed the GSE11783 sequencing data of IC/BPS patients and investigated the role and mechanism of CXCL13/CXCR5 axis and TAK-779 in the mouse model of experimental autoimmune cystitis (EAC). They verified that CXCL13 and CXCR5 were significantly up-regulated in EAC model. EAC mice exhibited increased bladder inflammatory factors (IL-6, TNF- α , IL-1 β), apoptosis-related proteins (Bax, Caspase-3, Caspase-8), frequency of voiding. Using TAK779 to block CXCL13/CXCR5 axis significantly attenuated these inflammatory damages and efficiently improved bladder function (significant reduction in micturition frequency, significant prolongation of inter-contraction interval). Further investigation showed that inhibition of JNK and NF-kappaB activation, the bioinformatics analysis-indicated downstream signalling of CXCL13/CXCR5 axis, is responsible for the protective effect of TAK779. Taken together, they demonstrate that activation of the CXCL13/CXCR5 axis is involved in the pathophysiology of IC/BPS and EAC. Blocking CXCL13/CXCR5 axis activation by TAK-779 reduces bladder inflammation and improves bladder function in EAC mice.

SUPERVISED MACHINE LEARNING ALGORITHM IDENTIFIED KRT20, BATF AND TP63 AS BIOLOGICALLY RELEVANT BIOMARKERS FOR BLADDER BIOPSY SPECIMENS FROM INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS

Tomohiko Kamasako, Kanya Kaga, Ken-Ichi Inoue, Masanori Hariyama, Tomonori Yamanishi. Int J Urol. 2022 Jan 31. doi: 10.1111/iju.14795. Online ahead of print. PMID: 35102612 DOI: 10.1111/iju.14795

This study from Japan was carried out to identify biomarkers that distinguish Hunner-type interstitial cystitis from non-Hunner-type interstitial cystitis patients. Total ribonucleic acid was purified from 212 punch biopsy specimens of 89 individuals who were diagnosed as interstitial cystitis/bladder pain syndrome. To examine the expression profile of patients' bladder specimens, 68 urothelial master transcription factors and nine known markers (E-cadherin, cytokeratins, uroplakins and sonic hedgehog) were selected. To classify the biopsy samples, principal component analysis was carried out. A decision tree algorithm was adopted to identify critical determinants, in which 102 and 116 bladder specimens were used for learning and validation, respectively. Principal component analysis segregated tissues from Hunner-type and non-Hunner-type interstitial cystitis specimens in principal component axes 2 and 4. Principal components 2 and 4 contained urothelial stem/progenitor transcription factors and cytokeratins, respectively. A decision tree identified KRT20, BATF and TP63 to classify non-Hunner-type and Hunner-type interstitial cystitis specimens. KRT20 was lower in tissues from Hunner-type compared with non-Hunner-type interstitial cystitis specimens. TP63 was lower in Hunner's lesions compared with adjacent mucosa from Hunner-type interstitial cystitis patients. Blinded validation using additional biopsy specimens verified that the decision tree showed fairly precise concordance with cystoscopic diagnosis. KRT20, BATF and TP63 were identified as biologically relevant biomarkers to classify tissues from IC/BPS specimens. The biologically explainable determinants could contribute to defining the elusive interstitial cystitis/bladder pain syndrome pathogenesis.

[INTEGRATING SINGLE-CELL RNA SEQUENCING WITH SPATIAL TRANSCRIPTOMICS REVEALS IMMUNE LANDSCAPE FOR INTERSTITIAL CYSTITIS](#)

Liao Peng, Xi Jin, Bo-Ya Li, Xiao Zeng, Bang-Hua Liao, Tao Jin, Jia-Wei Chen, Xiao-Shuai Gao, Wei Wang, Qing He, Guo Chen, Li-Na Gong, Hong Shen, Kun-Jie Wang, Hong Li, De-Yi Luo. Signal Transduct Target Ther. 2022 May 20;7(1):161. doi: 10.1038/s41392-022-00962-8. PMID: 35589692.

Interstitial cystitis (IC) is a severely debilitating and chronic disorder with unclear etiology and pathophysiology, which makes the diagnosis difficult and treatment challenging. To investigate the role of immunity in IC bladders, Peng and colleagues from China sequenced 135,091 CD45+ immune cells from 15 female patients with IC and 9 controls with stress urinary incontinence using single-cell RNA sequencing (scRNA-seq). 22 immune subpopulations were identified in the constructed landscape. Among them, M2-like macrophages, inflammatory CD14+ macrophages, and conventional dendritic cells had the most communications with other immune cells. Then, a significant increase of central memory CD4+ T cells, regulatory T cells, GZMK+CD8+ T cells, activated B cells, un-switched memory B cells, and neutrophils, and a significant decrease of CD8+ effector T cells, Th17 cells, follicular helper T cells, switched memory B cells, transitional B cells, and macrophages were noted in IC bladders. The enrichment analysis identified a virus-related response during the dynamic change of cell proportion, furthermore, the human polyomavirus-2 was detected with a positive rate of 95% in urine of patients with IC. By integrating the results of scRNA-seq with spatial transcriptomics, they found nearly all immune subpopulations were enriched in the urothelial region or located close to fibroblasts in IC bladders, but they were discovered around urothelium and smooth muscle cells in control bladders. These findings depict the immune landscape for IC and might provide valuable insights into the pathophysiology of IC.

[USE OF URINARY CYTOKINE AND CHEMOKINE LEVELS FOR IDENTIFYING BLADDER CONDITIONS AND PREDICTING TREATMENT OUTCOMES IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Wan-Ru Yu, Yuan-Hong Jiang, Jia-Fong Jhang, Hann-Chorng Kuo. Biomedicines. 2022 May 17;10(5):1149. doi: 10.3390/biomedicines10051149. PMID: 35625885.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a condition causing bladder inflammation. Urinary biomarkers have been assessed as suitable for the diagnosis and treatment. This study from Taiwan aimed at investigating the role of urinary biomarkers in identifying bladder conditions and predicting the treatment outcome of IC/BPS. A total of 309 patients with IC/BPS and 30 controls were enrolled in this study. All patients underwent a comprehensive urological workup of symptoms, pain severity, and cystoscopic hydrodistention findings including maximal bladder capacity (MBC) and glomerulation grade. Urine samples were collected to investigate the levels of urinary cytokines and chemokines. According to MBC and glomerulation grade, patients with IC/BPS were further classified into the Hunner's IC (HIC) and non-HIC groups. The urinary biomarkers between IC/BPS and control groups and HIC and non-HIC groups were compared. Moreover, the treatment response was graded according to global response assessment (GRA) scores, and urinary biomarker levels were analyzed based on different GRAs. Patients with IC/BPS had significantly high urinary monocyte chemoattractant protein-1, eotaxin, tumor necrosis factor -alpha (TNF- α), and prostaglandin E2 levels. Significantly higher levels of urinary interleukin-8, C-X-C motif chemokine ligand 10 (CXCL 10), brain-derived

neurotrophic factor, eotaxin, and regulated-on-activation, normal T-cell expressed and secreted (RANTES) were noted in HIC than those with non-HIC and controls. Among all biomarkers, TNF- α had the best sensitivity, specificity, positive predictive value, and negative predictive value. There was a significant correlation between biomarker levels and GRA. Significantly higher urine cytokines and chemokine levels were found in patients with IC/BPS. Most urinary biomarkers were significantly associated with MBC, glomerulation grade, and treatment outcome.

LECTINS AS BIOMARKERS OF IC/BPS DISEASE: A COMPARATIVE STUDY OF GLYCOSYLATION PATTERNS IN HUMAN PATHOLOGIC UROTHELIUM AND IC/BPS EXPERIMENTAL MODELS

Dominika Peskar, Tadeja Kuret, Jera Jeruc,, Andreja Erman. Diagnostics (Basel). 2022 Apr 25;12(5):1078. doi: 10.3390/diagnostics12051078. PMID: 35626233.

Pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) remains poorly understood, as well as its effective diagnosis and therapy. Studying changes in tissue glycosylation patterns under pathological conditions is a promising way of discovering novel biomarkers and therapeutic targets. The authors from Slovenia note that glycobiology of IC/BPS is largely understudied, and therefore they compared glycosylation patterns of normal human urothelium with the urothelium of IC/BPS patients using a selection of 10 plant-based lectins with different monosaccharide preferences. They also compared lectin binding to human urothelium with the two most cited experimental models of IC/BPS, specifically, TNF α -treated human urothelial cell line RT4 and cyclophosphamide-induced chronic cystitis in C57BL6/J mice. Furthermore, binding of four of the selected lectins (ConA, DSL, Jacalin and WGA) was evaluated qualitatively by means of fluorescence microscopy, and quantitatively by fluorescence intensity (F.I.) measurements. Their results reveal a significant reduction in F.I. of Jacalin, as well as a prominent change in the WGA labeling pattern in the urothelium of IC/BPS patients, suggesting their potential use as promising additional biomarkers for histopathological diagnosis of IC/BPS. They have also shown that urothelial glycosylation patterns between selected experimental models and patients with IC/BPS are similar enough to offer an adequate platform for preclinical study of IC/BPS glycobiology.

THE INVOLVEMENT OF ENDOTHELIN PATHWAY IN CHRONIC PSYCHOLOGICAL STRESS-INDUCED BLADDER HYPERALGESIA THROUGH CAPSAICIN-SENSITIVE C-FIBER AFFERENTS

Chuying Qin, Yinhuai Wang, Sai Li, Yuanyuan Tang, Yunliang Gao. J Inflamm Res. 2022 Feb 22;15:1209-1226. doi: 10.2147/JIR.S346855. eCollection 2022. PMID: 35228812 PMCID: PMC8882030 DOI: 10.2147/JIR.S346855.

[Free full article](#)

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a poorly understood chronic disorder characterized by bladder-related pain. Chronic psychological stress plays a key role in the exacerbation and development of IC/BPS via unclear mechanisms. This study from China aimed to investigate the role of endothelin 1 (ET-1) and its receptors in the development of chronic stress-induced bladder dysfunction. Wistar-Kyoto rats were exposed to chronic (10 days) water avoidance stress (WAS) or sham stress, with subgroups receiving capsaicin pretreatment to desensitize C-fiber afferents. Thereafter, cystometrograms (CMG) were obtained with visceromotor response (VMR) simultaneously during intravesical saline or ET-1 infusion. CMG recordings were analyzed for the first and the continuous voiding cycles, respectively. Endothelin receptor type A (ETAR) expression was examined in the bladder tissues and L6-S1 dorsal root ganglions (DRGs). Toluidine blue staining was to check the bladder inflammation and double-labeling immunofluorescence (IF) staining was to identify the locations of ETAR, respectively. During saline infusion, WAS rats elicited significant decreases in pressure threshold (PT) and in the ratio of VMR threshold/maximum intravesical pressure (IVPmax), and a significant increase in VMR duration and area under the curve (AUC). ET-1 infusion induced similar alternations in WAS rats, but further significantly diminished the pressure to trigger PT and VMR, together with a more forceful and longer VMR. The sole effect of WAS exposure or ET-1 administration on the micturition reflex could be suppressed by capsaicin pretreatment. WAS exposure significantly induced an increased number of total mast cells in the bladder, while capsaicin pretreatment possibly antagonized them. No significant difference in ETAR expression was found between all groups. IF staining indicated the co-localization of ETAR and calcitonin gene-related peptides in both bladder and DRGs. The activation of ET-1 receptors could enhance chronic stress-induced bladder hypersensitization and hyperalgesia through capsaicin-sensitive C-fiber afferents. Targeting the endothelin pathway may have therapeutic value for IC/BPS.

MULTIMODAL SINGLE-CELL ANALYSES OUTLINE THE IMMUNE MICROENVIRONMENT AND THERAPEUTIC EFFECTORS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Fei Su, Wei Zhang, Lingfeng Meng, Wei Zhang, Xiaodong Liu, Xiaorui Liu, Meng Chen, Yaoguang Zhang, Fei Xiao. *Adv Sci (Weinh)*. 2022 Apr 25;e2106063. doi: 10.1002/adv.202106063. Online ahead of print.

PMID: 35470584

Fei Su and colleagues from China report that interstitial cystitis/bladder pain syndrome (IC/BPS) has a significant impact on quality of life, but the etiopathogenesis remains largely unknown. The bladder microenvironment of patients with IC/BPS to obtain biological evidence supporting diagnosis and novel therapy is systematically characterized. Single-cell RNA sequencing (scRNA-seq) and image mass cytometry (IMC) are applied to bladder biopsies of the IC/BPS cohort. A total of 42 distinct cell clusters are identified from different groups. The increased hyperactivated Th1-biased response, but not Th2-biased response, and decreased immunosuppressive Treg are elucidated in the bladder microenvironment of non-Hunner-type IC (NHIC)/Hunner-type IC (HIC). M2/M2-like macrophage extends in the HIC and M1-like macrophage extends in NHIC, all of which secrete a range of chemokines with different pattern. The pro-inflammatory mediators, TNF- α , produced by tissue-resident macrophages and IL6, by the inflammatory fibroblasts are identified as key mediators of IC/BPS pathogenesis. Additionally, a regulatory network between different cell types is observed as a shift from structural cell communication in unaffected normal bladder to a Macrophage-Endothelial-dominated interactome in NHIC/HIC. The results demonstrate the high heterogeneity in NHIC/HIC, and provide an essential resource for diagnosis, and treatment of IC/BPS in the future by highlighting the importance of the microenvironment of bladder mucosa.

FUNCTIONAL GENOMIC ANALYSES OF IC/BPS PATIENT SUBGROUPS: A PILOT STUDY

Tyler Overholt, Robert J Evans, Gopal Badlani, Catherine A Matthews, Stephen J Walker. *Can J Urol*. 2022 Feb;29(1):11012-11019. PMID: 35150224

The purpose of this study from the USA was to further facilitate understanding of disease pathophysiology and patient stratification in IC/BPS, utilizing molecular phenotyping to compare three clinically distinct IC/BPS patient subgroups. Total RNA (miRNA and mRNA) was isolated via standard protocols from IC/BPS patient bladder biopsies and assayed on whole genome and microRNA expression arrays. Data from three patient subgroups: (1) low bladder capacity without Hunner's lesion, (2) low BC with Hunner's lesion, and (3) non-low BC were used in comparative analyses to evaluate the influence of BC and HL on gene expression profiles in IC/BPS. The BC comparison (Group 1 v 3) identified 54 miRNAs and 744 mRNAs. Eleven miRNAs mapped to 40 genes. Hierarchical clustering of miRNA revealed two primary clusters: (1) 3/4 low BC patients; (2) 4/4 non-low and 1/4 low BC patients. Clustering of mRNA provided clear separation based on BC. The HL comparison (Group 1 v 2) identified 16 miRNAs and 917 mRNAs. 4 miRNAs mapped to 13 genes. Clustering of miRNA and mRNA revealed clear separation based on HL status. Significant molecular differences in IC/BPS were found to be associated with the low BC phenotype (e.g., an upregulation of cell proliferation and inflammation marker genes), as well as additional molecular findings that further define the HL+ phenotype (e.g., upregulation of genes involved in bioenergetics reactions) and suggest oxidative stress may play a role.

WGCNA AND MOLECULAR DOCKING REVEAL KEY HUB GENES AND POTENTIAL NATURAL INHIBITOR IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Kuiqing Li, Cong Lai, Cheng Liu, Zhuohang Li, Kaixuan Guo, Kewei Xu. *Int Urogynecol J*. 2022 Mar 25. doi: 10.1007/s00192-022-05113-9. Online ahead of print. PMID: 35333927 DOI: 10.1007/s00192-022-05113-9

The etiology and treatment of interstitial cystitis/bladder pain syndrome are still controversial. The purpose of this study from China was to determine the key genes and specific regulatory pathways related to it and to find potential drug-active components through integrated bioinformatics. The data set GSE11783 was downloaded from GEO database. The modules significantly related to interstitial cystitis/bladder pain syndrome were identified by weighted correlation network analysis. The genes in the key modules were analyzed by functional enrichment and protein interaction by Cytoscape software, and finally the core hub genes were screened. Furthermore, the molecular docking verification of active components and key proteins was carried out by using AutoDock Vin software. Among the 14 modules derived from WGCNA, turquoise module had the highest correlation with IC/BPS. The genes in the module were mainly enriched in the biological processes such as the interaction between cytokines and cytokine receptors and chemokine signalling pathway. The genes in the related modules of differentially expressed genes and WGCNA traits were intersected to obtain the core hub genes. Protein-protein interaction network analysis showed that the key genes were upregulated genes CCR7 and CCL19. In terms of molecular docking, triptolide, the active component in the traditional anti-inflammatory drug *Tripterygium wilfordii*, can form effective molecular binding with both core hub genes. According to the authors, their study identified the core hub genes CCR7 and CCL19, which acted as essential components in interstitial cystitis/bladder pain syndrome. Furthermore, CCR7 and CCL19 can form effective binding with

triptolide, which will provide new insights into the development of new therapies for interstitial cystitis/bladder pain syndrome.

A PROSPECTIVE OBSERVATIONAL STUDY OF THE RECURRENCE CHARACTERISTICS OF HUNNER LESION AFTER REPEATED TRANSURETHRAL ABLATION IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Kwang Jin Ko, Hye Jin Byun, Seokhwan Bang, Kyu-Sung Lee. Int Neurourol J. 2022 May 25. doi: 10.5213/inj.2142408.204. Online ahead of print. PMID: 35619236.

The aim of this study from Korea was to investigate the rate and pattern of recurrence for patients with Hunner lesion (HL) type interstitial cystitis/bladder pain syndrome (IC/BPS) after transurethral ablation. This prospective study included 210 patients with HL type IC/BPS. The primary outcomes were the recurrence rate according to three patterns of recurrence: pattern A (according to the relationship with the previous surgical site), pattern B (according to the bladder zone), and pattern C (according to the number of lesions). The secondary outcomes were recurrence-free time after treatment according to pattern A and pattern C. The pattern A recurrence rate was 50.8% in the same site (A1), 6.7% at a new site (A2), and 42.5% at mixed sites (A3). The pattern B recurrence rate was 10.5% for the anterior wall, 59.0% for the posterior wall, 69.5% for the lateral wall, and 69.0% for the dome area. Multiple lesions recurred as multiple lesions in 75.8% of cases. The pattern C recurrence rate was 10.8% for C1 (single → single), 6.7% for C2 (single → multiple), 6.7% for C3 (multiple → single) and 75.8% for C4 (multiple → multiple). The recurrence-free time in pattern A was 13 months for A1, 12.5 months for A2, and 8 months for A3, with a significant difference between A1 and A3 ($p=0.008$). There was no significant difference in recurrence-free time in pattern C, either with single or multiple HLs. The distinct recurrence characteristics of HLs was not predictable despite repeated ablations. Complete remission should not be expected because the whole bladder was to have the potential to develop the HLs even after repeated transurethral ablation.

THE ROLE OF URINARY VEGF IN OBSERVATIONAL STUDIES OF BPS/IC PATIENTS: A SYSTEMATIC REVIEW

Pedro Abreu-Mendes, Aurora Costa, Ana Charrua, Rui Almeida Pinto, Francisco Cruz. Diagnostics (Basel). 2022 Apr 20;12(5):1037. doi: 10.3390/diagnostics12051037. PMID: 35626193 DOI: 10.3390/diagnostics12051037

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic pain condition, often underdiagnosed, with an important impact on patient quality of life. More recently, an association between VEGF and its receptors has been suggested in BPS/IC pathophysiology, due to their role in promoting angiogenesis and inflammation, which can enhance bladder pain. Eventually, VEGF may be used as a biomarker for the diagnosis and prognostication of BPS/IC. To further clarify this issue, this review from Portugal aims to critically summarize the available information, giving rise to a solid starting point for future studies. The authors systematically searched PubMed and Embase, using the queries "urinary VEGF", "urinary VEGF" AND "pain", "urinary VEGF" AND "lower urinary tract symptoms" and "urinary VEGF" AND "LUTS" from January 2016 to February 2022. A total of 1026 papers were identified from which 7 articles were included in this study, which assessed 1036 participants. Regarding VEGF levels, overactive bladder (OAB) and healthy patients were used for comparison with BPS/IC patients. VEGF concentration seems to be higher when compared to healthy patients and overactive bladder (OAB) patients. Higher levels of VEGF were associated with pain severity, while a decrease in VEGF concentration was associated with pain and symptom improvement in women. However, these findings were not constant in all studies. There is a trend toward a relevant association between increased VEGF levels and pain or symptom severity in BPS/IC patients. Although there are some discrepancies among the studies and the number of patients included is small, VEGF and its receptors should be considered for future studies regarding its use in BPS/IC pathophysiology, diagnosis and prognostication.

MONOCLONAL ANTIBODY THERAPY FOR THE TREATMENT OF INTERSTITIAL CYSTITIS

Ioannis Mykoniatis, Stavros Tsiakaras, Michael Samarinas, Anastasios Anastasiadis, Evangelos N Symeonidis, Petros Sountoulides. Biologics. 2022 May 20;16:47-55. doi: 10.2147/BTT.S290286. eCollection 2022. PMID: 35619987 PMCID: PMC9129098.

An emerging theory regarding the potentially autoimmune nature of painful bladder syndrome/interstitial cystitis (PBS/IC) had led to several studies being conducted to assess the possible therapeutic effect of immunotherapeutic options for PBS/IC. This review from Greece presents the available evidence regarding the potential autoimmunity-based pathogenesis of PBS/IC and focuses on a main representative of the immunotherapeutic modalities for PBS/IC, aiming to summarize, evaluate, and present available data regarding the potential therapeutic role of monoclonal antibodies for PBS/IC patients. A non-systematic

narrative and interpretative literature review was performed. The monoclonal antibodies included in the review were the anti-tumor necrosis factor- α (anti-TNF- α) agents adalimumab, which showed no difference compared to placebo, and certolizumab pegol, which showed statistically important differences in all outcome measures compared to placebo at the 18-week follow-up visit. Anti-nerve growth factor (anti-NGF) agents were also reviewed, including tanezumab, which showed both positive and negative efficacy results compared to placebo, and fulranumab, the study of which was discontinued owing to adverse events. In summary, monoclonal antibody therapy remains to be further researched in order for it to be proposed as a promising future treatment option for PBS/IC.

THE ROLE OF PIEZO1 IN URINARY BLADDER FUNCTION AND DYSFUNCTION IN A RODENT MODEL OF CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Katharine I K Beča, Beatrice M Girard, Thomas J Heppner, Grant W Hennig, Gerald M Herrera, Mark T Nelson, Margaret A Vizzard. Front Pain Res (Lausanne). 2021 Oct 12;2:748385. doi: 10.3389/fpain.2021.748385. eCollection 2021. PMID: 35295484 PMCID: PMC8915741.

In the urinary bladder, mechanosensitive ion channels (MSCs) underlie the transduction of bladder stretch into sensory signals that are relayed to the PNS and CNS. PIEZO1 is a recently identified MSC that is Ca²⁺ permeable and is widely expressed throughout the lower urinary tract. Recent research indicates that PIEZO1 is activated by mechanical stretch or by pharmacological agonism via Yoda1. Aberrant activation of PIEZO1 has been suggested to play a role in clinical bladder pathologies like partial bladder outlet obstruction and interstitial cystitis/bladder pain syndrome (IC/BPS). In the present study, the authors from the USA show that intravesical instillation of Yoda1 in female Wistar rats leads to increased voiding frequency for up to 16 hours after administration compared to vehicle treatment. In a cyclophosphamide (CYP) model of cystitis, they found that the gene expression of several candidate MSCs (Trpv1, Trpv4, Piezo1, and Piezo2) were all upregulated in the urothelium and detrusor following chronic CYP-induced cystitis, but not acute CYP-induced cystitis. Functionally with this model, they show that Ca²⁺ activity is increased in urothelial cells following PIEZO1 activation via Yoda1 in acute and intermediate CYP treatment, but not in naïve (no CYP) nor chronic CYP treatment. Lastly, they show that activation of PIEZO1 may contribute to pathological bladder dysfunction through the downregulation of several tight junction genes in the urothelium including claudin-1, claudin-8, and zona occludens-1. Together, these data suggest that PIEZO1 activation plays a role in dysfunctional voiding behaviour and may be a future, clinical target for the treatment of pathologies like IC/BPS.

ACTIVATION OF TRANSLOCATOR PROTEIN ALLEVIATES MECHANICAL ALLODYNIA AND BLADDER DYSFUNCTION IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS THROUGH REPRESSION OF BDNF-MEDIATED NEUROINFLAMMATION

Yong Huang, Minzhi Su, Chi Zhang, Hailun Zhan, Fei Yang, Zhentao Gao, Xiangfu Zhou, Bolong Liu. Eur J Pain. 2022 Mar 16. doi: 10.1002/ejp.1942. Online ahead of print. PMID: 35293071 DOI: 10.1002/ejp.1942

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a refractory disease accompanied by bladder-related pain and hyperactivity. Studies have shown that the translocator protein (TSPO) modulates neuroinflammation and central sensitisation associated with pain. Moreover, the authors from China note that they have previously demonstrated that brain-derived neurotrophic factor (BDNF) regulates neuroinflammation and mechanical allodynia in cyclophosphamide (CYP)-induced cystitis through activation of glial cells. Here, they aimed to explore whether activation of TSPO attenuates mechanical allodynia and bladder dysfunction by regulating BDNF induced neuroinflammation in a CYP-induced cystitis model. Injection of CYP was performed to form a rat model of BPS/IC. The expression of TSPO was regulated by intrathecal injection of the TSPO agonist Ro5-4864. The von Frey filament test was applied to evaluate suprapubic allodynia. Bladder function was assessed using filling cystometry. Western blotting was used to detect the expression of TSPO, BDNF, GFAP, Iba-1, p-p38, p-JNK, TNF- α , and IL-1 β , and double immunofluorescence was performed to localise TSPO in the L6-S1 spinal dorsal horn (SDH). TSPO was activated in the SDH after CYP injection and was primarily colocalised with astrocytes. Ro5-4864 reversed mechanical allodynia and bladder dysfunction induced by CYP. Moreover, the upregulation of BDNF and activation of astrocytes and microglia was suppressed by Ro5-4864, resulting in downregulation of p-p38, p-JNK, TNF- α , and IL-1 β . It was concluded that Ro5-4864 alleviated mechanical allodynia and bladder dysfunction in the CYP model, possibly by inhibiting the elevation of BDNF and consequent activation of astrocytes and microglia induced neuroinflammation. TSPO may be a potential target for the treatment of BPS/IC. This study examined the mechanism underlying the ability of the translocator protein to modulate bladder pain syndrome/interstitial cystitis.

BOSWELIC ACIDS, PENTACYCLIC TRITERPENES, ATTENUATE OXIDATIVE STRESS, AND BLADDER TISSUE DAMAGE IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Maryam Fatima, Irfan Anjum, Aamir Abdullah, Shaun Zshaan Abid, Muhammad Nasir Hayat Malik. *ACS Omega*. 2022 Apr 14;7(16):13697-13703. doi: 10.1021/acsomega.1c07292. eCollection 2022 Apr 26. PMID: 35559194 PMCID: PMC9088903.

Boswellic acids, derived from the *Boswellia serrata* plant, have been demonstrated to have anti-inflammatory properties in experimental animal models. The present study from Pakistan was aimed to evaluate the uro-protective effect of boswellic acids in rats with cyclophosphamide-induced cystitis. Interstitial cystitis was induced by cyclophosphamide (CYP). In order to analyze the reduction of the urothelial damage, the bladder weight, the nociception response, and the Evans blue dye extravasation from the bladder were evaluated. To investigate the involvement of lipid peroxidation and enzymatic antioxidants CAT, SOD, and GPX and MPO and NO were evaluated. IL-6 and TNF- α were measured by the ELISA immunoassay technique. The results showed that pretreatment with boswellic acids significantly reduced urothelial damage which was accompanied by a decrease in the activity of MDA, CPO, and NO levels and prevention of the depletion of CAT, SOD, and GPX. The levels of IL-6 and TNF- α were dramatically reduced by boswellic acids. Histopathological findings revealed a considerable reduction in cellular infiltration, edema, epithelial denudation, and bleeding. Their findings showed that boswellic acids, by their antioxidant and anti-inflammatory properties, negate the detrimental effects of cyclophosphamide on the bladder, suggesting boswellic acids as promising therapeutic alternatives for cystitis.

NEONATAL BLADDER INFLAMMATION RESULTS IN ADULT FEMALE MOUSE PHENOTYPE WITH INCREASED FREQUENCY AND NOCICEPTIVE RESPONSES TO BLADDER FILLING

Buffie Clodfelder-Miller, Timothy J Ness, Jennifer J DeBerry. *Front Syst Neurosci*. 2022 Mar 11;16:858220. doi: 10.3389/fnsys.2022.858220. eCollection 2022. PMID: 35359621 PMCID: PMC8963710 DOI: 10.3389/fnsys.2022.858220

[Free full article](#)

Bladder pain and hypersensitivity to bladder filling are clinically common, but animal models examining syndromes with these features are limited. A rat model of bladder hypersensitivity produced by neonatal bladder inflammation (NBI) has been reported to have many of the clinical features of bladder pain syndromes. The present study from the USA sought to determine whether similar hypersensitivity might be induced by NBI in mice. Female C57BL6/J mice had NBI induced on postnatal days P12-14 by the intravesical administration of zymosan. As adults (12-14 weeks of age), the mice were examined for hypersensitivity of their bladders as: spontaneous voiding and evoked cystometrograms at baseline, and visceromotor responses (VMRs) to urinary bladder distension (UBD) following a secondary insult (either repeated bladder inflammation or acute stress induced by footshock). Mice that experienced NBI demonstrated hypersensitivity, when compared with control mice, manifested as increased spontaneous voiding, increased frequency of evoked voids during intravesical saline infusion, and increased vigor of VMRs to UBD following either acute bladder inflammation or acute stress. This recapitulates the hallmark features of clinical painful bladder disorders and suggest utility of this murine model for the study of these disorders while allowing methodological expansion into well-established genetic and immunological models.

NEONATAL CYSTITIS LEADS TO ALTERATIONS IN SPINAL CORTICOTROPIN RELEASING FACTOR RECEPTOR-TYPE 2 CONTENT AND FUNCTION IN ADULT RATS FOLLOWING BLADDER RE-INFLAMMATION

Timothy J Ness, Cary DeWitte., Alan Randich. *Int J Gen Med Brain Res*. 2022 Apr 26;1788:147927. doi: 10.1016/j.brainres.2022.147927. Online ahead of print. PMID: 35477003 DOI: 10.1016/j.brainres.2022.147927

Spinal mechanisms associated with visceral hypersensitivity are poorly understood. One model of bladder hypersensitivity with phenotypic features similar to the disorder interstitial cystitis/bladder pain syndrome is the neonatal bladder inflammation (NBI) model. In this model, rat pup bladders are infused with zymosan solutions on post-partum days 14-16 and then rats are retested as adults. Studies of other sites of deep tissue hypersensitivity have suggested a role for corticotropin-releasing factor (CRF) receptors type 1 and 2 (CRFR1 and CRFR2). Using neurochemical measures, pharmacological manipulations and both reflex and neuronal responses to urinary bladder distension as endpoints, the present study probed the role of CRFR2s in bladder hyperalgesia secondary to NBI and acute bladder re-inflammation as an adult (ABI). ELISA measures of the lumbosacral spinal cord demonstrated increased CRFR1s and CRFR2s following pretreatment with both NBI + ABI as well as NBI-related increases in the CRFR2 agonist urocortin 2. Intrathecal CRFR2 antagonists, but not a CRFR1 antagonist, blocked the augmentation of visceromotor responses to distension following pretreatment with both NBI + ABI. Lumbosacral dorsal horn neuronal responses to distension in rats pretreated with NBI +

ABI were attenuated by the spinal topical administration of a CRFR2 antagonist. These studies suggest therapeutic value of CRFR2 antagonists in the treatment of painful bladder disorders.

NEONATAL CYSTITIS ALTERS MECHANISMS OF STRESS-INDUCED VISCERAL HYPERSENSITIVITY IN RATS

Timothy J Ness, Cary DeWitte, Meredith T Robbins, Jennifer J DeBerry. Neurosci Lett. 2022 Apr 4;778:136617. doi: 10.1016/j.neulet.2022.136617. Online ahead of print. PMID: 35390467.

Ness and colleagues from the USA report that in rodent models, conditioning with acute footshock (AFS) has been demonstrated to produce bladder hypersensitivity which is more robust when rats, tested as adults, had also been pretreated with neonatal bladder inflammation (NBI). The spinal neurochemical mechanisms of nociceptive processes in rats pretreated with NBI are not fully known and so the present study administered intrathecal (IT) opioid (naloxone) and NMDA receptor (MK-801) antagonists to determine whether these receptors' actions had been altered by NBI. Female Sprague-Dawley rat pups were intravesically pretreated on postnatal days P14-P16 with a 1% zymosan solution or with control procedures and then raised to adulthood (12-15 weeks of age). Bladder hypersensitivity was induced through use of an AFS paradigm. Visceromotor responses (VMRs; abdominal muscle contractions) to graded, air pressure-controlled urinary bladder distension were used as nociceptive endpoints. Immediately following AFS pretreatments, rats were anesthetized and surgically prepared. Pharmacological antagonists were administered via an IT catheter onto the lumbosacral spinal cord and VMRs determined 15 min later. Administration of IT naloxone hydrochloride (10 µg) to rats which had been pretreated only with AFS resulted in VMRs that were more robust than VMRs in similarly pretreated rats that received IT normal saline. In contrast, IT naloxone had no significant effect on rats that had been pretreated with both NBI&AFS, although MK-801 was inhibitory. These effects of IT naloxone suggest the presence of inhibitory influences in normal rats that are absent in rats pretreated with NBI. Absence of inhibitory influences produced by AFS was also demonstrated in rats pretreated with NBI&AFS using measures of thermal paw withdrawal latency (PWL): rats pretreated with only AFS had longer PWLs than rats pretreated with both NBI&AFS. Together, a reduction in anti-nociceptive mechanisms coupled with pro-nociceptive NMDA-linked mechanisms results in more robust nociceptive responses to distension in rats which had experienced NBI.

IMATINIB MESYLATE REDUCES NEUROTROPHIC FACTORS AND PERK AND PAKT EXPRESSION IN URINARY BLADDER OF FEMALE MICE WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Megan Perkins, Beatrice M Girard, Susan E Campbell, Grant W Hennig, Margaret A Vizzard. Front Syst Neurosci. 2022 Apr 22;16:884260. doi: 10.3389/fnsys.2022.884260. eCollection 2022. PMID: 35528149 PMCID: PMC9072830.

Free full article

Imatinib mesylate is a tyrosine kinase inhibitor that inhibits platelet-derived growth factor receptor (PDGFR)- α , - β , stem cell factor receptor (c-KIT), and BCR-ABL. PDGFR α is expressed in a subset of interstitial cells in the lamina propria (LP) and detrusor muscle of the urinary bladder. PDGFR α + interstitial cells may contribute to bladder dysfunction conditions such as interstitial cystitis/bladder pain syndrome (IC/BPS) or overactive bladder (OAB). The authors from the USA report that they have previously demonstrated that imatinib prevention via oral gavage or treatment via intravesical infusion improves urinary bladder function in mice with acute (4 hour, h) cyclophosphamide (CYP)-induced cystitis. Here, they investigate potential underlying mechanisms mediating the bladder functional improvement by imatinib using a prevention or treatment experimental design. Using qRT-PCR and ELISAs, they examined inflammatory mediators (NGF, VEGF, BDNF, CCL2, IL-6) previously shown to affect bladder function in CYP-induced cystitis. They also examined the distribution of phosphorylated (p) ERK and pAKT expression in the LP with immunohistochemistry. Imatinib prevention significantly ($0.0001 \leq p \leq 0.05$) reduced expression for all mediators examined except NGF, whereas imatinib treatment was without effect. Imatinib prevention and treatment significantly ($0.0001 \leq p \leq 0.05$) reduced pERK and pAKT expression in the upper LP (U. LP) and deeper LP (D. LP) in female mice with 4 h CYP-induced cystitis. Although they have previously demonstrated that imatinib prevention or treatment improves bladder function in mice with cystitis, the current studies suggest that reductions in inflammatory mediators contribute to prevention benefits of imatinib but not the treatment benefits of imatinib. Differential effects of imatinib prevention or treatment on inflammatory mediators may be influenced by the route and frequency of imatinib administration and may also suggest other mechanisms (e.g., changes in transepithelial resistance of the urothelium) through which imatinib may affect urinary bladder function following CYP-induced cystitis.

[NEW THERAPEUTIC APPROACH WITH EXTRACELLULAR VESICLES FROM STEM CELLS FOR INTESTINAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Ahmed Abdal Dayem, Kwonwoo Song, Soobin Lee, Aram Kim, Ssang-Goo Cho. *BMB Rep.* 2022 Apr 12;5585. Online ahead of print. PMID: 35410640

[Free full article.](#)

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating chronic disorder characterized by suprapubic pain and urinary symptoms such as urgency, nocturia, and frequency. The prevalence of IC/BPS is increasing as diagnostic criteria become more comprehensive. Conventional pharmacotherapy against IC/BPS has shown suboptimal effects, and consequently, patients with end-stage IC/BPS are subjected to surgery. The novel treatment strategies should have two main functions, anti-inflammatory action and the regeneration of glycosaminoglycan and urothelium layers. Stem cell therapy has been shown to have dual functions. Mesenchymal stem cells (MSCs) are a promising therapeutic option for IC/BPS, but they come with several shortcomings, such as immune activation and tumorigenicity. MSC-derived extracellular vesicles (MSC-EVs) hold numerous therapeutic cargos and are thus a viable cell-free therapeutic option. In this review, the authors from Korea provide a brief overview of IC/BPS pathophysiology and limitations of the MSC-based therapies. Then they provide a detailed explanation and discussion of therapeutic applications of EVs in IC/BPS as well as the possible mechanisms. They believe their review will give an insight into the strengths and drawbacks of EV-mediated IC/BPS therapy and will provide a basis for further development.

[EFFECT OF THE NEUROPATHIC PAIN RECEPTOR P2X3 ON BLADDER FUNCTION INDUCED BY INTRAPERITONEAL INJECTION OF CYCLOPHOSPHAMIDE \(CYP\) IN INTERSTITIAL CYSTITIS RATS](#)

Lei Pang, Jinkai Shao, Xiaodong Wen, Dong Liu, Zhijia Zhang, Weibing Shuang. *Transl Androl Urol.* 2022 Mar;11(3):304-312. doi: 10.21037/tau-22-23. PMID: 35402189 PMCID: PMC8984976.

[Free full article](#)

The role of purinergic receptor P2X3 in pathological bladder dysfunction and chronic pelvic pain remains unclear. The authors from China aimed to investigate the effect of P2X3 on bladder function in interstitial cystitis (IC) through the IC rat model induced by cyclophosphamide (CYP). A total of 120 female Sprague-Dawley (SD) rats were randomly divided into 6 groups: control, CYP-4h, CYP-48h, CYP-10d, CYP-30d, and CYP-45d groups. The control group was injected with normal saline. The rats in the CYP-4h and CYP-48h groups were given a single high dose. The rats in the CYP-10d, CYP-30d, and CYP-45d groups were given a low dose of CYP repeatedly every three days. Bladder voiding function was measured using urodynamic techniques to observe the effect of the P2X3 receptor on bladder function in CYP-induced IC. The rats in the CYP-4h group showed significant overactivity of the bladder compared with the control group, the bladder voiding interval was shortened ($P<0.01$), and the maximal voiding pressure was increased ($P<0.01$). At the same time, the degree of overactive bladder in the CYP-48h, CYP-10d, CYP-30d, and CYP-45d groups became increasingly serious, the interval of bladder micturition was shortened stepwise ($P<0.01$), and the maximal micturition pressure was increased stepwise ($P<0.01$). Compared with the control group, the CYP-48h group mainly showed a shorter bladder voiding interval ($P<0.01$), lower voiding volume, and higher activation of mast cells and inflammatory factors in the bladder. In the CYP-10d group, bladder mast cell activation and inflammatory factors increased significantly. Intrathecal injection (IT) of A-317491 significantly prolonged the bladder voiding intervals in CYP-4h, CYP-48h, CYP-10d, CYP-30d, and CYP-45d rats ($P<0.01$), and the maximal voiding pressure of the CYP-4h, CYP-48h, CYP-10d, CYP-30d, and CYP-45d groups was significantly decreased ($P<0.05$), while the maximal voiding pressure of the CYP-10d group was not significantly affected. P2X3 receptors in dorsal root ganglion (DRG) play an important role in bladder function induced by intraperitoneal injection of CYP in rats. IT of P2X3 inhibitors can significantly improve the grade of bladder voiding dysfunction and chronic pelvic pain.

[DEFINING MOLECULAR TREATMENT TARGETS FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: UNCOVERING ADHESION MOLECULES](#)

Guldal Inal-Gultekin, Zeliha Gormez, Naside Mangir. *Front Pharmacol.* 2022 Mar 25;13:780855. doi: 10.3389/fphar.2022.780855. eCollection 2022. PMID: 35401223 PMCID: PMC8990855.

[Free full article](#)

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating pain syndrome of unknown etiology that predominantly affects females. Clinically, BPS/IC presents in a wide spectrum where all patients report severe bladder pain together with one or more urinary tract symptoms. On bladder examination, some have normal-appearing bladders on cystoscopy, whereas others may have severely inflamed bladder walls with easily bleeding areas (glomerulations) and ulcerations (Hunner's lesion). Thus, the reported prevalence of BPS/IC is also highly variable, between 0.06% and 30%. Nevertheless, it is rightly defined as a rare disease

(ORPHA:37202). The aetiopathogenesis of BPS/IC remains largely unknown. Current treatment is mainly symptomatic and palliative, which certainly adds to the suffering of patients. BPS/IC is known to have a genetic component. However, the genes responsible are not defined yet. In addition to traditional genetic approaches, novel research methodologies involving bioinformatics are evaluated to elucidate the genetic basis of BPS/IC. This article from Turkey and Germany reviews current evidence on the genetic basis of BPS/IC to determine the most promising targets for possible novel treatments.

[A MODEL IN FEMALE RATS WITH PHENOTYPIC FEATURES SIMILAR TO INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Timothy J Ness, Cary DeWitte, Jennifer J DeBerry, Morgan P Hart, Buffie Clodfelder-Miller, Jianguo G Gu, Jennifer Ling, Alan Randich. Front Pain Res (Lausanne). 2021 Dec 7;2:791045. doi: 10.3389/fpain.2021.791045. eCollection 2021. PMID: 35295535 PMCID: PMC8915626

This report from the USA describes methodological and exploratory investigations of the zymosan-induced neonatal bladder inflammation (NBI) model of interstitial cystitis/bladder pain syndrome (IC/BPS) in female rats. These results validate and extend the currently employed model by evaluating critical timepoints for obtaining treatment effects and identified that a second insult as an adult including repeat intravesical zymosan, intravesical lipopolysaccharide, acute footshock stress, neuropathic nociception (facial) or somatic inflammation (hindpaw) all resulted in magnified visceromotor responses to urinary bladder distension (UBD) in rats which had experienced NBI when compared with their controls. NBI also resulted in increased tone and reactivity of pelvic floor musculature to UBD, as well as increased responsiveness to intravesical potassium chloride solutions, abnormal anxiety measures (elevated plus maze) and an increased number of submucosal petechial hemorrhages following 30 min of hydrodistension of the bladder. These phenotypic findings have correlates to the clinical features of IC/BPS in humans and so support use of this model system to examine mechanisms of and treatments for IC/BPS.

[EMERGING MOLECULAR MECHANISMS AND GENETIC TARGETS FOR DEVELOPING NOVEL THERAPEUTIC STRATEGIES FOR TREATING BLADDER DISEASES](#)

Randa Zoqlam, Sandra Lazauskaite, Scott Glickman, Lyubov Zaitseva, Petre-Cristian Ilie, Sheng Qi. Eur J Pharm Sci. 2022 Mar 15;106167. doi: 10.1016/j.ejps.2022.106167. Online ahead of print. PMID: 35304859

Bladder diseases affect millions of patients worldwide and compromise their quality of life with a substantial economic impact. The not well understood aetiologies of bladder diseases limit the current diagnosis and therapeutic options to primarily symptomatic treatment. In addition, bladder targeted drug delivery is challenging due to its unique anatomical features and its natural physiological function of urine storage and frequent voiding. Therefore, current treatment options often fail to provide a highly effective, precisely targeted and long-lasting treatment. Thus, comprehensive studies are needed to provide a better understanding of the molecular mechanisms underpinning bladder diseases to identify novel gene therapeutic targets and biomarkers for treating bladder diseases and develop novel treatments such as gene loaded nanoparticles. This review from the United Kingdom examined the recent development on the discovery of molecular mechanisms of bladder diseases and discussed recently proposed new treatments, including novel bladder targeted gene therapies using nanoparticle-based formulations and probiotics adjuvant therapies.

[THE TRPM8 CHANNEL AS A POTENTIAL THERAPEUTIC TARGET FOR BLADDER HYPERSENSITIVE DISORDERS](#)

Naoki Aizawa, Tomoe Fujita. J Smooth Muscle Res. 2022;58(0):11-21. doi: 10.1540/jsmr.58.11. PMID: 35354708 DOI: 10.1540/jsmr.58.11

[Free full article](#)

Aizawa and Fujita from Japan note that in the lower urinary tract, transient receptor potential (TRP) channels are primarily involved in physiological function, especially in cellular sensors responding to chemical and physical stimuli. Among TRP channels, TRP melastatin 8 (TRPM8) channels, responding to cold temperature and/or chemical agents, such as menthol or icilin, are mainly expressed in the nerve endings of the primary afferent neurons and in the cell bodies of dorsal root ganglia innervating the urinary bladder (via A δ - and C-fibers); this suggests that TRPM8 channels primarily contribute to bladder sensory (afferent) function. Storage symptoms of overactive bladder, benign prostatic hyperplasia, and interstitial cystitis are commonly related to sensory function (bladder hypersensitivity); thus, TRPM8 channels may also contribute to the pathophysiology of bladder hypersensitivity. Indeed, it has been reported in a pharmacological investigation using rodents that TRPM8 channels contribute to the pathophysiological bladder afferent hypersensitivity of mechanosensitive C-fibers. Similar findings have also been reported in humans. Therefore, a TRPM8 antagonist would be a promising therapeutic target for bladder hypersensitive disorders, including urinary urgency or nociceptive

pain. In this review article, the functional role of the TRPM8 channel in the lower urinary tract and the potential of its antagonist for the treatment of bladder disorders was described.

[THE EFFECT OF CHRONIC PSYCHOLOGICAL STRESS ON LOWER URINARY TRACT FUNCTION: AN ANIMAL MODEL PERSPECTIVE](#)

Yunliang Gao, Larissa V Rodriguez. Front Physiol. 2022 Mar 21;13:818993. doi: 10.3389/fphys.2022.818993. eCollection 2022. PMID: 35388285 PMCID: PMC8978557.

[Free full article](#)

Chronic psychological stress can affect urinary function and exacerbate lower urinary tract (LUT) dysfunction (LUTD), particularly in patients with overactive bladder (OAB) or interstitial cystitis-bladder pain syndrome (IC/BPS). An increasing amount of evidence has highlighted the close relationship between chronic stress and LUTD, while the exact mechanisms underlying it remain unknown. The application of stress-related animal models has provided powerful tools to explore the effect of chronic stress on LUT function. The authors from China and the USA systematically reviewed recent findings and identified stress-related animal models. Among them, the most widely used was water avoidance stress (WAS), followed by social stress, early life stress (ELS), repeated variable stress (RVS), chronic variable stress (CVS), intermittent restraint stress (IRS), and others. Different types of chronic stress condition the induction of relatively distinguished changes at multiple levels of the micturition pathway. The voiding phenotypes, underlying mechanisms, and possible treatments of stress-induced LUTD were discussed together. The advantages and disadvantages of each stress-related animal model were also summarized to determine the better choice. Through the present review, the authors hope to expand current knowledge of the pathophysiological basis of stress-induced LUTD and inspire robust therapies with better outcomes.

[SYNTHETIC STUDIES ON THE INDANE SHIP1 AGONIST AQX-1125](#)

Otto M Dungan, Shawn Dormann, Sandra Fernandes, Brian C Duffy, Daniel G Effiong, William G Kerr, John D Chisholm. Org Biomol Chem. 2022 May 4. doi: 10.1039/d2ob00555g. Online ahead of print. PMID: 35506893

AQX-1125 is an indane based SHIP1 agonist that has been evaluated in the clinic for the treatment of bladder pain syndrome/interstitial cystitis. The authors from the USA report that to support their own studies on SHIP1 agonists as potential treatments for IBD and Crohn's disease, a new synthetic route to the SHIP1 agonist AQX-1125 has been developed. This sequence utilizes a hydroxy-acid intermediate which allows for ready differentiation of the C6 and C7 positions. The role of the C17 alkene in the biological activity of the system is also investigated, and this functional group is not required for SHIP1 agonist activity. While AQX-1125 shows SHIP1 agonist activity in enzyme assays, it does not show activity in cell based assays similar to other SHIP1 agonists, which limits the utility of this molecule.

[ANTI-INFLAMMATORY EFFECTS OF LAVENDER AND EUCALYPTUS ESSENTIAL OILS ON THE IN VITRO CELL CULTURE MODEL OF BLADDER PAIN SYNDROME USING T24 CELLS](#)

Adrienn Horváth, Edina Pandur, Katalin Sipos, Giuseppe Micalizzi, Luigi Mondello, Andrea Böszörményi, Péter Birinyi, Györgyi Horváth. BMC Complement Med Ther. 2022 Apr 30;22(1):119. doi: 10.1186/s12906-022-03604-2. PMID: 35490236 PMCID: PMC9055718.

[Free full article](#)

Interstitial cystitis (IC) has a chronic chemical irritation and inflammation of non-bacterial origin in the bladder wall leading to various severe symptoms. There is evidence that chronic inflammation is significantly associated with abnormal urothelial barrier function, epithelial dysfunction. This is the underlying cause of urothelial apoptosis and sterile inflammation. The anti-inflammatory effects of lavender and eucalyptus essential oils (EOs) and their main components (linalool and eucalyptol) were investigated by the authors from Hungary in the T24 human bladder epithelial cell line on TNF α stimulated inflammation, at 3 types of treatment schedule. The mRNA of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8) were measured by Real Time PCR. Human IL-8 ELISA measurement was performed as well at 3 types of treatment schedule. The effects of lavender and eucalyptus EOs and their main components were compared to the response to NF κ B inhibitor ACHP (2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(4-piperidinyl)-3-pyridinecarbonitrile). There is no significant difference statistically, but measurements show that lavender EOs are more effective than eucalyptus EO. Long-term treatment (24 h) of both lavender EO and linalool showed higher effect in decreasing pro-inflammatory cytokine mRNA expression than ACHP inhibitor following TNF α pre-treatment. Moreover, both lavender EOs were found to be significantly more effective in decreasing IL-8 secretion of T24 cells after TNF α pre-treatment compared to the ACHP NF κ B-inhibitor. The lavender EOs may be suitable for

use as an adjunct to intravesical therapy of IC. Their anti-inflammatory effect could well complement glycosaminoglycan-regenerative therapy in the urinary bladder after appropriate pharmaceutical formulation.

EMERGING MOLECULAR MECHANISMS AND GENETIC TARGETS FOR DEVELOPING NOVEL THERAPEUTIC STRATEGIES FOR TREATING BLADDER DISEASES

Randa Zoqlam, Sandra Lazauskaite, Scott Glickman, Lyubov Zaitseva, Petre-Cristian Ilie, Sheng Qi. Eur J Pharm Sci. 2022 Mar 15;173:106167. doi: 10.1016/j.ejps.2022.106167. Online ahead of print. PMID: 35304859 DOI: 10.1016/j.ejps.2022.106167

[Free full article.](#)

Bladder diseases affect millions of patients worldwide and compromise their quality of life with a substantial economic impact. The not fully understood aetiologies of bladder diseases limit the current diagnosis and therapeutic options to primarily symptomatic treatment. In addition, bladder targeted drug delivery is challenging due to its unique anatomical features and its natural physiological function of urine storage and frequent voiding. Therefore, current treatment options often fail to provide a highly effective, precisely targeted and long-lasting treatment. With the growing maturity of gene therapy, comprehensive studies are needed to provide a better understanding of the molecular mechanisms underpinning bladder diseases and help to identify novel gene therapeutic targets and biomarkers for treating bladder diseases. In this review from the United Kingdom, molecular mechanisms involved in pathology of bladder cancer, interstitial cystitis and overactive bladder syndrome are reviewed, with focus on establishing potential novel treatment options. Proposed novel therapies, including gene therapy combined with nanotechnology, localised drug delivery by nanoparticles, and probiotics, are discussed in regard to their safety profiles, efficacy, treatment length, precise targeting, and in comparison to conventional treatment methods.

INFLAMMATION-INDEPENDENT ANTINOCICEPTIVE EFFECTS OF DF2755A, A CXCR1/2 SELECTIVE INHIBITOR: A NEW POTENTIAL THERAPEUTIC TREATMENT FOR PERIPHERAL NEUROPATHY ASSOCIATED TO NON-ULCERATIVE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Laura Brandolini, Andrea Aramini, Gianluca Bianchini, Anna Ruocco, Riccardo Bertini, Rubina Novelli, Patrizia Angelico, Anna Elisa Valsecchi, Roberto Russo, Vanessa Castelli, Annamaria Cimini, Marcello Allegretti. PMID: 35571079 PMCID: PMC9096165. Front Pharmacol. 2022 Apr 28;13:854238. doi: 10.3389/fphar.2022.854238. eCollection 2022.

[Free full article](#)

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic bladder disease of unknown etiology characterized by urinary frequency and episodic and chronic pain. Analgesic treatments for IC/BPS are limited, especially for patients with non-Hunner (non-ulcerative) type IC who usually have poor overall outcomes. Here, the authors from Italy demonstrate that oral treatment with DF2755A, a potent and selective inhibitor of chemokine receptors CXCR1/2, can prevent and reverse peripheral neuropathy associated to non-Hunner IC/BPS by directly inhibiting chemokine-induced excitation of sensory neurons. They tested DF2755A antinociceptive effects in a cyclophosphamide (CYP)-induced non-ulcerative IC rat model characterized by severe peripheral neuropathy in the absence of bladder inflammatory infiltrate, urothelial hyperplasia, and hemorrhage. Treatment with DF2755A prevented the onset of peripheral neuropathy and reversed its development in CYP-induced IC rats, showing a strong and long-lasting anti-hyperalgesic effect. Ex vivo and in vitro studies showed that DF2755A treatment strongly inhibited the expression of CXCR2 agonists, CXCL1/KC, and CXCL5 and of transient receptor potential vanilloid 1 (TRPV1) compared to vehicle, suggesting that its effects can be due to the inhibition of the nociceptive signaling passing through the CXCL1/CXCR1-2 axis and TRPV1. In conclusion, their results highlight the key pathophysiological role played by the CXCL1/CXCR1-2 axis and TRPV1 in the onset and development of peripheral neuropathy in non-Hunner IC and propose DF2755A as a potential therapeutic approach for the treatment of not only inflammatory painful conditions but also neuropathic ones and in particular non-Hunner IC/BPS.

SUPERVISED MACHINE LEARNING ALGORITHM IDENTIFIED KRT20, BATF AND TP63 AS BIOLOGICALLY RELEVANT BIOMARKERS FOR BLADDER BIOPSY SPECIMENS FROM INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS

Tomohiko Kamasako, Kanya Kaga, Ken-Ichi Inoue, Masanori Hariyama, Tomonori Yamanishi. Int J Urol. 2022 May;29(5):406-412. doi: 10.1111/iju.14795. Epub 2022 Jan 31. PMID: 35102612.

This study from Japan was carried out to identify biomarkers that distinguish Hunner-type interstitial cystitis from non-Hunner-type interstitial cystitis patients. Total ribonucleic acid was purified from 212 punch biopsy specimens of 89 individuals who were diagnosed as interstitial cystitis/bladder pain syndrome. To examine the

expression profile of patients' bladder specimens, 68 urothelial master transcription factors and nine known markers (E-cadherin, cytokeratins, uroplakins and sonic hedgehog) were selected. To classify the biopsy samples, principal component analysis was carried out. A decision tree algorithm was adopted to identify critical determinants, in which 102 and 116 bladder specimens were used for learning and validation, respectively. Principal component analysis segregated tissues from Hunner-type and non-Hunner-type interstitial cystitis specimens in principal component axes 2 and 4. Principal components 2 and 4 contained urothelial stem/progenitor transcription factors and cytokeratins, respectively. A decision tree identified KRT20, BATF and TP63 to classify non-Hunner-type and Hunner-type interstitial cystitis specimens. KRT20 was lower in tissues from Hunner-type compared with non-Hunner-type interstitial cystitis specimens ($P < 0.001$). TP63 was lower in Hunner's lesions compared with adjacent mucosa from Hunner-type interstitial cystitis patients ($P < 0.001$). Blinded validation using additional biopsy specimens verified that the decision tree showed fairly precise concordance with cystoscopic diagnosis. KRT20, BATF and TP63 were identified as biologically relevant biomarkers to classify tissues from interstitial cystitis/bladder pain syndrome specimens. The biologically explainable determinants could contribute to defining the elusive interstitial cystitis/bladder pain syndrome pathogenesis.

EXTRACELLULAR VESICLES DERIVED FROM MESENCHYMAL STEM CELLS ALLEVIATE NEUROINFLAMMATION AND MECHANICAL ALLODYNIA IN INTERSTITIAL CYSTITIS RATS BY INHIBITING NLRP3 INFLAMMASOME ACTIVATION

Chi Zhang, Yong Huang, Fubing Ouyang, Minzhi Su, Wenbiao Li, Jialiang Chen, Hengjun Xiao, Xiangfu Zhou, Bolong Liu. J Neuroinflammation. 2022 Apr 6;19(1):80. doi: 10.1186/s12974-022-02445-7. PMID: 35387668 PMCID: PMC8988382.

[Free full article](#)

Neuroinflammation in spinal dorsal horn (SDH) plays an important role in the pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS). Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) exert potent anti-inflammatory activities in the treatment of various diseases. This study from China aimed to determine the therapeutic effects of MSC-EVs on IC and to investigate the potential mechanism to attenuate neuroinflammation. Female IC rat model was established by intraperitoneal injection of cyclophosphamide (50 mg/kg, every 3 days for 3 doses). Inhibition of NLRP3 inflammasome was performed by intraperitoneal injection of MCC950 (10 mg/kg). MSC-EVs were isolated from the culture supernatants of human umbilical cord derived MSCs using ultracentrifugation, and then injected intrathecally into IC rats (20 μ g in 10 μ l PBS, every other day for 3 doses). Suprapubic mechanical allodynia was assessed using up-down method with von Frey filaments, and micturition frequency was examined by urodynamics. The expression of NLRP3 inflammasome components (NLRP3 and Caspase-1), glial cell markers (IBA-1 and GFAP), proinflammatory cytokines (TNF- α , IL-1 β , IL-6 and IL-18) and TLR4/NF- κ B signal pathway (TLR4, p65 NF- κ B and phospho-p65 NF- κ B) in L6-S1 SDH was measured by Western blot analysis. The cellular localization of NLRP3 in SDH was detected using immunofluorescence co-staining. NLRP3 inflammasome was activated in neurons in SDH of IC rats. NLRP3 inflammasome activation contributed to activation of glial cells and process of spinal neuroinflammation in IC rats, and was related to suprapubic mechanical allodynia and frequent micturition. Intrathecal injection of MSC-EVs alleviated suprapubic mechanical allodynia and frequent micturition in IC rats, restrained activation of glial cells and attenuated neuroinflammation in SDH. In addition, MSC-EV treatment significantly inhibited activation of both NLRP3 inflammasomes and TLR4/NF- κ B signal pathway. NLRP3 inflammasome activation is involved in the neuroinflammation of IC. Intrathecal injection of MSC-EVs alleviates neuroinflammation and mechanical allodynia in IC by inhibiting the activation of NLRP3 inflammasome, and TLR4/NF- κ B signal pathway may be the potential regulatory target.

UPREGULATION OF TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL SUBFAMILY M MEMBER-3 IN BLADDER AFFERENTS IS INVOLVED IN CHRONIC PAIN IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Mengmeng Zhao, Lei Liu, Zhenghao Chen, Ning Ding, Jiliang Wen, Jiabin Liu, Nan Ge, Xiulin Zhang. Pain. 2022 Feb 21. doi: 10.1097/j.pain.0000000000002616. Online ahead of print. PMID: 35413036.

The transient receptor potential cation channel subfamily M member-3 (TRPM3) channel is a recently recognized noxious heat sensor that is involved in inflammatory thermal hyperalgesia. To examine its involvement in the development of hyperalgesia in interstitial cystitis/painful bladder syndrome (IC/PBS), rats with cyclophosphamide (CYP)-induced chronic cystitis were used as a model of IC/PBS. Mechanical and thermal hyperalgesia in lower abdominal region overlying the bladder in CYP rats were measured using von Frey filaments and radiant heat, respectively. Transient receptor potential cation channel subfamily M member-3 expression at the mRNA, protein, and functional levels in dorsal root ganglion neurons innervating

the bladder was detected using RNA in situ hybridization (RNAscope), Western blotting, immunohistochemistry, and Ca²⁺ imaging, respectively. Transient receptor potential cation channel subfamily M member-3 channels were expressed on most of the bladder primary afferent nerve terminals containing calcitonin gene-related peptide and their cell bodies in L6-S1 dorsal root ganglion. Activation of TRPM3 in the bladder wall by its specific agonist pregnenolone sulphate or CIM0216 induced spontaneous bladder pain, calcitonin gene-related peptide release, and neurogenic inflammation that was evidenced by edema, plasma extravasation, inflammatory cell accumulation, and mast cell infiltration. In CYP rats, pretreatment with the TRPM3 antagonist primidone (2 mg/kg, i.p.) significantly alleviated the mechanical and thermal hyperalgesia, bladder submucosal edema, mast cell infiltration, and bladder hyperactivity. Cyclophosphamide-induced cystitis was associated with TRPM3 upregulation at the mRNA, protein, and functional levels in bladder afferent neurons. The authors from China are of the opinion that their results suggest that upregulation of TRPM3 channels is involved in the development of chronic pain in CYP-induced cystitis, and targeting TRPM3 may be a pharmacological strategy for treating bladder pain in IC/PBS.

PEPTIDOMICS ANALYSIS REVEALS CHANGES IN SMALL URINARY PEPTIDES IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Md Shadman Ridwan Abid, Haowen Qiu, Bridget A Tripp, Aline de Lima Leite, Heidi E Roth, Jiri Adamec, Robert Powers, James W Checco. Sci Rep. 2022 May 18;12(1):8289. doi: 10.1038/s41598-022-12197-2. PMID: 35585122 DOI: 10.1038/s41598-022-12197-2

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic and debilitating pain disorder of the bladder and urinary tract with poorly understood etiology. A definitive diagnosis of IC/BPS can be challenging because many symptoms are shared with other urological disorders. An analysis of urine presents an attractive and non-invasive resource for monitoring and diagnosing IC/BPS. The antiproliferative factor (APF) peptide has been previously identified in the urine of IC/BPS patients and is a proposed biomarker for the disorder. Nevertheless, other small urinary peptides have remained uninvestigated in IC/BPS primarily because protein biomarker discovery efforts employ protocols that remove small endogenous peptides. The purpose of this study from the USA was to investigate the profile of endogenous peptides in IC/BPS patient urine, with the goal of identifying putative peptide biomarkers. Here, a non-targeted peptidomics analysis of urine samples collected from IC/BPS patients were compared to urine samples from asymptomatic controls. The results show a general increase in the abundance of urinary peptides in IC/BPS patients, which is consistent with an increase in inflammation and protease activity characteristic of this disorder. In total, 71 peptides generated from 39 different proteins were found to be significantly altered in IC/BPS. Five urinary peptides with high variable importance in projection (VIP) coefficients were found to reliably differentiate IC/BPS from healthy controls by receiver operating characteristic (ROC) analysis. In parallel, the authors also developed a targeted multiple reaction monitoring method to quantify the relative abundance of the APF peptide from patient urine samples. Although the APF peptide was found in moderately higher abundance in IC/BPS relative to control urine, their results show that the APF peptide was inconsistently present in urine, suggesting that its utility as a sole biomarker of IC/BPS may be limited. Overall, their results revealed new insights into the profile of urinary peptides in IC/BPS that will aid in future biomarker discovery and validation efforts.

NEW FRONTIERS OF EXTRACORPOREAL SHOCK WAVE MEDICINE IN UROLOGY FROM BENCH TO CLINICAL STUDIES

Po-Yen Chen, Jai-Hong Cheng, Zong-Sheng Wu, Yao-Chi Chuang. Biomedicines. 2022 Mar 15;10(3):675. doi: 10.3390/biomedicines10030675. PMID: 35327477 PMCID: PMC8945448 DOI: 10.3390/biomedicines10030675

[Free full article](#)

A shock wave (SW), which carries energy and propagates through a medium, is a type of continuous transmitted sonic wave that can achieve rapid energy transformations. SWs have been applied for many fields of medical science in various treatment settings. In urology, high-energy extracorporeal SWs have been used to disintegrate urolithiasis for 30 years. However, at lower energy levels, SWs enhance the expression of vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), proliferating cell nuclear antigen (PCNA), chemoattractant factors, and the recruitment of progenitor cells, and inhibit inflammatory molecules. Low energy extracorporeal shock wave (LESW) therapy has been used in urology for treating chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), interstitial cystitis/bladder pain syndrome (IC/BPS), overactive bladder, stress urinary incontinence, and erectile dysfunction through the mechanisms of anti-inflammation, neovascularization, and tissue regeneration. Additionally, LESW have been proven to temporarily increase tissue permeability and facilitate intravesical botulinum toxin delivery for treating overactive bladders in animal studies and in a human clinical trial. LESW assisted drug delivery was also

suggested to have a synergistic effect in combination with cisplatin to improve the anti-cancer effect for treating urothelial cancer in an in vitro and in vivo study. LESW assisted drug delivery in uro-oncology is an interesting suggestion, but no comprehensive clinical trials have been conducted as of yet. Taken together, LESW is a promising method for the treatment of various diseases in urology. However, further investigation with a large scale of clinical studies is necessary to confirm the real role of LESW in clinical use. This article from Taiwan provides information on the basics of SW physics, mechanisms of action on biological systems, and new frontiers of SW medicine in urology.

[THERAPEUTIC EFFICACY OF INTRAVESICAL PLATELET-RICH PLASMA INJECTIONS FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME-A COMPARATIVE STUDY OF DIFFERENT INJECTION NUMBER, ADDITIVES AND CONCENTRATIONS](#)

Yuan-Hong Jiang, Jia-Fong Jhang, Teng-Yi Lin, Han-Chen Ho, Yung-Hsiang Hsu, Hann-Chorng Kuo. Front Pharmacol. 2022 Mar 22;13:853776. doi: 10.3389/fphar.2022.853776. eCollection 2022. PMID: 35392571 PMCID: PMC8980355.

[Free full article](#)

Intravesical platelet-rich plasma (PRP) injections have been demonstrated effective in relieving symptoms among patients with interstitial cystitis/bladder pain syndrome (IC/BPS). This study from Taiwan compared the clinical efficacy among different injection numbers, adding solution, and concentrations of PRP. A total of 63 patients with IC/BPS were enrolled and randomly allocated to four subgroups who received single high-dose PRP (from 100 ml whole blood) plus 10 ml of normal saline or plasma injected over 20 or 40 sites. Patients were followed up at 1, 3, and 6 months for changes in the IC symptom index (ICSI) and problem index (ICPI), visual analog scale (VAS), global response assessment (GRA), and urodynamic parameters. Furthermore, the authors compared the clinical outcome with their previous study in a group of 55 IC/BPS patients who underwent four monthly low-dose PRP (from 50 ml whole blood) injections. Results: The result of this study showed significant improvements in IC symptoms (ICSI 11.9 ± 4.4 vs. 10.2 ± 4.9 , $p = 0.009$; ICPI 12.3 ± 3.4 vs. 10.6 ± 4.7 , $p = 0.003$); VAS (5.46 ± 2.96 vs. 3.83 ± 3.1 , $p = 0.000$), and maximum flow rate (10.4 ± 4.9 vs. 17.1 ± 11.5 ml/s, $p = 0.000$) at 3 months after single high-dose PRP injection. However, no significant differences in therapeutic results were observed among subgroups, regardless of the added component or injecting site. The improvements of ICSI, ICPI, and GRA at 6 months were lower in comparison with the results of four low-dose PRP injections. All patients were free of dysuria, urinary retention, or urinary tract infection after PRP treatment. It was concluded that intravesical PRP injection is effective for IC/BPS. The addition of normal saline or plasma and injection site had no influence on therapeutic efficacy. However, the symptom improvement and GRA after a single high-dose PRP injection was lower than that after four low-dose PRP injections 6 months after the first treatment. Limitation of the study is lack of sham control group.

[COMPARING SURGICAL INTERVENTIONS FOR INTERSTITIAL CYSTITIS: A SYSTEMATIC REVIEW](#)

Diego Agustín Abelleira Lastoria, Nicholas Raison, Abdullatif Aydin, Shamim Khan, Prokar Dasgupta, Kamran Ahmed. Low Urin Tract Symptoms. 2022 Apr 8. doi: 10.1111/luts.12441. Online ahead of print. PMID: 35393778 DOI: 10.1111/luts.12441

The purpose of this review from London, UK was to summarize and compare the efficacy among surgical interventions in terms of symptomatic relief in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). The review protocol was published on PROSPERO. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist was followed. Following database search, a narrative synthesis was performed. Data pertaining symptom scores, pain levels, and voiding frequency following surgery were summarized by calculating percentage change in these parameters. Multiple surgical treatments were identified. These included injections of hyaluronic acid (HA), botulinum toxin A (Botox A), triamcinolone, resineratoxin (RTX), platelet-rich plasma, and 50% dimethyl sulfoxide (DMSO) solution, neuromodulation, hydrodistension (HD), resection/fulguration of Hunner lesions, resection of ilioinguinal and iliohypogastric nerves, reconstructive surgery, and cystectomy. This review found no evidence suggesting that HD and RTX injections can ameliorate IC/BPS symptoms. Current evidence suggests that sacral neuromodulation, cystectomy, and transurethral resection/fulguration of Hunner lesions could lead to symptomatic relief in IC/BPS. Further research into the efficacy of Botox A, triamcinolone, 50% DMSO solution, and HA instillations is required. However, the best treatment options cannot be reliably stated due to the low level of evidence of the studies identified. Further research should report outcomes for Hunner-type IC and BPS separately given their differing histopathological characteristics. Performing high-quality randomized controlled trials could be hindered by the low prevalence of the condition and a small proportion of patients progressing to surgery.

RELATIONSHIP BETWEEN OPIOID PRESCRIPTIONS AND NUMBER OF CHRONIC PAIN CONDITIONS IN WOMEN WITH INTERSTITIAL CYSTITIS

Jordann-Mishael Duncan, Christopher X Hong, Heidi S Harvie, Lily A Brown, Lily A Arya, Edward K Kim. Female Pelvic Med Reconstr Surg. 2022 May 5. doi: 10.1097/SPV.0000000000001195. Online ahead of print. PMID: 35536666.

The aim of this study from the USA was to determine the relationship between opioid prescriptions and number of chronic pain conditions in women with interstitial cystitis (IC). This was a cross-sectional study. Women diagnosed with IC based on International Classification of Diseases, Ninth Revision/Tenth Revision codes over an 11-year period (2010-2020) were identified from electronic medical records. Data on comorbidities and ambulatory opioid prescriptions were also extracted. Univariable and multivariable logistic regressions were used to assess the relationship between opioid prescriptions and the number and type of coexisting chronic pain conditions. Of the 1,219 women with IC, 207 (17%) had received at least 1 opioid prescription. The proportions of women with opioid prescriptions for no, 1, 2, and 3 or more coexisting chronic pain conditions were 13%, 20%, 28%, and 32%, respectively. On univariable analysis, factors significantly associated with opioid use were higher body mass index ($P < 0.001$), depression ($P < 0.001$), sleep disorder ($P < 0.001$), endometriosis ($P < 0.05$), chronic pelvic pain ($P < 0.001$), fibromyalgia ($P < 0.05$), joint pain ($P < 0.001$), and number of coexisting chronic pain diagnoses ($P < 0.001$). On multivariable analysis, opioid prescriptions remained significantly associated with the number of coexisting chronic pain diagnoses: 1 diagnosis (adjusted odds ratio [aOR], 1.8; 95% confidence interval [CI], 1.3-2.7), 2 diagnoses (aOR, 2.6; 95% CI, 1.6-4.3), 3 or more diagnoses (aOR, 2.5; 95% CI, 1.1-5.5), diagnosis of chronic pelvic pain (aOR, 2.1; 95% CI, 1.3-3.5), endometriosis (aOR, 2.4; 95% CI, 1.4-4.3), chronic joint pain (aOR, 1.8; 95% CI, 1.1-2.9), and sleep disorders (aOR, 2.4; 95% CI, 1.6-3.6). The likelihood of opioid prescriptions in women with IC increases with the number and type of coexisting chronic pain conditions and sleep disorders.

PHARMACOLOGIC MANAGEMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Christopher J Chermansky, Marina O Guirguis. Urol Clin North Am. 2022 May;49(2):273-282. doi: 10.1016/j.ucl.2022.01.003. PMID: 35428433 DOI: 10.1016/j.ucl.2022.01.003

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined as persistent or chronic discomfort perceived to be related to the urinary bladder accompanied by urinary urgency or frequency. Pharmacotherapies used to treat IC/BPS include oral and intravesical agents. Oral therapies include amitriptyline, hydroxyzine, cyclosporine A, and pentosan polysulfate sodium (PPS), although the recent finding of pigmented maculopathy with chronic PPS is very concerning and must be discussed with patients, many of whom will choose to either come off this medicine or not even start it. Certolizumab pegol is a pharmacologic therapy that is currently in clinical development for treatment of IC/BPS symptoms.

PULSED ELECTROMAGNETIC FIELD (PEMF) AS AN ADJUNCT THERAPY FOR PAIN MANAGEMENT IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Christina Ross, Tyler Overholt, Raymond Xu, Gopal Badlani, Robert J Evans, Catherine A Matthews, Stephen J Walker. Int Urogynecol J. 2022 Mar;33(3):487-491. doi: 10.1007/s00192-021-04862-3. Epub 2021 Jun 8. PMID: 34100976 DOI: 10.1007/s00192-021-04862-3

Patients with interstitial cystitis/bladder pain syndrome (IC/BPS) often experience chronic pelvic and even systemic pain that can be difficult to clinically manage. Pulsed electromagnetic field (PEMF) therapy, a non-invasive strategy that has shown significant efficacy for pain reduction in other chronic pain conditions, may provide benefit for pain management in patients with IC/BPS. PEMF delivery to patients occurs via a bio-electromagnetic-energy device which consists of a flexible mat (180 × 50 cm) that the patient lies on for systemic, full-body delivery and/or a flexible pad (50 × 15 cm) for targeted delivery to a specific body region (e.g., pelvic area). The duration of individual sessions, number of sessions per day, total number of sessions, and follow-up observation period vary between previously published studies. Positive outcomes are typically reported as a significant reduction in visual analog scale (VAS) pain score and functional improvement assessed using validated questionnaires specific to the condition under study. The use of PEMF has been evaluated as a therapeutic strategy for pain management in several clinical scenarios. Randomized, double-blinded, placebo-controlled trials have reported positive efficacy and safety profiles when PEMF was used to treat non-specific low back pain, patellofemoral pain syndrome, chronic post-operative pain, osteoarthritis-related pain, rheumatoid arthritis-related pain, and fibromyalgia-related pain. Based on these positive outcomes in a variety of pain conditions, clinical trials to evaluate whether PEMF can provide a safe, non-invasive therapeutic approach to improve symptoms of chronic pain and fatigue in patients with IC/BPS are warranted.

NON-HUNNER'S INTERSTITIAL CYSTITIS IS DIFFERENT FROM HUNNER'S INTERSTITIAL CYSTITIS AND MAY BE CURABLE BY UTEROSACRAL LIGAMENT REPAIR

Klaus Goeschen, Darren M Gold, Bernhard Liedl, Alexander Yassouridis, Peter Petros. Urol Int. 2022 May 5;1-9. doi: 10.1159/000524321. Online ahead of print. PMID: 35512665 DOI: 10.1159/000524321

The posterior fornix syndrome (PFS) was first described in 1993 as a predictably occurring group of symptoms: chronic pelvic pain (CPP), urge, frequency, nocturia, emptying difficulties/urinary retention, caused by uterosacral ligament (USL) laxity, and cured by repair thereof. The authors from Germany and Australia hypothesised that non-Hunner's interstitial cystitis (IC) and PFS might be substantially equivalent conditions. The primary objective was to determine if there was a causal relationship between IC and pelvic organ prolapse (POP). The secondary objective was to assess whether other pelvic symptoms were present in patients with POP-related IC and if so, which ones? How often did they occur? A retrospective study was performed in 198 women who presented with CPP, uterine/apical prolapse (varying degrees), and PFS symptoms, all of whom had been treated by posterior USL sling repair. They compared their PFS symptoms with known definitions of IC, CPP, and bladder symptoms. To check their hypothesis for truth or falsity, they used a validated questionnaire, "simulated operations" (mechanically supporting USLs with a vaginal speculum test to test for reduction of urge and pain), transperineal ultrasound and urodynamics. 198 patients had CPP and 313 had urinary symptoms which conformed to the definition for non-Hunner's IC. The cure rate after USL sling repair was CPP 74%, urge incontinence 80%, frequency 79.6%, abnormal emptying 53%, nocturia 79%, obstructive defecation 80%. The authors are of the opinion that their findings seem to support their hypothesis that non-Hunner's IC and PFS may be similar conditions; also, non-Hunner IC/BPS may be a separate or lesser disease entity from "Hunner lesion disease". More rigorous scientific investigation, preferably by RCT, will be required.

IMPROVED SYMPTOMS AND SIGNS OF REFRACTORY INTERSTITIAL CYSTITIS IN WOMEN AFTER INTRAVESICAL NANO-FAT PLUS PLATELET-RICH PLASMA GRAFTING: A PILOT STUDY

Man-Jung Hung, Ching-Pei Tsai, Tsung-Ho Ying, Gin-Den Chen, Hong-Lin Su, Chih-Jen Tseng. J Chin Med Assoc. 2022 Apr 26. doi: 10.1097/JCMA.0000000000000735. Online ahead of print. PMID: 35507021.

Interstitial cystitis/Bladder pain syndrome (IC/BPS) is characterized by bladder pain accompanied by irritative urinary symptoms, and typical cystoscopic and histological features. In this pilot study from Taiwan, the authors assessed the impact of lesion-targeted bladder injection therapy using a bio-cellular regenerative medicine on patients with refractory IC/BPS. The medicine, which was an autologous emulsified fat (Nanofat) and platelet-rich plasma (PRP) combination, was prepared intraoperatively. Six patients (aged 40-54 years), who completed a standard protocol of four consecutive treatments at 3-month intervals, were followed up at six months postoperatively. All (100%) patients reported marked (+3; +3~-3) improvement of their overall bladder conditions. Mean bladder pain (from 8.2 to 1.7; range: 0~10), IC related symptoms (from 18.5 to 5.7; range: 0~20) and bother (from 14.8 to 3.8; range: 0~16) improved significantly ($p < 0.01$). The normalization of bladder mucosal morphology with treatments was remarkable under cystoscopic examination and no significant adverse events were found. The cultured mesenchymal stem cells from Nanofat samples of the six patients were verified in vitro. Preliminary results suggest novel intravesical therapy with autologous Nanofat plus PRP grafting is safe and effective for refractory IC/BPS. Surgical efficacy might be attributed to an in vivo tissue engineering process.

INTERSTITIAL CYSTITIS CAN BE IMPROVED WITH INTRAVESICAL INSTILLATION OF PLATELET-RICH PLASMA

Timothy J Hardy. Cureus. 2022 Mar 1;14(3):e22747. doi: 10.7759/cureus.22747. eCollection 2022 Mar. PMID: 35251873 PMCID: PMC8887874 DOI: 10.7759/cureus.22747

Free full article.

Intravesical instillation of platelet-rich plasma has the potential to improve symptoms and reduce pain in patients who have interstitial cystitis and painful bladder syndrome by utilizing the body's own growth factors found in platelets. Interstitial cystitis is a disease of the bladder that causes pain, urinary frequency, urgency, and nocturia. It is difficult to treat and has unknown etiology. Patients who have interstitial cystitis have high rates of anxiety as a comorbid condition. People with anxiety are known to have dysregulation of serotonin. These concepts are interrelated.

DOES RESPONSE TO PERCUTANEOUS TIBIAL NERVE STIMULATION PREDICT SIMILAR OUTCOME TO SACRAL NERVE STIMULATION?

Konstantinos Kapriniotis, Julie Jenks, Bogdan Toia, Mahreen Pakzad, Helena Gresty, Ross Stephens, Sachin Malde, Arun Sahai, Tamsin Greenwell, Jeremy Ockrim. Neurourol Urodyn. 2022 Apr 28. doi: 10.1002/nau.24944. Online ahead of print. PMID: 35481714.

Percutaneous tibial nerve stimulation (PTNS) is a simple neuromodulation technique to treat an overactive bladder. It is unclear whether the response to PTNS would suggest a similar response to sacral nerve stimulation (SNS), and whether PTNS could be utilized as an alternative test phase for an SNS implant. This study from London, United Kingdom assessed whether PTNS response was a reliable indicator for subsequent SNS trials. The authors performed a retrospective review of the hospital databases to collect all patients who had PTNS and who subsequently had an SNS trial in two tertiary hospitals from 2014 to 2020. Response to both interventions was assessed. A 50% reduction in overactive symptoms (frequency-volume charts) was considered a positive response. McNemar's tests using exact binomial probability calculations were used. The statistical significance level was set to 0.05. Twenty-three patients who had PTNS subsequently went on to a trial of SNS. All patients except one had previously poor response to PTNS treatment. Eight of them also failed the SNS trial. However, 15 patients (including the PTNS responder) had a successful SNS trial and proceeded with the second-stage battery implantation. The difference in response rates between the PTNS and SNS trial was statistically significant ($p < 0.001$). It was concluded that poor response to PTNS does not seem to predict the likelihood of patients responding to SNS. A negative PTNS trial should not preclude a trial of a sacral nerve implant. The predictive factors for good and poor responses will be the subject of a larger study.

EXAMINING VAGINAL AND VULVAR HEALTH AND SEXUAL DYSFUNCTION IN PATIENTS WITH INTERSTITIAL CYSTITIS (UNICORN-1 STUDY)

Nobuo Okui, Machiko Okui, Marco Gambacciani. Int Urogynecol J. 2022 May 11. doi: 10.1007/s00192-022-05220-7. Online ahead of print. PMID: 35543734

The Vaginal Health Index Score (VHIS) and vulvodynia swab tests are used to assess vaginal health and vulvodynia. However, few studies have used these tests in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). IC/BPS is a chronic, debilitating disorder, characterised by urinary frequency, urinary urgency and pelvic pain. It adversely affects organs adjacent to the urinary system, leading to complications of sexual dysfunction. This study from Italy and Japan was aimed at understanding sexual dysfunction in patients with IC/BPS, as well as deterioration of vaginal health and vulvodynia. This study compared the vaginal health of IC/BPS patients with that of asymptomatic control individuals. The Pain Urgency Frequency (PUF) score, Female Sexual Function Index (FSFI), VHIS, and vulvodynia swab tests, were used as tools. The PUF and FSFI are questionnaire-based surveys of bladder symptoms and sexual function respectively. VHIS evaluation and vulvodynia swab tests are performed by physicians. The PUF was used to assess baseline IC/BPS symptoms to validate the patient population, and FSFI, vulvodynia swab tests and VHIS were used to determine between-group differences. Thirty-seven patients were recruited in each group. The IC/BPS group had a higher PUF score (18.19 ± 3.51 vs 3.56 ± 2.35 ; $p < 0.05$), worse total FSFI (15.72 ± 4.46 vs 26.3 ± 4.93 ; $p < 0.05$), and worse vulvodynia swab test and total VHIS (11.59 ± 2.87 vs 22.05 ± 3.05 ; $p < 0.05$) scores than those of the control group. Asian women with IC/BPS experienced greater sexual dysfunction, worsened vaginal health and increased vulvodynia compared with control individuals. Information on vaginal and vulva health is very useful in evaluating IC/BPS patients.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS): SINGLE-CENTER 20 YEAR EXPERIENCE AND TREATMENT RESULTS IN INDIA

Nagendra N Mishra. Neurourol Urodyn. 2022 May 21. doi: 10.1002/nau.24959. Online ahead of print. PMID: 35598079 DOI: 10.1002/nau.24959

Interstitial cystitis/bladder pain syndrome (IC/BPS) is an enigmatic disease that is difficult to treat. Even among physicians, the prevalent belief is that patients do not improve over time. In this study, Mishra and colleagues from India retrospectively reviewed their experience and treatment results for patients diagnosed with IC/BPS at their clinic in India over the past 20 years. Three hundred and eighty IC/BPS patients diagnosed between January 2001 and December 2020 were included. Patients underwent cystoscopy and hydrodistension and were treated with oral drugs, intravesical instillations, and surgery as needed. From January 2021 to June 2021, all patients were contacted by telephone. The study had 380 participants, but only 231 could be contacted for analysis. Follow-up averaged 6.37 years and the median was 14 years. Eighteen percent showed no improvement, 2% showed a slight improvement on Global Response Assessment (GRA) questionnaire and were considered nonresponders (NR). Yet, 67% reported notable improvements, and 13% moderate improvements, all of which make up 80% responders (R). In 11 patients who were operated on for ileocystoplasty, 9 showed significant improvements. In addition, three patients developed Urothelial

Malignancy. Pregnancy did not affect the disease in any way. Long-term results have been encouraging for IC/BPS patients. Unfortunately, Hunner lesions patients need a more intensive treatment regimen. Re-evaluation with cystoscopy is recommended in NR. In spite of good results of surgery in this series, it is best to perform surgery only as a last resort.

LONGITUDINAL CHANGES IN THE PELVIC PAIN ONLY AND WIDESPREAD PAIN PHENOTYPES OVER ONE YEAR IN THE MAPP-I UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS) COHORT

Henry Lai, Emine O Bayman, Michael O Bishop, Richard Landis, Steven E Harte, Quentin Clemens, Larissa V Rodriguez, Siobhan Sutcliffe, Bayley J Taple, Bruce D Naliboff, MAPP Research Network. Urology. 2022 Mar;161:31-35. doi: 10.1016/j.urology.2021.12.016. Epub 2022 Jan 10. PMID: 35021046.

The purpose of this MAPP study was to examine how often urologic chronic pelvic pain syndrome (UCPPS) patients progressed from Pelvic Pain Only at baseline to Widespread Pain, or vice versa, during 1-year longitudinal follow-up. Men and women with UCPPS enrolled in the MAPP-I Epidemiology and Phenotyping Study completed a self-report body map to indicate their locations of pain every 2 months over 12 months. Patients were categorized at each assessment into one of three pain phenotypes: (1) Pelvic Pain Only, (2) an Intermediate group, (3) Widespread Pain. Only patients who completed 3 or more follow-ups were included in this longitudinal analysis. The primary outcome measure was pain classification at the majority ($\geq 60\%$) of follow-up assessments. Longitudinal trends of somatic symptom burden were also assessed. Among the 93 UCPPS participants with Pelvic Pain Only at baseline, only 2% showed a Widespread Pain phenotype for the majority of assessments over 12 months. Among the 121 participants who had Widespread Pain at baseline, 6% demonstrated Pelvic Pain Only for the majority of assessments over 12 months. Over half of participants ($\geq 53\%$) stayed in their baseline phenotypic group. Somatic symptom burden remained stable over 12 months for each of the groups with high intra-class correlation coefficient (0.67 to 0.82). It was uncommon for UCPPS patients to progress from Pelvic Pain Only to Widespread Pain, or vice versa, over 12 months. These data suggest that Pelvic Pain Only and Widespread Pain are distinct UCPPS phenotypes that are relatively stable over 12 months of follow up.

(For more information about the MAPP Research Network, [click here](#))

IS PELVIC FLOOR MUSCLE TENDERNESS A DISTINCT UROLOGIC CHRONIC PELVIC PAIN SYNDROME (UCPPS) PHENOTYPE?: FINDINGS FROM THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP) RESEARCH NETWORK SYMPTOMS PATTERN STUDY (SPS)

Priyanka Gupta, Robert Gallop, Theresa Spitznagle, Henry Lai, Frank Tu, John N Krieger, J Quentin Clemens, Catherine S Bradley, Claire Yang, Siobhan Sutcliffe, Robert Moldwin, Karl Kreder, Jason Kutch, Larissa V Rodriguez. J Urol. 2022 Mar 28;101097JU0000000000002679. doi: 10.1097/JU.0000000000002679. Online ahead of print. PMID: 35344391.

85% of women with interstitial cystitis/bladder pain syndrome (IC/BPS) and men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPSP) have concomitant pelvic floor muscle tenderness (PFT). The significance of this finding is incompletely understood. This study examines PFT among participants in the MAPP Research Network, and its relationship with urologic chronic pelvic pain syndrome (UCPPS) symptom severity, in order to determine whether this is a phenotypic predictor in UCPPS. Participants in the MAPP Network Symptom Patterns Study (SPS) underwent a standardized pelvic examination (PEX). Trained examiners palpated six locations evaluating the pelvic musculature for PFT. Participants were assigned a 0 to 6 PEX score based on the number of areas with tenderness on PEX. Using regression tree models, PEX scores were divided into low (0-1), mid (2,3,4,5), and high (6). The relationship between PFT and UCPPS symptoms was examined using several validated questionnaires. The study cohort consisted of 562 UCPPS participants (375 females and 187 males), and 69 controls. Diagnoses included IC/BPS (n=397), CP/CPSP (n=122), both (n=34), or no diagnosis (n=9). 81% of UCPPS participants had PFT on PEX compared to 9% of controls: 107 (19%) low, 312 (56%) mid, and 143 (25%) high. Participants with higher PFT scores had more severe disease burden (worse pelvic pain and urinary symptoms), worse quality of life, and more widespread distribution of non-pelvic pain. It was concluded that UCPPS patients with more widespread PFT have severe pain and urinary symptoms, worse quality of life, and a more centralized pain phenotype.

RELIABILITY AND VALIDITY OF PAIN AND URINARY SYMPTOM SEVERITY ASSESSMENT IN UROLOGIC CHRONIC PELVIC PAIN; A MAPP NETWORK ANALYSIS

Bruce D Naliboff, Kenneth Locke Jr, D Schrepf, James W Griffith, Robert Moldwin, John N Krieger, Larissa V Rodriguez, Alisa J Stephens-Shields, J Quentin Clemens, H Henry Lai, Siobhan Sutcliffe, Bayley J Taple, David Williams, Michael A Pontari, Chris Mullins, J Richard Landis, MAPP Research Network. J Urol. 2022 Jan

21;101097JU000000000002438. doi: 10.1097/JU.000000000002438. Online ahead of print. PMID: 35060778
DOI: 10.1097/JU.000000000002438

The purpose of this MAPP study was to assess reliability and validity of an efficient severity assessment for pelvic pain and urinary symptoms in urologic chronic pelvic pain syndrome (UCPPS), which consists of interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). 578 patients were assessed using brief, empirically derived self-report scales for Pelvic Pain Severity (PPS) and Urinary Symptoms Severity (USS) four times during a one-month period and baseline clinic visit that included urologic, pain and illness-impact measures. Mild, moderate and severe categories on each dimension were examined for measurement stability and construct validity. PPS and USS severity categories had adequate reliability and both discriminant validity (differential relationships with specific clinical and self-report measures) and convergent validity (common association with non-urological somatic symptoms). For example, increasing PPS was associated with pelvic tenderness and widespread pelvic pain, whereas USS was associated with urgency during a bladder filling test and increased sensory sensitivity. PPS and USS categories were independently associated with non-urological pain and emotional distress. A descriptive analysis identified higher likelihood characteristics associated with having moderate to severe PPS or USS or both. Lack of sex interactions indicated that the measures are comparable in IC/BPS and CP/CPPS. Women and men with UCPPS can be reliably subgrouped using brief self-report measures of mild, moderate or severe pelvic pain and urinary symptoms. Comparisons with a broad range of clinical variables demonstrate the validity and potential clinical utility of these classifications, including use in clinical trials, health services and biological research.

LOW-ENERGY SHOCK WAVE PLUS INTRAVESICAL INSTILLATION OF BOTULINUM TOXIN A FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: PATHOPHYSIOLOGY AND PRELIMINARY RESULT OF A NOVEL MINIMALLY INVASIVE TREATMENT

Yuan-Hong Jiang, Jia-Fong Jhang, Yu-Khun Lee, Hann-Chorng Kuo. *Biomedicines*. 2022 Feb 7;10(2):396. doi: 10.3390/biomedicines10020396. PMID: 35203604 DOI: 10.3390/biomedicines10020396

Low-energy shock wave (LESW) therapy is known to facilitate tissue regeneration with analgesic and anti-inflammatory effects. LESW treatment has been demonstrated to be effective in treating chronic prostatitis and pelvic pain syndrome as well as overactive bladder, and it has a potential effect on interstitial cystitis/bladder pain syndrome (IC/BPS) in humans. LESW reduces pain behavior, downregulates nerve growth factor expression, and suppresses bladder overactivity by decreasing the expression of inflammatory proteins. Previous rat IC models have shown that LESW can increase urothelial permeability, facilitate intravesical delivery of botulinum toxin A (BoNT-A), and block acetic acid-induced hyperactive bladder, suggesting that LESW might be a potential therapeutic module for relieving bladder inflammatory conditions, such as bladder oversensitivity, IC/BPS, and overactive bladder. A recent clinical trial showed that LESW monotherapy was associated with a significant reduction in pain scores and IC symptoms. BoNT-A detrusor injection or liposome-encapsulated BoNT-A instillation could also inhibit inflammation and improve IC symptoms. However, BoNT-A injection requires anesthesia and certain complications might occur. The preliminary study from this team from Taiwan using LESW plus intravesical BoNT-A instillation every week demonstrated an improvement in global response assessment without any adverse events. Moreover, an immunohistochemistry study revealed the presence of cleaved SNAP25 protein in the suburothelium of IC bladder tissue, indicating that BoNT-A could penetrate across the urothelial barrier after application of LESW. These results provide evidence for the efficacy and safety of this novel IC/BPS treatment by LESW plus BoNT-A instillation, without anesthesia, and no bladder injection. This article reviews the current evidence on LESW and LESW plus intravesical therapeutic agents on bladder disorders and the pathophysiology and pharmacological mechanism of this novel, minimally invasive treatment model for IC/BPS.

DEEP PHENOTYPING OF WOMEN WITH ENDOMETRIOSIS-ASSOCIATED PAIN AND BLADDER PAIN SYNDROME: THE TRIPP (TRANSLATIONAL RESEARCH IN PELVIC PAIN) STUDY PROTOCOL

Lysia Demetriou, Lydia Coxon, Michal Krassowski, Nilufer Rahmioglu, Lars Arendt-Nielsen, Qasim Aziz, Christian M Becker, Judy Birch, Francisco Cruz, Anja Hoffman, Andrew W Horne, Lone Hummelshoj, Stephen McMahon, Jane Meijlink, Esther Pogatzki-Zahn, Christine B Sieberg, Irene Tracey, Rolf-Detlef Treede, Stacey A Missmer, Krina T Zondervan, Jens Nagel, Katy Vincent. *MedRxiv*. doi: <https://doi.org/10.1101/2022.05.16.22274828>
(This article is a preprint and has not been certified by peer review. It reports new medical research that has yet to be evaluated and so should not be used to guide clinical practice.)

Free full text

Chronic pelvic pain is common, poorly understood, and many women suffer for years without proper diagnosis and effective treatment. The Translational Research in Pelvic Pain (TRiPP) project takes a phenotyping

approach, with a particular focus on endometriosis-associated pain (EAP) and bladder pain syndrome (IC/BPS), to improve fundamental understanding of chronic pelvic pain. Demetriou and colleagues believe that reconceptualising these conditions in the context of the multisystem dysfunction known for other chronic pain conditions rather than as end-organ pathologies has the potential to improve understanding of the conditions. Their approach combines clinical, biological, physiological and psychological data to establish perturbations in the functions of pain-relevant systems that are specific to EAP and IC/BPS, and those that overlap both conditions and chronic pelvic pain more generally and associated quantitative biomarker profiles. They believe that TRiPP's novel methodological approach will produce clinical data to aid understanding of pelvic pain and identify underlying pathways for the development of refined animal models and targeted therapeutic treatments.

Note: Further information about IMI-PainCare and the TRiPP project can be found at <https://www.imi-paincare.eu/>

PAIN MANAGEMENT IN A MODEL OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME BY A VACCINAL STRATEGY

Céline Augé, Lilian Basso, Catherine Blanpied, Nathalie Vergnolle, Xavier Gamé, Sophie Chabot, Philippe Lluet, Gilles Dietrich. Front Pain Res (Lausanne). 2021 Mar 8;2:642706. doi: 10.3389/fpain.2021.642706. eCollection 2021. PMID: 35295433 PMCID: PMC8915701.

Current analgesic treatments for Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) are limited. Here, the authors from France and Canada propose a novel antinociceptive strategy exploiting the opioid-mediated analgesic properties of T lymphocytes to relieve from bladder pain. In a chronic model of IC/BPS in rats, they show that a secondary T cell response against intravesically administered ovalbumin prevents from visceral pain in OVA-primed animals. The analgesic effect is associated with the recruitment of T lymphocytes within the inflamed mucosa and is reversed by naloxone-methiodide, a peripheral opioid receptor antagonist. Similarly, intravesical instillation of BCG or tetanus toxoid antigens in vaccinated rats protects from pain in the same model. They show opioid-dependent analgesic properties of local vaccine antigen recall in a preclinical rat model of chronic cystitis. Since BCG bladder instillation is regularly used in humans (as anticancer therapy), their results open it as a new therapeutic positioning for a pain management indication for IC/BPS patients.

DO MEDICATION PRESCRIPTION PATTERNS FOLLOW GUIDELINES IN A COHORT OF WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME?

Lauren N Tholemeier, Catherine Bresee, Amanda M De Hoedt, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger. Neurourol Urodyn. 2022 Apr 7. doi: 10.1002/nau.24923. Online ahead of print. PMID: 35391498 DOI: 10.1002/nau.24923

The purpose of this study from the USA was to describe prescription prevalence of oral bladder pain medications among women with interstitial cystitis/bladder pain syndrome (IC/BPS) and to compare with current treatment guidelines. The authors sampled female patients with an ICD-9/10 diagnosis of IC/BPS (595.1/N30.10) by querying active users of the Veterans Health Administration. Medical records were reviewed to determine whether patients met IC/BPS diagnostic criteria. A cohort of women with other pelvic pain disorders was identified. Prescription prevalence of typical non-narcotic oral bladder pain medications was compared between the two groups and healthy controls. Prescription prevalence was also compared before and after the diagnosis of IC/BPS was made using Poisson regression. There were 641 women who met criteria for IC/BPS and 197 women with "Other pelvic pain" disorders. Women with IC/BPS were prescribed a pain medication more often than those with "Other pelvic pain" (77% vs. 59%, $p < 0.0001$). Of the women with IC/BPS, 44% tried three or more pain medications. Of women with a diagnosis of IC/BPS, only 67% were prescribed an American Urological Association-recommended medication. Prescription prevalence increased after diagnosis for both pentosan polysulfate (10%-29%, $p < 0.0001$) and hydroxyzine (17%-40%, $p < 0.0001$), but not for amitriptyline or cimetidine. Amitriptyline was prescribed to 223 women with IC/BPS, only 125 of whom (56%) had a documented history of depression. Many women with IC/BPS required multiple bladder prescriptions, highlighting the difficulty in finding an effective treatment for IC/BPS. Pentosan polysulfate and hydroxyzine were preferred IC/BPS medications. The next step will be to analyze treatment patterns in those patients who did not receive medications.

[INTRAVESICAL INSTILLATIONS FOR INFLAMMATORY AND SENSORY CHRONIC BLADDER DISEASES: LITERATURE REVIEW AND GUIDE TO CLINICAL PRACTICE]

[Article in French]

F Meyer, É Chen, N Berrogain, P O Bosset, S Campagne-Loiseau, V Cardot, T Charles, X Deffieux, L Donon, L Even, F Girard, J-F Hermieu, S Hurel, J Klap, L Peyrat, C Thuillier, B Tibi, A Vidart, L Wagner, J-N Cornu. Prog Urol. 2022 Feb 4;S1166-7087(22)00010-0. doi: 10.1016/j.purol.2021.12.011. Online ahead of print. PMID: 35125316 DOI: 10.1016/j.purol.2021.12.011

Inflammatory and sensory chronic bladder diseases have a significant impact on quality of life. These pathologies share alteration of the layer between urine and urothelium, making the use of topical agents appropriate. The purpose of this study from France was to review the efficacy and tolerance of intravesical treatments for these pathologies and to give practical guidelines for the use of agents currently available in France. A narrative review was performed in March 2021 using PubMed/MEDLINE, Google Scholar and the international guidelines. Pharmaceutical companies and pharmacies were interviewed. Although numerous molecules were tested over the last 5 decades, only dimethylsulfoxide and glycosaminoglycans are available in France today. Results are promising: response rates are up to 95% and 84% respectively in bladder pain syndrome. In urinary tract infections, glycosaminoglycans could decrease annual number of cystitis by 2.56 (95% confidence interval and increase the time to first cystitis recurrence by 130 days. In radiation cystitis, results could be comparable to hyperbaric oxygen regarding pain and frequency of voiding. However, the literature has a low level of evidence. Chronic bladder diseases have limited treatment options. Intravesical agents are a good alternative, although their cost is significant and their outcome uncertain.

EFFECT OF FOCAL AND DIFFUSE HYPERVASCULARIZATION AS CYSTOSCOPIC FINDINGS ON PREDICTING INTRAVESICAL THERAPY RESPONSE IN PATIENTS WITH BLADDER PAIN SYNDROME

Bulent Erol, Huseyin Ozgur Kazan, Ferhat Keser, Ozgur Efiloglu, Yavuz Onur Danacioğlu, Rahmi Onur. Turk J Urol. 2021 Jul;47(4):325-337. doi: 10.5152/tju.2021.21093. PMID: 35118960 DOI: 10.5152/tju.2021.21093

The purpose of this study from Istanbul, Turkey was to define the relationship between cystoscopic findings, including novel findings such as the hypervascularization, of bladder pain syndrome/interstitial cystitis (BPS/IC) and the response to intravesical therapy. The authors retrospectively evaluated cystoscopy findings in patients who had a preliminary diagnosis of BPS/IC. All patients received early intravesical combined therapy (ICT), ie, within 2 hours after hydrodistention. Additionally, ICT was continued according to their protocol. Cystoscopic findings were classified as glomerulations, hypervascularization, and Hunner's lesion (HL). The therapy responses were evaluated at 1st, 3rd, 6th, and 12th months using the visual analog scale (VAS), O'Leary/Sant interstitial cystitis symptom index (ICSI), and interstitial cystitis problem index (ICPI) scores. Out of 61 patients, HL was diagnosed during cystoscopy in six (9.8%) patients, glomerulations in 35 (57.4%) patients, and hypervascularization in 15 (24.6%) patients. No pathological findings were defined in five (8.2%) patients. In the glomerulation and hypervascularization group, the median VAS, ICSI, and ICPI scores were lower than those in the preoperative period in the follow-up. In patients with HL, the median VAS scores were lower in the entire follow-up compared to the preoperative period, with an increase at 1st year compared to 6th month, and ICSI scores were lower than preoperative period in the entire follow-up, with an increase at 3rd month and 1st year. ICPI scores were also lower during the follow-up, with an increase observed in the 1st year. The presence of hypervascularization should be defined since it might show different characteristics that may affect the ICT response. Patients with glomerulations might be good candidates for early combined intravesical therapy.

EFFICACY OF PERCUTANEOUS AND TRANSCUTANEOUS POSTERIOR TIBIAL NERVE STIMULATION ON IDIOPATHIC OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

Amirhossein Ghavidel-Sardsahra, Morteza Ghojazadeh, Mohammad Sajjad Rahnama'i, Amirreza Naseri, Shahabodin Yazdandoost, Taha Khezerloo, Sepideh Seyedi-Sahebari, Hossein Hosseinifard, Nafiseh Vahed, Hadi Mostafaei, Hanieh Salehi-Pourmehr, Sakineh Hajebrahimi. Neurourol Urodyn. 2022 Feb;41(2):539-551. doi: 10.1002/nau.24864. Epub 2022 Jan 15. PMID: 35032328 DOI: 10.1002/nau.24864

Percutaneous and transcutaneous posterior tibial nerve stimulation (PTNS and TTNS) showed a promising effect on overactive bladder (OAB) and interstitial cystitis/painful bladder syndrome. The authors from Iran, Germany and Austria aimed to give a systematic review and meta-analysis on the efficacy and safety of these therapeutic methods as well. They searched studies available on PubMed, Embase, Cochrane, Scopus, Web of Science, and ProQuest on March 31, 2021, to find both published and unpublished studies. The retrieved articles were screened by two independent researchers and then the selected studies were critically appraised by Cochrane risk-of-bias tool for randomized trials, and Joanna Briggs Institute's checklist for quasi-experimental studies. Finally, the results of studies were synthesized using Review Manager (RevMan) 5.4 statistical software when the data were homogenous. The meta-analysis was performed by calculating the

effect size (mean difference) and their 95% confidence intervals (CIs). Of the total 3194 publications, 68 studies were included in their qualitative evaluation and 9 studies (11 trials) in the quantitative stage. When TTNS or PTNS were compared to sham, placebo, no treatment, or conservative management, a decrease in frequency of urination was observed in both TTNS (mean difference [MD]: -3.18, 95% CI: -4.42 to -1.94, and $p < 0.00001$), and PTNS (MD: -2.84, 95% CI: -4.22 to -1.45, and $p < 0.00001$), and overall TTNS or PTNS (MD: -2.95, 95% CI: -4.01 to -1.88, and $p < 0.00001$). Significant improvements in mean voiding volume (MVV) and decreasing nocturia were also observed. Nerve stimulations either PTNS or TTNS appear to be effective interventions in treating refractory idiopathic OAB in terms of daily voiding frequency, MVV, urgency episodes, and nighttime voiding frequency. However, the result did not show any improvement in terms of urinary incontinence, postvoid residual volume or urge incontinence, and maximum cystometric capacity which emphasized the efficacy of these modalities on dry-OAB rather than wet-OAB.

RECOMMENDATIONS ON THE USE OF INTRAVESICAL HYALURONIC ACID INSTILLATIONS IN BLADDER PAIN SYNDROME

[Article in English, Spanish]

B Madurga Patuel, R González-López, L Resel Folkersma, G Machado Fernández, J M Adot Zurbano, M Á Bonillo, R Vozmediano Chicharro, C Zubiaur Libano. Actas Urol Esp (Engl Ed). 2022 Mar 4;S2173-5786(22)00014-2. doi: 10.1016/j.acuroe.2022.02.007. Online ahead of print. PMID: 35256323 DOI: 10.1016/j.acuroe.2022.02.007

Bladder pain syndrome (BPS) is a complex syndrome, without a clearly defined etiology that encompasses different entities, such as interstitial cystitis. This leads to difficulties in establishing a precise definition, obtaining accurate prevalence data, and defining diagnostic criteria and standardized assessment methods. Moreover, there is no consensus regarding the treatment of BPS. Intravesical instillations with hyaluronic acid (HA) are an option, although no specific recommendations have been made yet. The purpose of this study from Spain was to synthesize the scientific evidence on the therapeutic options available for BPS and to establish a work plan and recommendations for the use of intravesical instillations with HA. The Spanish Association of Urology, through the Functional, Female, and Urodynamic Urology Group, created a commission of experts. This commission was in charge of reviewing literature (evidence), agreeing on the work plan, and proposing recommendations. There is great variability in literature on the treatment of BPS, without a standard regimen of intravesical instillation with HA (frequency and duration of initial and maintenance treatment). Intravesical HA instillations (usual dose of 40 mg) are effective and safe. They can be combined with other options, with efficacy still to be determined in some cases. Treatment is divided into several initial weekly sessions, followed by maintenance treatment, usually monthly (unestablished duration of cycles). Recommendations on the management of BPS were agreed, with diagnostic criteria and guidelines for treatment with intravesical HA (initiation, reassessment, and follow-up).

AMITRIPTYLINE

Amit Thour, Raman Marwaha

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

2022 Feb 7. 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 sialorrhoea. 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.

COMORBIDITIES OF BLADDER PAIN SYNDROME IN THE CONTEXT OF THE HITOP DISTRESS CATEGORY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Linda Fischer-Grote 1, Vera Fössing, Martin Aigner, Markus Boeckle, Elisabeth Fehrmann. Int Urogynecol J. 2022 Mar 9. doi: 10.1007/s00192-022-05129-1. Online ahead of print. PMID: 35262767 DOI: 10.1007/s00192-022-05129-1

The aim of this systematic review and meta-analysis from Austria is, looking at different care settings, to examine prevalence rates of psychological distress-level comorbidities in female interstitial cystitis/bladder pain syndrome (IC/BPS) patients, their impact on Quality of Life (QoL), and the correlation between such comorbidities and symptom severity. A systematic literature search according to PRISMA guidelines was conducted in PubMed, PsycInfo, Web of Science, Science Direct, and Google Scholar. Twenty-nine studies were

found that met inclusion criteria. Prevalence rates of depression and anxiety are higher in IC/BPS patients compared to the general population; however, due to a wide array of measurements, statistical comparisons between care settings were only possible in two cases showing mixed results. No studies meeting inclusion criteria exist that examine PTSD and borderline personality disorder, though rates of past traumatic experiences seem to be higher in patients than in healthy controls. Psychological comorbidities of the distress category, especially depression, are found in most studies to be related to symptom severity, also yielding statistically significant associations. While there is still need for studies focused on some of the comorbidities as well as on different care settings, the data already show that psychological comorbidities of the distress category play an important role in IC/BPS patients regarding suffering, QoL, and symptom severity, thus emphasizing the need for highly specialized interdisciplinary treatment.

HUNNER LESION

CAN WE USE URINARY CYTOKINE/CHEMOKINE ANALYSIS IN DISCRIMINATING ULCER-TYPE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME?

Yuan-Hong Jiang, Jia-Fong Jhang, Hann-Chorng Kuo. *Diagnostics (Basel)*. 2022 Apr 27;12(5):1093. doi: 10.3390/diagnostics12051093. PMID: 35626252 DOI: 10.3390/diagnostics12051093

Interstitial cystitis/bladder pain syndrome (IC/BPS) has ulcer (HIC) and non-ulcer subtypes. Differentiation of these two subtypes could only be based by cystoscopy. This study from Taiwan analyzed the urinary cytokines and chemokines among IC/BPS subtypes and controls for discriminating HIC from non-HIC and controls. A total of 309 consecutive patients with clinically diagnosed IC/BPS were enrolled. All patients received cystoscopic hydrodistention under anesthesia and urine samples were collected prior to the procedure. Enrolled patients were classified into subtypes based on the glomerulation grade, maximal bladder capacity (MBC), and presence of Hunner's lesion. Inflammation-related cytokines and chemokines in urine samples, including interleukin-8 (IL-8), C-X-C motif chemokine ligand 10 (CXCL10), monocyte chemoattractant protein-1 (MCP-1), brain-derived neurotrophic factor (BDNF), eotaxin-1 (eotaxin), IL-6, macrophage inflammatory protein-1 beta (MIP-1 β), regulated upon activation, normally T-expressed, and presumably secreted (RANTES), tumor necrosis factor-alpha (TNF- α), and prostaglandin E2 (PGE2) were assayed using commercially available microspheres with the Milliplex[®] Human Cytokine/Chemokine Magnetic Bead-based Panel kit. The clinical data and urine levels of analytes between IC/BPS patients and controls, and among HIC, non-HIC, and controls were analyzed. Among the 10 proteins, MCP-1, eotaxin, MIP-1 β , TNF- α , and PGE2 were significantly different between IC/BPS and control, while IL-8, CXCL10, BDNF, IL-6, and RANTES were significantly higher in HIC than non-HIC patients. The receiver operating characteristic curve was used to analyze each urine biomarker in the patients with IC/BPS and controls. Among the 10 urine biomarkers, MIP-1 β and TNF- α had an area under curve of ≥ 0.70 to predict IC/BPS from controls, however, the predictive values of these urine biomarkers to predict HIC from non-HIC were low. Combined cut-off values of MIP-1 β and TNF- α can only have a 50% sensitivity and 39.6% specificity in identifying HIC from non-HIC. The results of this study demonstrate that urine cytokines and chemokines may be useful to discriminate patients with HIC from controls. An elevation of urine levels of IL-8, CXCL 10, BDNF, IL-6, and RANTES in IC/BPS patients should prompt physicians to consider the diagnosis of HIC.

INTEGRATED ANALYSIS OF MICROARRAY STUDIES TO IDENTIFY NOVEL DIAGNOSTIC MARKERS IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS WITH HUNNER LESION

Xiao-Feng Cheng, Zhen-Hao Zeng, Wen Deng, Yi-Fu Liu, Xiao-Chen Zhou, Cheng Zhang, Gong-Xian Wang. *Int J Gen Med*. 2022 Mar 19;15:3143-3154. doi: 10.2147/IJGM.S351287. eCollection 2022. PMID: 35342305 PMCID: PMC8943715.

Free full article

The aim of this study from China was to identify novel genetic features of Hunner's lesion interstitial cystitis (HIC) via comprehensive analysis of the Gene Expression Omnibus (GEO) database. The GSE11783 and GSE28242 datasets were downloaded from GEO for further analysis. Differentially expressed genes (DEGs) were identified and analyzed for functional annotation. The diagnostic markers for HIC were screened and validated using the least absolute shrinkage and selection operator (LASSO) logistic regression and support vector machine recursive feature elimination (SVM-RFE) algorithms. Finally, the cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT) algorithm was adopted to investigate the correlation between immune cell infiltration and diagnostic markers in HIC. A total of 7837 DEGs were identified in GSE11783 and 1583 DEGs in GSE28242. Venn diagrams were used to obtain 16 overlapping upregulated and 67 overlapping downregulated DEGs separately. The LASSO logistic model and SVM-RFE algorithm were used to identify 6 genes including KRT20, SLFN11, CD86, ITGA4, PLAC8, and BTN3A3 from DEGs

as diagnostic markers for HIC. Their diagnostic potential in HIC and bladder pain syndrome/interstitial cystitis (BPS/IC) were acceptable. PLAC8 exhibited the best diagnostic performance in BPS/IC with an area under the curve of 0.916. The results of immune infiltration involving GSE11783 revealed that the plasma cell ratio ($p = 0.017$), activated memory CD4+ T cells ($p = 0.009$), activated dendritic cells ($p = 0.01$), eosinophils ($p = 0.004$), and neutrophils ($p = 0.03$) were significantly higher in HIC than in normal samples, in contrast to resting mast cells ($p = 0.022$). A positive correlation existed between diagnostic markers and infiltrating immune cells. It was concluded that KRT20, SLFN11, CD86, ITGA4, PLAC8, and BTN3A3 represent novel and potent diagnostic markers for HIC. They also exhibit certain diagnostic potential in BPS/IC. Immune cell infiltration might play a key role in the pathogenesis and progression of BPS/IC.

CYSTECTOMY FOR PATIENTS WITH HUNNER-TYPE INTERSTITIAL CYSTITIS AT A TERTIARY REFERRAL CENTER IN JAPAN

Yoshiyuki Akiyama, Aya Niimi, Yasuhiko Igawa, Akira Nomiya, Yuta Yamada, Yusuke Sato, Taketo Kawai, Daisuke Yamada, Haruki Kume, Yukio Homma. Low Urin Tract Symptoms. 2022 Mar;14(2):102-108. doi: 10.1111/luts.12416. Epub 2021 Oct 26. PMID: 34704374 DOI: 10.1111/luts.12416

The purpose of this study from Japan was to evaluate the outcomes of partial and total cystectomy in patients with refractory Hunner-type interstitial cystitis (HIC). Patients with end-stage HIC who underwent supratrigonal partial cystectomy with augmentation ileocystoplasty (PC-CP) or total cystectomy with ileal conduit (TC-IC) were identified retrospectively. Changes in the 11-point numerical rating scale of bladder pain and in 7-grade quality of life (QOL) scores were evaluated. Changes in the O'Leary and Sant's Symptom Index (OSSI) and O'Leary and Sant's Problem Index (OSPI) were analyzed in patients with PC-CP. Peri- and postoperative complications and patient satisfaction with overall outcomes were examined. Four patients (one female) underwent PC-CP and 13 (nine females) underwent TC-IC. Bladder pain persisted in three PC-CP patients, but resolved completely in all TC-IC patients. Pain scale and QOL scores improved significantly in patients with TC-IC ($P < .01$), but not in those with PC-CP. OSSI/OSPI scores did not improve significantly in patients with PC-CP. Three PC-CP patients required clean intermittent catheterization due to voiding dysfunction or persistent pain. Two TC-IC patients developed stricture of the ureteroileal anastomosis, resulting in permanent placement of a ureteral stent in one case and nephrostomy in the other. Satisfaction rate was higher in the TC-IC than in the PC-CP group. TC-IC provided reliable pain relief and improved QOL in patients with end-stage HIC, but the small case number and limited methodology restrict interpretation of the results. Further studies are needed to identify appropriate candidates and optimal surgical procedures.

EFFECTS OF HUMAN MUSE CELLS ON BLADDER INFLAMMATION, OVERACTIVITY, AND NOCICEPTION IN A CHEMICALLY INDUCED HUNNER-TYPE INTERSTITIAL CYSTITIS-LIKE RAT MODEL

Akira Furuta, Yasumasa Kuroda, Tokunori Yamamoto, Shin Egawa, Mari Dezawa, Naoki Yoshimura. Int Urogynecol J. 2022 Mar 25. doi: 10.1007/s00192-022-05166-w. Online ahead of print. PMID: 35333929 DOI: 10.1007/s00192-022-05166-w.

Furuta and colleagues from Japan and the USA investigated the effects of locally administered human multilineage-differentiating stress enduring (Muse) cells, nontumorigenic pluripotent-like endogenous stem cells, on bladder tissues, function, and nociceptive behavior in a chemically induced Hunner-type interstitial cystitis (HIC)-like rat model without immunosuppressant. Chemical cystitis was induced by intravesical instillation of 0.2 N hydrochloride (HCl) for 15 min in female F344 rats. SSEA-3+ Muse cells, SSEA-3- non-Muse cells or Hanks' balanced salt solution (HBSS; vehicle) were injected into the anterior and posterior bladder wall at each 1×10^4 cells/ $10 \mu\text{l}$ 6 h after HCl application. The sham group received HBSS without HCl instillation. Urinary frequency was assessed using metabolic cages, cystometrograms, nociceptive behavior, and histological analysis of the bladder and L6 spinal cord. Increases in urinary frequency and decreases in bladder capacity compared with the sham group were observed in the vehicle and non-Muse groups, but not in the Muse group, at 1 week. Significant increases in nociceptive behavior compared with the sham group and the expression of TNF α in the bladder and c-Fos in the bilateral dorsal horns of L6 spinal cord were also observed in the vehicle and non-Muse groups, whereas these changes were not seen in the Muse group at 1 week. Histological analysis exhibited a higher proportion of injected Muse cells remaining in the urothelial basal layer and lamina propria of the bladder than non-Muse cells until 4 weeks. It was concluded that Muse cell therapy could be a promising modality for treating HIC.

IDENTIFICATION OF DIAGNOSTIC SERUM BIOMARKERS FOR HUNNER-TYPE INTERSTITIAL CYSTITIS

Kazumasa Torimoto, Tomohiro Ueda, Masato Kasahara, Akihide Hirayama, Chie Matsushita, Yoshihiro Matsumoto, Daisuke Gotoh, Yasushi Nakai, Makito Miyake, Katsuya Aoki, Kiyohide Fujimoto. Low Urin Tract

Symptoms. 2022 Mar 20. doi: 10.1111/luts.12439. Online ahead of print. PMID: 35307976 DOI: 10.1111/luts.12439

Diagnosis of Hunner-type interstitial cystitis (HIC) relies on the ability to identify Hunner lesions endoscopically, which can lead to storage symptom misdiagnosis. Here, Torimoto and colleagues from Japan examined serum biomarkers for HIC and verified their utility. Based on the previous definition of the Japanese guidelines, which did not distinguish HIC and non-HIC diseases, the authors searched for serum biomarkers in 25 patients with interstitial cystitis (IC) and 25 control participants using metabolomics during 2013-2014. In 2019, they conducted a validation study in HIC and control groups. Serum samples were analyzed using liquid chromatography-tandem mass spectrometry, and candidate biomarker concentrations were compared between the groups using Mann-Whitney test. Metabolomics targeted 678 metabolites and revealed that the levels of 14 lysolipids, seven γ -glutamyl amino acids, and two monoacylglycerols were significantly different between the IC and control groups. The following metabolites were selected from each metabolite category as candidates: 1-linoleoylglycerophosphocholine (1-linoleoyl-GPC [18:2]), γ -glutamylisoleucine (γ -Glu-Ile), and 1-arachidonylglycerol (1-AG). The serum concentrations of 1-linoleoyl-GPC (18:2) in the HIC and control groups were $27\,920 \pm 6261$ and $40\,360 \pm 1514$ ng/mL ($P = 0.0003$), respectively. The serum concentrations of γ -Glu-Ile and 1-AG were not significantly different between the groups. When the cut-off value of 1-linoleoyl-GPC (18:2) was set at 28 400 ng/mL, the sensitivity and specificity were 68% and 84%, respectively. Serum 1-linoleoyl-GPC (18:2) is a candidate diagnostic biomarker for HIC. Additional studies on whether this biomarker can distinguish HIC from other diseases with high urination frequency are required for its clinical use.

REDUCTION OF BLADDER CAPACITY UNDER ANESTHESIA FOLLOWING MULTIPLE RECURRENCES AND REPEATED SURGERIES OF HUNNER LESIONS IN PATIENTS WITH INTERSTITIAL CYSTITIS

Akira Furuta, Yasuyuki Suzuki, Taro Igarashi, Takahiro Kimura, Shin Egawa, Naoki Yoshimura. *Int Neurourol J*. 2022 Mar;26(1):45-51. doi: 10.5213/inj.2142102.051. Epub 2022 Mar 31. PMID: 35368185 DOI: 10.5213/inj.2142102.051

[Free full article](#)

The purpose of this study from Japan and the USA was to investigate the influence of multiple recurrences and repeated surgeries of Hunner lesions on bladder capacity under general anesthesia in patients with interstitial cystitis (IC). Furuta and colleagues retrospectively reviewed the clinical records of Hunner-type IC (HIC) patients who underwent transurethral fulguration or resection of Hunner lesions combined with hydrodistension by a single surgeon between 2011 and 2020. Recurrence was defined as reappearance of uncontrolled urinary symptoms in association with new Hunner lesions identified by cystoscopy. Recurrent Hunner lesions were then treated by transurethral surgeries. The recurrence-free rate, potential predictive factors of recurrence, and changes in bladder capacity under anesthesia were examined at each surgical procedure. A total of 92 surgeries were performed in 47 HIC patients, 23 (49%) of whom required multiple procedures (range, 1-5 times). The mean recurrence-free time after the first surgery was 21.7 months. The recurrence-free rate was 53% at 24 months, and decreased to 32% at 48 months. There were no significant differences in age, sex, bladder capacity under anesthesia at the first surgery, duration from symptom onset to the first surgery, O'Leary-Sant questionnaire including symptom and problem indexes, visual analogue scale pain score, and the number of comorbidities between the cases with or without recurrence. Bladder capacity under anesthesia was gradually decreased as the number of surgeries was increased, and bladder capacity at the fourth procedure was significantly decreased to 80% of the capacity at the first surgery. It was concluded that these results suggest that multiple recurrences and repeated surgeries of Hunner lesions result in a reduction of bladder capacity under anesthesia in HIC patients, although no predictive factors for recurrence of Hunner lesions were detected.

SUPRATRIGONAL CYSTECTOMY AND AUGMENTATION CYSTOPLASTY WITH ILEUM OR ILEOCECUM IN THE TREATMENT OF ULCERATIVE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A 14-YEAR FOLLOW-UP

Fabian Queissert, Benedict Bruecher, Arndt van Ophoven, Andres J Schrader. *Int Urogynecol J*. 2022 Mar 1. doi: 10.1007/s00192-022-05110-y. Online ahead of print. PMID: 35230481 DOI: 10.1007/s00192-022-05110-y

This study from Germany analyzes the long-term results of supratrigonal cystectomy and augmentation cystoplasty in patients with severe ulcerative interstitial cystitis/bladder pain syndrome (IC/BPS) and reduced bladder capacity. Outcome data were retrospectively and prospectively collected and analyzed in women who underwent supratrigonal cystectomy and augmentation cystoplasty for ulcerative IC/BPS at Muenster University Hospital between 1991 and 2006. The authors used cross-tabulation and Pearson's Chi-squared test to examine how outcome is influenced by age, preoperative functional bladder volume, and choice of augmentation material. After a median 171-month follow-up, analysis could be done in 26 of 27 patients.

Persistent pain necessitated early revision in 2 patients (7.7%). Mean postoperative O'Leary Sant IC Score was 12.7 in the prospectively questioned patients. Responses to Patient Global Impression of Improvement (PGI-I) were: "very much better" in 15 cases (65.2%) and "much better" in 7 (30.4%). Twelve patients (52.2%) emptied their augmented bladder voluntarily, whereas 7 (32%) needed intermittent self-catheterization (ISC). The rate of patients requiring ISC tended to be lower when detubularized ileocecal bowel was used. All 5 patients (19.2%) with late relapse of ulcerative IC/BPS needed ISC. Severe ulcerative IC/BPS can be curatively treated in some patients by supratrigonal cystectomy and augmentation, which is associated with a high satisfaction rate and few long-term complications even over a very long follow-up. In their analysis, the need for ISC is a risk factor for late relapse, although ileocecal augmentation could increase the proportion of patients with sufficient voluntary micturition.

OVERLAPPING IC/BPS AND OVERACTIVE BLADDER (OAB)

PATHOPHYSIOLOGY, ASSESSMENT, AND TREATMENT OF OVERACTIVE BLADDER SYMPTOMS IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Amy D Dobberfuhl. *Neurourol Urodyn.* 2022 May 24. doi: 10.1002/nau.24958. Online ahead of print. PMID: 35607890.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is prevalent, difficult to treat, and has close symptom overlap with overactive bladder (OAB). A review of the pathophysiology, assessment, and treatment of IC/BPS patients with overlapping OAB symptoms has not been summarized recently in the published literature. A review of the published literature on the overlap of IC/BPS and OAB was conducted in the USA using MeSH terminology (1992-2022). The pathophysiology of IC/BPS is not fully understood. Animal research has found the bladder trigone and base are richly populated by afferent fibers, including many small unmyelinated C-fibers that may be upregulated in IC/BPS. Successful therapies with multimodal effects on OAB symptoms in patients with IC/BPS are likely to exert beneficial effects on both pain and lower urinary tract symptoms. Potentially efficacious therapies for the treatment of OAB in IC/BPS include pelvic floor physical therapy, oral pharmacotherapy (antimuscarinics and beta-3 agonists), sacral neuromodulation, percutaneous tibial nerve stimulation, and botulinum toxin A (BTA). Antimuscarinics and beta-3 agonists have yielded partial efficacy in IC/BPS, although may help differentiate symptoms of OAB from those associated with IC/BPS. The transvaginal trigone treatment (T3) intradetrusor injection approach allows for delivery of therapeutics to the bladder without the need for a cystoscope and appears to be feasible. Further research is needed to understand the pathophysiology of IC/BPS and symptom overlap with OAB, which in turn should enable the development of more personalized therapeutics.

PREVALENCE OF OVERACTIVE BLADDER SYMPTOMS AMONG WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Alexandra Dubinskaya, Lauren N Tholemeier, Tyler Erickson, Amanda M De Hoedt, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger. *Female Pelvic Med Reconstr Surg.* 2022 Mar 1;28(3):e115-e119. doi: 10.1097/SPV.0000000000001166. PMID: 35272344 DOI: 10.1097/SPV.0000000000001166

Symptoms of urinary frequency, urgency, and urinary leakage are characteristic of overactive bladder (OAB) syndrome. However, frequency and urgency symptoms are also present in most patients with interstitial cystitis/bladder pain syndrome (IC/BPS). The objective of this study from the USA was to describe urge incontinence among women with IC/BPS, which may indicate true overlap of OAB and IC/BPS. This was a prospective study of women with IC/BPS diagnosed clinically in the Veterans Affairs Health Care system. Patients completed the OAB and Female Genitourinary Pain Index (F-GUPI) questionnaires. Questions from the OAB questionnaire were used to analyze symptoms of urinary urgency and urge incontinence. Pain symptoms, urinary symptoms, and impact on quality of life were assessed based on the F-GUPI. Patient demographics, comorbidities, and symptoms were reviewed. Within the cohort of 144 women with IC/BPS, 100 (69%) had urinary leakage associated with the strong desire to void and were more likely to have incontinence compared with healthy controls. The IC/BPS group also had higher total and pain scores on the F-GUPI, but pain scores were not affected by the presence of incontinence. The prevalence of OAB symptoms of urinary leakage is high among women with IC/BPS. This may explain the efficacy of OAB medication and third-line therapies in this population.

NEUROMODULATION

CURRENT ADVANCES IN NEUROMODULATION TECHNIQUES IN UROLOGY PRACTICES: A REVIEW OF LITERATURE

Bulent Erol, Yavuz Onur Danacioglu, Kenneth M Peters. Turk J Urol. 2021 Sep;47(5):375-385. doi: 10.5152/tud.2021.21152. PMID: 35118977 DOI: 10.5152/tud.2021.21152

Neuromodulation has become a valid therapeutic option for patients with various lower urinary tract disorders. In clinical practice, the most used and recommended neuromodulation techniques are sacral neuromodulation (SNM), pudendal neuromodulation (PN), and percutaneous tibial nerve stimulation (PTNS). There are many theories concerning the mechanism of action of neuromodulation. Although SNM, PN, and PTNS show their activities through different nerve roots, all provide central and peripheral nervous system modulations. SNM has been approved for the treatment of overactive bladder (OAB), nonobstructive urinary retention, and faecal incontinence, while PTNS has been approved for OAB treatment. However, they are also used off-label in other urinary and nonurinary pelvic floor disorders, such as neurogenic lower urinary system disorder, interstitial cystitis, chronic pelvic pain, and sexual dysfunction. Minor and nonsurgical reversible complications are usually seen after neuromodulation techniques. In addition, in the last few years, there have been various developments in neuromodulation technology. Some of the examples of these developments are rechargeable batteries with wireless charging, improvements in programming, less invasive single-stage implantation in outpatient settings, and lower-cost new devices. The authors from Turkey and the USA performed a literature search using Medline (PubMed), Cochrane Library, EMBASE, and Google scholar databases in the English language from January 2010 to February 2021. They included reviews, meta-analyses, randomized controlled trials, and prospective and retrospective studies to evaluate the activities and reliability of SNM, PN, and PTNS and the developments in this area in the last decade based on the current literature.

PLACEBO & NOCEBO

THE PLACEBO AND NOCEBO EFFECTS IN FUNCTIONAL UROLOGY

Mostafaei H, Jilch S, Carlin GL, Mori K, Quhal F, Pradere B, Laukhtina E, Schuettfort VM, Aydh A, Sari Motlagh R, Roehrborn CG, Shariat SF, Hajebrahimi S. Nat Rev Urol. 2021 Dec 23. doi: 10.1038/s41585-021-00545-2. Epub ahead of print. PMID: 34949831.

A placebo is an inert substance normally used in clinical trials for comparison with an active substance. However, a placebo has been shown to have an effect on its own; commonly known as the placebo effect. A placebo is an essential component in the design of conclusive clinical trials but has itself become the focus of intense research. The placebo effect is partly the result of positive expectations of the recipient on the state of health. Conversely, a nocebo effect is when negative expectations from a substance lead to poor treatment outcomes and/or adverse events. Randomized controlled trials in functional urology have demonstrated the importance of the placebo and nocebo effects across different diseases such as overactive bladder, urinary incontinence, lower urinary tract symptoms and interstitial cystitis/painful bladder syndrome, as well as male and female sexual dysfunction. Understanding the true nature of the placebo-nocebo complex and the scope of its effect in functional urology could help urologists to maximize the positive effects of this phenomenon while minimizing its potentially negative effects.

KETAMINE CYSTITIS

THERAPEUTIC EFFECT OF PLATELET-RICH PLASMA IMPROVES BLADDER OVERACTIVITY IN THE PATHOGENESIS OF KETAMINE-INDUCED ULCERATIVE CYSTITIS IN A RAT MODEL

Kuang-Shun Chueh, Kuan-Hua Huang, Jian-He Lu, Tai-Jui Juan, Shu-Mien Chuang, Rong-Jyh Lin, Yi-Chen Lee, Cheng-Yu Long, Mei-Chen Shen, Ting-Wei Sun, Yung-Shun Juan. Int J Mol Sci. 2022 May 21;23(10):5771. doi: 10.3390/ijms23105771. PMID: 35628581

This study from Taiwan attempted to elucidate whether intravesical instillation of platelet-rich plasma (PRP) could decrease bladder inflammation and ameliorate bladder hyperactivity in ketamine ulcerative cystitis (KIC) rat model. Female Sprague Dawley (S-D) rats were randomly divided into control group, ketamine-treated group, ketamine with PRP treated group, and ketamine with platelet-poor plasma (PPP) treated group. Cystometry and micturition frequency/volume studies were performed to investigate bladder function. The morphological change of bladder was investigated by Mason's trichrome staining. Western blotting analysis were carried out to examine the protein expressions of inflammation, urothelial differentiation, proliferation, urothelial barrier function, angiogenesis and neurogenesis related proteins. The results revealed that treatment with ketamine significantly deteriorated bladder capacity, decreased voiding function and enhanced bladder overactivity. These pathological damage and interstitial fibrosis may via NF-κB/COX-2 signaling

pathways and muscarinic receptor overexpression. PRP treatment decreased inflammatory fibrotic biosynthesis, attenuated oxidative stress, promoted urothelial cell regeneration, and enhanced angiogenesis and neurogenesis, thereafter recovered bladder dysfunction and ameliorated the bladder hyperactivity in KIC rat model. These findings suggested that the PRP therapy may offer new treatment options for those clinical KIC patients.

[KETAMINE-INDUCED UROPATHY: A DIAGNOSTIC PITFALL IN AN INCREASING HEALTHCARE ISSUE IN YOUNGSTERS](#)

Glenn Lamers, Johan Van Dyck, Stijn Schapmans, Katrien De Coster, Dries Mortier, Natalia Zabegalina. *Urol Case Rep.* 2022 Feb 1;42:102019. doi: 10.1016/j.eucr.2022.102019. eCollection 2022 May. PMID: 35530548 PMID: PMC9073215.

Free full article

Ketamine induced uropathy (KIU) is a urological condition increasing in prevalence, with similar symptoms to UTI, OAB syndrome or interstitial cystitis/bladder pain syndrome. The authors from Belgium present the case of an 18-year old male who established severe LUTS and acute kidney injury due to KIU, in a short time-span of 6 months. Since cessation of ketamine is the cornerstone of treating KIU, correct and early diagnosis is essential. Physicians should therefore consider KIU as a differential diagnosis in storage LUTS, especially in younger patients with therapy-resistant LUTS.

[KETAMINE TOXICITY](#)

Vwaire J. Orhurhu, Rishik Vashisht, Lauren E. Claus, Steven P. Cohen. *In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2022 Apr 4.* PMID: 31082131 Bookshelf ID: NBK541087

Free Books & Documents

Ketamine is a structural analog of the dissociative anesthetic and recreational drug phencyclidine (PCP). Similar to phencyclidine, ketamine causes analgesia and amnesia without the cardiovascular and respiratory depression associated with common anesthetics. Originally called CI-581, ketamine has one-tenth the potency of PCP and causes less severe dysphoria and hallucinations. After the chemist Calvin Stevens first synthesized ketamine in 1962, ketamine was tested in clinical trials performed in pediatric and adult surgical patients, and the Food and Drug Administration approved it for human use in 1970. Ketamine was the most common battlefield anesthetic used during the Vietnam War (fact file on ketamine). Intramuscular and intravenous forms of ketamine are commonly used to provide pediatric anesthesia, especially for high-risk children or patients in limited-resource settings. In surgical settings, ketamine is typically combined with benzodiazepines, which can reduce the adverse psychological symptoms that occur during emergence. Off-label, subanesthetic doses of ketamine also have a use for acute and chronic pain management, sedation, and treatment of severe depression. Like its chemical cousin phencyclidine, ketamine's psychomimetic effects have made it a popular recreational drug. In low doses, its euphoric and dissociative effects are sometimes referred to as "k-land," whereas at high doses, the immobilizing and hallucinogenic effects are referred to as being in a "k-hole." In the context of an illegal, recreational drug, ketamine goes by the street names "K," "vitamin K," "super K," "special K," "super C," "special LA coke," "jet," "superacid," and "green." Ketamine toxicity can cause a variety of neurological, cardiovascular, psychiatric, urogenital, and abdominal symptoms, which are dose-dependent, and depend on whether ketamine administration was in an iatrogenic or illicit context. For example, some experts have attributed the higher incidence of ulcerative cystitis in recreational users to the adulterants with which the drug is mixed. Emergency medicine providers should be aware of the various mechanisms to treat ketamine toxicity and to prevent acute complications such as rhabdomyolysis, seizures, and chronic complications such as psychiatric disturbances and ulcerative cystitis.

[NORKETAMINE, THE MAIN METABOLITE OF KETAMINE, INDUCES MITOCHONDRIA-DEPENDENT AND ER STRESS-TRIGGERED APOPTOTIC DEATH IN UROTHELIAL CELLS VIA A CA 2+-REGULATED ERK1/2-ACTIVATING PATHWAY](#)

Jhe-Wei Lin, Yi-Chun Lin, Jui-Ming Liu, Shing-Hwa Liu, Kai-Min Fang, Ren-Jun Hsu, Chun-Fa Huang, Kai-Yao Chang, Kuan-I Lee, Kai-Chih Chang, Chin-Chuan Su, Ya-Wen Chen. *Int J Mol Sci.* 2022 Apr 23;23(9):4666. doi: 10.3390/ijms23094666. PMID: 35563057 PMID: PMC9102902

Free full article

Ketamine-associated cystitis is characterized by suburothelial inflammation and urothelial cell death. Norketamine (NK), the main metabolite of ketamine, is abundant in urine following ketamine exposure. NK has been speculated to exert toxic effects in urothelial cells, similarly to ketamine. However, the molecular

mechanisms contributing to NK-induced urothelial cytotoxicity are almost unclear. Here, Lin and colleagues from Taiwan aimed to investigate the toxic effects of NK and the potential mechanisms underlying NK-induced urothelial cell injury. In this study, NK exposure significantly reduced cell viability and induced apoptosis in human urinary bladder epithelial-derived RT4 cells that NK (0.01-0.5 mM) exhibited greater cytotoxicity than ketamine (0.1-3 mM). Signals of mitochondrial dysfunction, including mitochondrial membrane potential (MMP) loss and cytosolic cytochrome c release, were found to be involved in NK-induced cell apoptosis and death. NK exposure of cells also triggered the expression of endoplasmic reticulum (ER) stress-related proteins including GRP78, CHOP, XBP-1, ATF-4 and -6, caspase-12, PERK, eIF-2 α , and IRE-1. Pretreatment with 4-phenylbutyric acid (an ER stress inhibitor) markedly prevented the expression of ER stress-related proteins and apoptotic events in NK-exposed cells. Additionally, NK exposure significantly activated JNK, ERK1/2, and p38 signalling and increased intracellular calcium concentrations ([Ca²⁺]_i). Pretreatment of cells with both PD98059 (an ERK1/2 inhibitor) and BAPTA/AM (a cell-permeable Ca²⁺ chelator), but not SP600125 (a JNK inhibitor) and SB203580 (a p38 inhibitor), effectively suppressed NK-induced mitochondrial dysfunction, ER stress-related signals, and apoptotic events. The elevation of [Ca²⁺]_i in NK-exposed cells could be obviously inhibited by BAPTA/AM, but not PD98059. Taken together, these findings suggest that NK exposure exerts urothelial cytotoxicity via a [Ca²⁺]_i-regulated ERK1/2 activation, which is involved in downstream mediation of the mitochondria-dependent and ER stress-triggered apoptotic pathway, consequently resulting in urothelial cell death. Their findings suggest that regulating [Ca²⁺]_i/ERK signalling pathways may be a promising strategy for treatment of NK-induced urothelial cystitis.

URINARY TRACT INFECTION

[A RETROSPECTIVE COHORT STUDY TO IDENTIFY THE RISK FACTORS FOR URINARY TRACT INFECTION AFTER OFFICE PROCEDURES](#)

Araba A Jackson, Cori Ackerman, Nina Alesna, Kimiah Hicks, Jean Paul Tanner, Eric S Chang, Allison M Wyman, Renee Bassaly, Ryan J Hidalgo, Kristie A Greene. Female Pelvic Med Reconstr Surg. 2022 Mar 1;28(3):165-172. doi: 10.1097/SPV.0000000000001151. PMID: 35272324 DOI: 10.1097/SPV.0000000000001151

The objective of this study from the USA is to identify the incidence of and risk factors for urinary tract infection (UTI) after office cystoscopy and urodynamic studies (UDS) in a female population. This was a retrospective cohort study investigating incidence of and risk factors for UTI after office testing. Inclusion criteria included women presenting for either cystoscopy or UDS from September 2019 to February 2020. Modified Poisson regression with robust error variance was used to identify risk factors for UTI after cystoscopy and UDS in a female population. A total of 274 patients met inclusion criteria. One hundred eighty-five patients underwent office cystoscopy. Nine (4.8%) had a postcystoscopy UTI. Significant risk factors for postcystoscopy UTI included recurrent UTI (relative risk, 7.51; 95% confidence interval, 1.66-34.05) and a history of interstitial cystitis (relative risk, 4.56; 95% confidence interval, 1.52-13.73). Of those with recurrent UTI, 13.7% had a postcystoscopy UTI. Among patients with interstitial cystitis, 25% had a postcystoscopy UTI. One hundred ninety-two patients underwent UDS. Ten (5.2%) developed a post-UDS UTI. No risk factors were identified. Patients with recurrent UTI were 7.51 times more likely to develop a UTI after cystoscopy, whereas those with interstitial cystitis were 4.56 times more likely to develop a UTI after cystoscopy. The incidence of UTI after UDS was low overall. Understanding who is at higher risk of postprocedural UTIs may help identify subpopulations that may benefit from prophylactic strategies.

[GUIDELINE OF GUIDELINES: MANAGEMENT OF RECURRENT URINARY TRACT INFECTIONS IN WOMEN](#)

Michael Kwok, Stephen McGeorge, Johanna Mayer-Coverdale, Bianca Graves, David L Paterson, Patrick N A Harris, Rachel Esler, Caroline Dowling, Sumudu Britton, Matthew J Roberts. BJU Int. 2022 May 17. doi: 10.1111/bju.15756. Online ahead of print. PMID: 35579121 DOI: 10.1111/bju.15756

The purpose of this study from Australia was to compare recurrent urinary tract infection (rUTI) guidelines from major urological and non-urological organisations internationally and identify areas of consensus and discrepancy. PubMed, Google Scholar and the official webpages of major urological, gynaecological, infectious diseases and general practice organisations were searched for rUTI guidelines in March 2022. Nine guidelines were included for review: European Association of Urology, National Institute for Health and Care Excellence (NICE), Society of Obstetricians and Gynaecologists of Canada, American Academy of Family Physicians, Mexican College of Gynaecology and Obstetrics Specialists, Swiss Society of Gynaecology and Obstetrics, Spanish Society of Infectious Diseases and Clinical Microbiology, German Association of Scientific Medical Societies, and the combined American Urological Association/Canadian Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction. The definition and evaluation of rUTIs,

and antibiotic prophylaxis strategies, were mostly consistent across guidelines, and emphasised the importance of obtaining urine cultures and limiting cystoscopy and upper tract imaging in women without risk factors. Variable recommendations were noted for symptomatic treatment, self-initiated antibiotics, and antibiotic-sparing preventative strategies such as cranberry, vaginal oestrogen, immunoactive prophylaxis with OM-89, intravesical glycosaminoglycan instillation, and phytotherapeutics. Recent randomised evidence supports the use of methenamine hippurate. Either continuous or post-coital prophylactic antibiotics were supported by all guidelines. None of the guidelines were tailored to the management recurrent complicated UTI. Multiple rUTI guidelines were identified and mostly limited their recommendations to otherwise healthy non-pregnant women with uncomplicated cystitis. Variation was noted, particularly in antibiotic-sparing preventative strategies. Some conflicting recommendations are due to more recent guidelines including updated evidence. Future guidelines should consider recommendations to assist management of complex patient groups, such as recurrent complicated UTI.

MANAGEMENT OF UNCOMPLICATED RECURRENT URINARY TRACT INFECTIONS

Mary Zare, Maria J G T Vehreschild, Florian Wagenlehner. BJU Int. 2022 Jun;129(6):668-678. doi: 10.1111/bju.15630. Epub 2021 Nov 17. PMID: 34741796 DOI: 10.1111/bju.15630

[Free full article](#)

The purpose of this review from Germany was to discuss optimal management of recurrent urinary tract infections (UTIs) in women. About every second woman experiences at least one UTI in her lifetime, of those 30% experience another UTI, and 3% further recurrences. Especially young healthy women without underlying anatomical deficiencies suffer from recurrent UTIs (rUTI), which are associated with significant morbidity and reduction in quality of life. This is a narrative review, investigating publications dealing with recurrent UTI in women. Risk factors and options for management are discussed. The increased susceptibility of women to rUTI is based on the female anatomy in addition to behavioural, genetic, and urological factors. However, why some women are more likely than others to develop and maintain rUTI remains to be clarified. Invasive characteristics of certain uropathogenic *Escherichia coli* that are able to form extra- and intracellular biofilms and may therefore cause delayed release of bacteria into the bladder, may play a role in this setting. Treatment recommendations for an acute episode of rUTI do not differ from those for isolated episodes. Given the nature of rUTI, different prophylactic approaches also play an important role. Women with rUTI should first be counselled to use non-antibiotic strategies including behavioural changes, anti-adhesive treatments, antiseptics, and immunomodulation, before antibiotic prophylaxis is considered. In addition to the traditional treatment and prophylactic therapies, new experimental strategies are emerging and show promising effects, such as faecal microbiota transfer (FMT), a treatment option that transfers microorganisms and metabolites of a healthy donor's faecal matter to patients using oral capsules, enemas, or endoscopy. Initial findings suggest that FMT might be a promising treatment approach to interrupt the cycle of rUTI. Furthermore, bacteriophages, infecting and replicating in bacteria, have been clinically trialled for UTIs. Due to the limitation of available data, novel treatment options require further clinical research to objectify the potential in treating bacterial infections, particularly UTIs.

UROBIOME / MICROBIOME

BLADDER MICROBIOME IN THE CONTEXT OF UROLOGICAL DISORDERS-IS THERE A BIOMARKER POTENTIAL FOR INTERSTITIAL CYSTITIS?

Thomas Bschiepfer, Isabell Karl. Diagnostics (Basel). 2022 Jan 22;12(2):281. doi: 10.3390/diagnostics12020281. PMID: 35204374 DOI: 10.3390/diagnostics12020281

[Free full article](#)

Since the development of modern cultivation and sequencing techniques, the human microbiome has increasingly become the focus of scientific attention. Even in the bladder, long considered to be a sterile niche, a highly variable and complex microbial colonization has now been demonstrated. Especially in the context of diseases such as interstitial cystitis, whose etiopathogenesis is largely unknown, and whose diagnosis is based on a process of exclusion of confusable diseases, science hopes to gain far-reaching insights for etiology and diagnosis, including the identification of potential biomarkers. While for functional disorders such as urge urinary incontinence and overactive bladder syndrome, initial associations have been demonstrated between reduced microbial diversity and increased symptomatology, as well as shifts in the abundance of specific microorganisms such as *Lactobacillus* or *Proteus*, studies in interstitial cystitis show conflicting results and have failed to identify a putative organism or urotype that clearly distinguishes the urinary microbiome of patients with IC/BPS from that of healthy controls. At the present time, therefore, the new insights into the bladder

microbiome and its potential influence on urologic disease cannot yet be used in the context of elucidating possible etiopathogenetic causes, as well as in the use of a biomarker for diagnostic or prognostic purposes. Further studies should focus primarily on uniform procedures and detection methods to achieve better comparability of results and increase the likelihood of detecting hidden patterns.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

AGE-RELATED MACULAR DEGENERATION MASQUERADE: A REVIEW OF PENTOSAN POLYSULFATE MACULOPATHY AND IMPLICATIONS FOR CLINICAL PRACTICE

Chirantan Mukhopadhyay, Timothy M Boyce, Karen M Gehrs, James C Folk, Robert F Mullins, Yi Luo, Karl Kreder, Elliott H Sohn. Asia Pac J Ophthalmol (Phila). 2022 Mar-Apr 01;11(2):100-110. doi: 10.1097/APO.0000000000000504. PMID: 35533330 PMCID: PMC9096915.

Free full article

Pentosan polysulfate (PPS) sodium (Elmiron) is the only Food and Drug Administration (FDA)-approved oral medication to treat interstitial cystitis, also known as bladder pain syndrome. A symptomatic pigmentary maculopathy associated with PPS was reported in 2018. Since then, recognition of this unique drug toxicity has increased rapidly. This potentially sight-threatening side effect prompted the FDA in June 2020 to update the label for PPS to warn about "retinal pigmentary changes." A challenging feature of pentosan maculopathy is its ability to mimic many other retinal conditions, including inherited retinal dystrophies such as pattern dystrophy, mitochondrially inherited diabetes and deafness, and Stargardt disease, and age-related macular degeneration. In this review, the authors from the USA discuss the history of PPS maculopathy and its implications for thousands of at-risk interstitial cystitis patients. They use published literature and an illustrative case from their institution to highlight the importance of diagnosing PPS maculopathy. They also compare PPS maculopathy to age-related macular degeneration, explain why differentiating between the 2 is clinically important, and highlight avenues for further research. Finally, they highlight the paucity of data on patients of color and why this lack of understanding may impact patient care.

REDEFINING THE SPECTRUM OF PENTOSAN POLYSULFATE RETINOPATHY: MULTIMODAL IMAGING FINDINGS FROM A CROSS-SECTIONAL SCREENING STUDY

Andrew C Dieu, Samuel A Whittier, Amitha Domalpally, Jeong W Pak, Rick P Volland, Kelly M Boyd, Justin L Gottlieb, Gordon S Crabtree, Dobie L Giles, Sarah E McAchran, Mihai Mititelu. Ophthalmol Retina. 2022 Mar 23;S2468-6530(22)00131-2. doi: 10.1016/j.oret.2022.03.016. Online ahead of print. PMID: 35339727 DOI: 10.1016/j.oret.2022.03.016

There is growing evidence of a direct association between Pentosan polysulfate (PPS) therapy and the development of macular changes. Using standardized visual acuity testing and multimodal imaging, Dieu and colleagues from the USA investigated the impact on vision and describe an expanded spectrum of imaging findings among PPS users, in a cross-sectional screening study with 39 patients who were current or recent users of PPS. Participants underwent a brief eye exam and answered a comprehensive medical and ophthalmic history questionnaire. Color fundus photography, fundus autofluorescence (FAF) and spectral domain optical coherence tomography (SD-OCT) were obtained. Images were evaluated by expert graders at the Wisconsin Reading Center. Abnormalities were categorized as definitive toxicity (DT) if seen on both FAF and SD-OCT and questionable toxicity (QT) if seen on either FAF or SD-OCT. Early Treatment Diabetic Retinopathy Study (ETDRS) and Snellen visual acuity (VA), dosage and duration of PPS exposure, prevalence of retinal toxicity on imaging. Mean ETDRS and Snellen VA of the study cohort was 85 letters and 20/22, respectively. The mean PPS daily dose was 282 mg (88-400 mg), while the mean cumulative dose was 915 g (19-3650 g) over a mean period of 8.8 years (2 months-25 years). 41% of eyes evidenced retinopathy; DT was identified in 24 (31%) eyes and QT in 8 (10%) eyes. Retinal pigment epithelium (RPE) abnormalities (thickening and/or thinning) were present in all DT eyes. RPE atrophy was seen in 7 (9%) eyes. In addition to well-established findings, unique SD-OCT features of this cohort include interdigitation zone abnormalities and the presence of a flying-saucer-type defect. FAF abnormalities were seen in 24 (30.8%) of eyes, with 20 (66.7%) of these exhibiting abnormalities located outside the central subfield and extending beyond the arcades. It was concluded that findings from masked grading of multimodal imaging at a centralized reading center suggest a wider phenotypic spectrum of structural abnormalities among patients taking PPS. Macular changes selectively involve the RPE and outer retina, with a range of findings often seen beyond the arcades. The subtle and atypical findings in this cohort should prompt clinicians to consider lowering the threshold for diagnosing PPS retinopathy.

RISK OF MACULOPATHY WITH PENTOSAN POLYSULFATE SODIUM USE

Steven S Bae, Mohit Sodhi, David Maberley, Abbas Kezouh, Mahyar Etminan. *Br J Clin Pharmacol*. 2022 Mar 12. doi: 10.1111/bcp.15303. Online ahead of print. PMID: 35277990 DOI: 10.1111/bcp.15303

Recent epidemiologic studies have examined the risk of maculopathy with pentosan polysulfate sodium (PPS), a drug indicated for the treatment of interstitial. However, results have been contradictory. Thus, the authors from Canada quantified the risk of maculopathy with PPS with a focus on risk with duration of use. They used a new user, retrospective cohort study with an active comparator. They created a cohort of mutually exclusive 6,221 PPS users and 89,744 amitriptyline users, a tricyclic antidepressant also used for the treatment of pain secondary to interstitial cystitis. Subjects were selected from the PharMetrics Plus database (IQVIA, Durham, NC) from 2006 to 2020. Cohort members were followed to the first event of the study outcome (maculopathy) or end of enrollment. A Cox regression model was constructed to adjust for potential confounders. The mean follow-up was 3.0 years for PPS users and amitriptyline users. The adjusted hazard ratio (HR) for maculopathy in PPS users was 2.64 (95% confidence interval [CI]:1.90-3.68). The HR for the sensitivity analysis that combined maculopathy and age-related macular degeneration (AMD) was 1.38 (95% CI:1.16-1.65). A cumulative duration-response pattern was observed, with use greater than 3 years having a 9.5-fold risk of maculopathy (HR=9.56, 95% CI:3.60-25.37) compared to a 2.3-fold risk of maculopathy with use for one year or less (HR=2.27, 95% CI:1.50-3.43). The number needed to harm for the first 4 years of use was 250. The results of this study suggest an increased risk of maculopathy with PPS use, particularly with longer duration of use.

OTHER OCULAR SIDE EFFECTS OF BLADDER MEDICATION

OCULAR ADVERSE EFFECTS OF BLADDER MEDICATION: A SYSTEMATIC REVIEW

Arshpreet Bassi, Daiana Roxana Pur, Anthony Chifor, Monali S Malvankar-Mehta. *Cutan Ocul Toxicol*. 2022 May 11;1-8. doi: 10.1080/15569527.2022.2052889. Online ahead of print. PMID: 35546446 DOI: 10.1080/15569527.2022.2052889

With the ageing population, lower urinary tract symptoms are becoming more prevalent with an estimate that by 2025, 52 million adults in the USA will be affected. After lifestyle modifications fail to resolve symptoms, second-line therapy with medications is often recommended by both the European Association of Urology and the American Urological Association. Considering the vulnerability of older patients to co-morbidities, physicians must be more aware of adverse side effects. This study from Canada and the USA aims to identify a linkage between common overactive bladder and interstitial cystitis medication and adverse ocular symptoms. A comprehensive literature search was conducted in MEDLINE, EMBASE, CINAHL, PsycInfo, and HealthSTAR alongside a grey literature search in clinicaltrials.gov to include all articles relating to bladder medication and vision-threatening loss. Covidence review software was utilised to conduct the systematic review. In total, 222 articles were screened, and 23 articles met the inclusion criteria. Comprehensive coverage of 10 available medications was analysed. All medications reported adverse vision effects stratified over 15 categories. The most common adverse effect was reported to be blurred vision (n = 12 studies). Mirabegron had the most number of adverse types of ocular symptoms that covered 6 categories. Cizolirithine Citrate and Elocatitol had the least amount of ocular side effects reported. From the total of 8459 patients that were treated for either overactive bladder syndrome or interstitial cystitis with oral medications, 422 reported adverse vision effects. This review suggests that ocular safety should be assessed in patients requiring systematic drug therapy in order to guide future research, focussing on long-term tolerability.

GUIDELINES

DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Clemens JQ, Erickson DR, Varela NP, Lai HH. *J Urol*. 2022 May 10;101097JU0000000000002756. doi: 10.1097/JU.0000000000002756. Online ahead of print. *The Journal of Urology*® (2022), doi:10.1097/JU.0000000000002756. PMID: 35536143.

Free full article (unedited manuscript that has been accepted for publication)

This article provides an overview of the amended 2022 version of the AUA IC/BPS Guideline. This guideline provides direction to clinicians and patients regarding how to recognize interstitial cystitis/bladder pain syndrome (IC/BPS), conduct a valid diagnostic process, and approach treatment with the goals of maximizing symptom control and patient quality of life while minimizing adverse events and patient burden. An initial systematic review of the literature using the MEDLINE® database (search dates 1/1/83-7/22/09) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of IC/BPS. The review yielded an evidence base of 86 treatment articles after application of inclusion/exclusion criteria. In July

2013, the Guideline underwent an Update Literature Review, a process in which an additional literature search is conducted and a systematic review is produced in order to maintain guideline currency with newly published literature. The 2013 review identified an additional 31 articles relevant to treatment. An Update Literature Review in 2022 (search dates: 06/2013-01/2021) identified 63 studies, 53 of which were added to the evidence base. In contrast to the prior versions, the 2022 updated Guideline no longer divides treatments into first-line through sixth-line tiers. Instead, treatment is categorized into behavioral/non-pharmacologic, oral medicines, bladder instillations, procedures, and major surgery. This approach reinforces that the clinical approach for IC/BPS needs to be individualized and based on the unique characteristics of each patient. In addition, new statements were written to provide guidance on cystoscopy for patients with Hunner lesions, shared decision-making, and potential adverse events from pentosan polysulfate. The supporting text on major surgery also has been completely revised. IC/BPS is a heterogeneous clinical syndrome. Even though patients present with similar symptoms of bladder/pelvic pain and pressure/discomfort associated with urinary frequency and strong urge to urinate, there are subgroups or phenotypes within IC/BPS. Except for patients with Hunner lesions, initial treatment should typically be nonsurgical. Concurrent, multi-modal therapies may be offered.

Note: AUA Guideline on Diagnosis and Treatment Interstitial Cystitis/Bladder Pain Syndrome (2022) can be found at:

[https://www.auanet.org/guidelines/guidelines/diagnosis-and-treatment-interstitial-cystitis/bladder-pain-syndrome-\(2022\)](https://www.auanet.org/guidelines/guidelines/diagnosis-and-treatment-interstitial-cystitis/bladder-pain-syndrome-(2022))

[S2K GUIDELINE ON THE DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS (IC/BPS) : DISCUSSION OF THE CURRENT GUIDELINE USING A CASE STUDY]

[Article in German]

J Tolle, B T Kaftan, Th Bschiepfer. Urologe A. 2022 Mar;61(3):250-259. doi: 10.1007/s00120-021-01753-9. Epub 2022 Jan 17. PMID: 35037970 DOI: 10.1007/s00120-021-01753-9

IC/BPS is a chronic progressive disorder that is often difficult and unsatisfactory for the person affected and the treating therapist. Treatment should therefore be comprehensive, interdisciplinary, multimodal and take into account the biopsychosocial model. The guideline forms a thread through the diverse diagnostic and therapeutic options and provides extensive background information on the definition, epidemiology and aetiopathogenesis of this rare disease. However, practice and theory/guideline are different. Adaptation to the individual case is therefore necessary and explicitly desired. The guideline should therefore serve as a source of ideas for colleagues to compile their own standards suitable for their practice. On the one hand, therapy approaches that have been tried and tested in everyday clinical practice are passed on. On the other hand, the frequent lack of evidence should also be viewed critically. Further studies, if possible multi-centre, specifically designed for different aspects of IC/BPS would be desirable. Close networking between therapists in private practice and special centres is essential for the best possible treatment of people with IC/BPS. The guideline is intended to show the limits of what can be done in practices and outpatient clinics and to provide guidance on when patients should be referred to a "Centre for Interstitial Cystitis and Pelvic Pain". Overall, the guideline has improved the presence of this rare disease among colleagues. A comprehensive supplement, update and further substantiation with the state of current research is thus desirable.

ICD-11 AND (CHRONIC) PAIN

IS CHRONIC PAIN A DISEASE?

Jane C Ballantyne, Mark D Sullivan. J Pain. 2022 May 13;S1526-5900(22)00318-2. doi: 10.1016/j.jpain.2022.05.001. Online ahead of print. PMID: 35577236

It was not until the twentieth century that pain was considered a disease. Before that it was managed medically as a symptom. The motivations for declaring chronic pain a disease, whether of the body or of the brain, include increasing its legitimacy as clinical problem and research focus worthy of attention from healthcare and research organizations alike. But one problem with disease concepts is that having a disease favors medical solutions and tends to reduce patient participation. The authors from the USA argue that chronic pain, particularly chronic primary pain (recently designated a first tier pain diagnosis in ICD 11), is a learned state that is not intransigent even if it has biological correlates. Chronic pain is sometimes a symptom and may sometimes be its own disease. But here Ballantyne and Sullivan question the value of a disease focus for much of chronic pain for which patient involvement is essential, and which may need a much broader societal approach than is suggested by the disease designation. This article examines whether designating chronic pain a disease of the body or brain is helpful or harmful to patients. Can the disease designation help

advance treatment, and is it needed to achieve future therapeutic breakthrough? Or does it make patients over-reliant on medical intervention and reduce their engagement in the process of recovery?

CHRONIC PAIN IN THE 11TH REVISION OF THE INTERNATIONAL CLASSIFICATION OF DISEASES: USERS' QUESTIONS ANSWERED

Beatrice Korwisi, Antonia Barke, Winfried Rief, Rolf-Detlef Treede, Maria Kleinstäuber. Pain. 2021 Dec 3. doi: 10.1097/j.pain.0000000000002551. Online ahead of print. PMID: 34862338 DOI: 10.1097/j.pain.0000000000002551

For the first time, the upcoming International Classification of Diseases and Related Health Problems, Eleventh Revision (ICD-11) will include a comprehensive classification of chronic pain, which is based on the biopsychosocial definition of chronic pain. This presents a great opportunity for pain research and clinical practice. The new classification consists of 7 main diagnostic categories of chronic pain, which are further divided into increasingly specific levels of diagnoses. Each diagnosis is characterized by clearly defined operationalized criteria. Future users will need to familiarize themselves with the new system and its application. The aim of the present publication is to provide users of the ICD-11 chronic pain classification with answers to frequently asked questions regarding the ICD-11 as a whole, the ICD-11 chronic pain classification, and its application to common pain syndromes. The questions compiled in this study reached the International Association for the Study of Pain Task Force through different routes (eg, at conferences, by letter, or during field testing). Furthermore, the authors collected questions posted to the ICD-11 browser and contacted early users of the classification to enquire about their most frequent difficulties when applying the new diagnoses. The authors of the present publication prepared answers to these frequently asked questions. This publication intends to act as a guide for the future users of the new ICD-11 chronic pain classification, hence facilitating its implementation.

PAIN SEVERITY RATINGS IN THE 11TH REVISION OF THE INTERNATIONAL CLASSIFICATION OF DISEASES: A VERSATILE TOOL FOR RAPID ASSESSMENT

Ginea Hay, Beatrice Korwisi, Winfried Rief, Blair H Smith, Rolf-Detlef Treede, Antonia Barke. Pain. 2022 Mar 22. doi: 10.1097/j.pain.0000000000002640. Online ahead of print. PMID: 35316821 DOI: 10.1097/j.pain.0000000000002640

An improved classification of chronic pain is included in the 11th revision of the International Classification of Diseases and Related Health Problems. For all diagnoses of chronic pain, an optional dimensional code for the chronic pain severity will supplement the categorical diagnoses. Pain severity combines pain intensity, pain-related interference, and pain-related distress. Each component is rated by the patient on a numerical rating scale (NRS) from 0 to 10 and subsequently translated into severity stages ("mild," "moderate," and "severe"). This study aimed to evaluate this severity code by comparing the ratings with established psychometric measures of pain-related interference and distress. An online survey was posted to self-help groups for chronic pain, and 595 participants (88.7% women, 59.5 ± 13.5 years) rated each of the severity parameters (pain intensity, pain-related interference, and pain-related distress) on an NRS from 0 to 10 and completed the Pain Disability Index and the Pain Coping Questionnaire (FESV, 3 subscales). The participants reported a mean pain intensity of 6.4 ± 1.9, mean pain-related interference of 6.7 ± 2.1, and mean pain-related distress of 5.7 ± 2.5. The respective NRS ratings showed substantial correlations with the Pain Disability Index score ($r = 0.65$) and the FESV subscales ($r = 0.65$, $r = 0.56$, $r = 0.37$). The extension code for pain severity is a valid and efficient way of recording additional dimensional pain parameters, which can be used to monitor the course of chronic pain and its treatment. The specifier's efficiency makes it possible to use the code when a questionnaire would not be feasible due to time constraints, such as in primary care.

CLASSIFICATION ALGORITHM FOR THE INTERNATIONAL CLASSIFICATION OF DISEASES-11 CHRONIC PAIN CLASSIFICATION: DEVELOPMENT AND RESULTS FROM A PRELIMINARY PILOT EVALUATION

Beatrice Korwisi, Ginea Hay, Nadine Attal, Qasim Aziz, Michael I Bennett, Rafael Benoliel, Milton Cohen, Stefan Evers, Maria Adele Giamberardino, Stein Kaasa, Eva Kosek, Patricia Lavand'homme, Michael Nicholas, Serge Perrot, Stephan Schug, Blair H Smith, Peter Svensson, Johan W S Vlaeyen, Shuu-Jiun Wang, Rolf-Detlef Treede, Winfried Rief, Antonia Barke. Pain. 2021 Jul 1;162(7):2087-2096. doi: 10.1097/j.pain.0000000000002208. PMID: 33492033.

The International Classification of Diseases-11 (ICD-11) chronic pain classification includes about 100 chronic pain diagnoses on different diagnostic levels. Each of these diagnoses requires specific operationalized diagnostic criteria to be present. The classification comprises more than 200 diagnostic criteria. The aim of the Classification Algorithm for Chronic Pain in ICD-11 (CAL-CP) is to facilitate the use of the classification by

guiding users through these diagnostic criteria. The diagnostic criteria were ordered hierarchically and visualized in accordance with the standards defined by the Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. The resulting linear decision tree underwent several rounds of iterative checks and feedback by its developers, as well as other pain experts. A preliminary pilot evaluation was conducted in the context of an ecological implementation field study of the classification itself. The resulting algorithm consists of a linear decision tree, an introduction form, and an appendix. The initial decision trunk can be used as a standalone algorithm in primary care. Each diagnostic criterion is represented in a decision box. The user needs to decide for each criterion whether it is present or not, and then follow the respective yes or no arrows to arrive at the corresponding ICD-11 diagnosis. The results of the pilot evaluation showed good clinical utility of the algorithm. The CAL-CP can contribute to reliable diagnoses by structuring a way through the classification and by increasing adherence to the criteria. Future studies need to evaluate its utility further and analyze its impact on the accuracy of the assigned diagnoses.

COPING EXPECTANCIES AND DISABILITY ACROSS THE NEW ICD-11 CHRONIC PAIN CATEGORIES: A LARGE-SCALE REGISTRY STUDY

Alice Munk, Henrik Børsting Jacobsen, Silje Endresen Reme. Eur J Pain. 2022 May 23. doi: 10.1002/ejp.1979. Online ahead of print. PMID: 35603479.

Recently a new classification system for chronic pain was included in the 11th edition of the International Classification of Diseases (ICD-11). This study from Norway investigated how expectancies of coping, i.e. pain catastrophizing and general self-efficacy, are associated with ICD-11 chronic pain categories in a large pain clinic population. They also investigated how coping expectancies are associated with pain-related disability, cross-sectionally and longitudinally across the novel pain classifications. The sample was retrieved from the Oslo University Hospital Pain Registry and included baseline data from 2875 chronic pain patients and 12-months follow up data for 920 patients. Demographic and clinical variables were compared across the ICD-11 chronic pain categories through ANOVA. Multiple regression models were carried out to investigate cross-sectional and longitudinal associations. With the exception of age, their data showed no significant differences across the ICD-11 chronic pain categories. Coping expectancies were associated with disability at baseline. At 12-months follow up, coping expectancies did not predict pain-related disability when controlling for baseline levels of disability, pain intensity and pain duration. Pain classification (primary versus secondary) did not contribute significantly to the models. Helplessness had the strongest simple relationship to disability, compared with global pain catastrophizing and its additional subscales, both cross-sectionally and longitudinally. Coping expectancies, pain intensity and pain-related disability appear similar across the novel chronic pain classifications, indicating that all pain patients may benefit from targeting these variables. Consistent with recent developments in stress theory, helplessness and self-efficacy were cross-sectionally associated with negative pain outcomes.

CENTRAL SENSITIZATION

SCIENTIFIC KNOWLEDGE GRAPH AND TREND ANALYSIS OF CENTRAL SENSITIZATION: A BIBLIOMETRIC ANALYSIS.

Li Z, Xu C, Fu J, Zulipikaer M, Deng T, Chen J. J Pain Res. 2022;15:561-575. <https://doi.org/10.2147/JPR.S348946>. PMID: 35237073 PMCID: PMC8885163.

Central sensitization refers to a state of hypersensitivity in the central nervous system and is associated with the development and maintenance of chronic pain. Central sensitization plays an essential role in various diseases. Nevertheless, there has been no bibliometric analysis before in this field. The purpose of this study from China was to provide critical themes and trends in the area of central sensitization, to build a network of knowledge, and to facilitate the future development of relevant basic and clinical research. Publications on central sensitization were extracted from the Science Citation Index-Expanded. Li and colleagues used R software to systematically analyze the countries, institutions, authors, journals, references, and keywords of the publications. Besides, conceptual structure, intellectual structure, and social structure were constructed. A total of 4466 publications were included. Research in the field of central sensitization generally showed a steady upward trend. The three structural networks showed that the United States is the leading country in this field. Arendt-Nielsen L and Woolf CJ were the most productive and influential authors, respectively. "Pain" was the journal with the most studies. Most journals that published and cited articles about central sensitization were academically influential. Cluster analysis revealed that research in central sensitization contains three main conceptual clusters, and the themes of research evolve frequently. Current research focuses on the pathogenesis of central sensitization in neuropathic pain, the role of central sensitization in

different diseases, and related clinical double-blind trials. Central sensitization received widespread attention. The United States led the way in academic activity. In this field, the current situation of cooperation and communication between different countries and institutions is positive. The present research hotspots were the pathogenesis of central sensitization in neuropathic pain, the role of central sensitization in different diseases, and related clinical double-blind trials.

CHRONIC PELVIC PAIN

MANAGEMENT OF CHRONIC PRIMARY PELVIC PAIN SYNDROMES

Brian A Parsons, Andrew P Baranowski, Bary Berghmans, Jan Borovicka, Angela M Cottrell, Paulo Dinis-Oliveira, Sohier Elneil, John Hughes, Bert E J Messelink, Amanda C de C Williams, Pedro Abreu-Mendes, Valentin Zumstein, Daniel S Engeler. BJU Int. 2022 May;129(5):572-581. doi: 10.1111/bju.15609. Epub 2021 Oct 27. PMID: 34617386 DOI: 10.1111/bju.15609

Free full text.

Management of chronic pelvic pain (CPP) remains a huge challenge for care providers and a major burden for healthcare systems. Treating chronic pain that has no obvious cause warrants an understanding of the difficulties in managing these conditions. Chronic pain has recently been accepted as a disease in its own right by the World Health Organization, with chronic pain without obvious cause being classified as chronic primary pain. Despite innumerable treatments that have been proposed and tried to date for CPP, unimodal therapeutic options are mostly unsuccessful, especially in unselected individuals. In contrast, individualised multimodal management of CPP seems the most promising approach and may lead to an acceptable situation for a large proportion of patients. In the present review, the interdisciplinary and interprofessional European Association of Urology Chronic Pelvic Pain Guideline Group gives a contemporary overview of the most important concepts to successfully diagnose and treat this challenging disease.

Note: to view the 2022 EAU guidelines on chronic pelvic pain, please go to:

<https://uroweb.org/guidelines/chronic-pelvic-pain>

SIGMA-1 RECEPTOR CHANGES OBSERVED IN CHRONIC PELVIC PAIN PATIENTS: A PILOT PET/MRI STUDY

Daehyun Yoon, Angela M Fast, Peter Cipriano, Bin Shen, Jessa B Castillo, Christopher R McCurdy, Carina Mari Aparici, Deirdre Lum, Sandip Biswal. Front Pain Res (Lausanne). 2021 Oct 20;2:711748. doi: 10.3389/fpain.2021.711748. eCollection 2021. PMID: 35295458 PMCID: PMC8915714

Chronic pelvic pain is a highly prevalent pain condition among women, but identifying the exact cause of pelvic pain remains a significant diagnostic challenge. This study from the USA explored a new diagnostic approach with PET/MRI of the sigma-1 receptor, a chaperone protein modulating ion channels for activating nociceptive processes. Their approach was implemented by a simultaneous PET/MRI scan with a novel radioligand [¹⁸F]FTC-146, which is highly specific to the sigma-1 receptor. They recruited 5 chronic pelvic pain patients and 5 healthy volunteers and compared their PET/MRI findings between these two groups. All five patients showed abnormally increased radioligand uptake on PET compared to healthy controls at various organs, including the uterus, vagina, pelvic bowel, gluteus maximus muscle, and liver. However, on MRI, only 2 patients showed abnormalities that could be potentially associated with the pain symptoms. For a subset of patients, the association of pain and the abnormally increased radioligand uptake was further validated by successful pain relief outcomes following surgery or trigger point injections to the identified abnormalities. In this preliminary study, sigma-1 receptor PET/MRI demonstrated potential for identifying abnormalities associated with chronic pelvic pain. Future studies will need to correlate samples with imaging findings to further validate the correlation between S1R distribution and pathologies of chronic pelvic pain.

FEMALE PELVIC CONDITIONS: CHRONIC PELVIC PAIN

Geneen T Gin, Elizabeth Rosenblum, Lesley D Wilkinson, Patricia H Brady. FP Essent. 2022 Apr;515:11-19. PMID: 35420402

Chronic pelvic pain (CPP) is defined as at least 6 months of pain originating from the lower abdomen or pelvis that is not associated with pregnancy. Symptoms include abdominal bloating, low back pain, and dyspareunia. CPP is considered a symptom and not a diagnosis. The etiology may involve a specific organ or condition (eg, endometriosis, adhesions). The most common associated conditions are endometriosis, interstitial cystitis, irritable bowel syndrome, and depression. The history and physical examination are essential in the evaluation. A comprehensive history that encompasses the gynecologic, obstetric, surgical, and psychosocial histories is key. The psychosocial history should include screening for depression, anxiety, posttraumatic stress

disorder, and physical and sexual abuse because of their association with CPP. The physical examination should include musculoskeletal, abdominal, and gynecologic examinations. The choice of laboratory tests and imaging studies should be guided by the history and physical examination findings. Management is multimodal and involves management of associated conditions, pharmacotherapy, surgeries and procedures, physical therapy, and behavior and lifestyle therapies. The multidisciplinary care team typically consists of the primary care physician, subspecialty physicians (eg, gynecology, pain management, psychiatry, gastroenterology, urology), a physical therapist, and a behavioral health subspecialist.

CURRENT CHALLENGES IN THE MANAGEMENT OF CHRONIC PELVIC PAIN IN WOMEN: FROM BENCH TO BEDSIDE

Vânia Meira Siqueira-Campos, Mariana Siqueira Campos de Deus, Omero Benedicto Poli-Neto, Julio Cesar Rosa-E-Silva, José Miguel de Deus, Délio Marques Conde. Int J Womens Health. 2022 Feb 18;14:225-244. doi: 10.2147/IJWH.S224891. eCollection 2022. PMID: 35210869 PMCID: PMC8863341 DOI: 10.2147/IJWH.S224891

[Free full article](#)

Chronic pelvic pain (CPP) affects a significant proportion of women worldwide and has a negative impact on several aspects of these women's lives including mental health, work, relationships and sexual function, among others. This set of factors ultimately reflects negatively on quality of life. The physiopathology of CPP is complex and remains to be fully clarified; however, recent advances have increased understanding of the mechanisms involved in chronic pain in general, and more specifically, CPP. Nonetheless, even when a detailed clinical history is obtained, meticulous physical examination is performed and imaging resources are appropriately used, the organic cause of the pain may still fail to be identified in a substantial number of women with CPP. Management of CPP may therefore be challenging. This narrative review from Brazil was aimed at adding to the available literature on the subject, presenting and discussing the principal characteristics of CPP in women. The paper highlights gaps in the literature while providing the most up-to-date evidence associated with the physiopathology and classification of pain, its diagnosis and treatment. In addition, current challenges in the management of women with CPP are discussed.

WHAT IS PAIN-RELATED SUFFERING? CONCEPTUAL CRITIQUES, KEY ATTRIBUTES, AND OUTSTANDING QUESTIONS

Peter Stilwell, Anne Hudon, Keith Meldrum, M Gabrielle Pagé, Timothy H Wideman. J Pain. 2021 Nov 28;S1526-5900(21)00370-9. doi: 10.1016/j.jpain.2021.11.005. Online ahead of print. PMID: 34852304 DOI: 10.1016/j.jpain.2021.11.005

[Free full article.](#)

Suffering holds a central place within pain research, theory, and practice. However, the construct of pain-related suffering has yet to be operationalized by the International Association for the Study of Pain and is largely underdeveloped. Eric Cassell's seminal work on suffering serves as a conceptual anchor for the limited pain research that specifically addresses this construct. Yet, important critiques of Cassell's work have not been integrated within the pain literature. This Focus Article from Canada aims to take a preliminary step towards an updated operationalization of pain-related suffering by 1) presenting key attributes of pain-related suffering derived from a synthesis of the literature and 2) highlighting key challenges associated with Cassell's conceptualization of suffering. They present 4 key attributes: 1) pain and suffering are inter-related, but distinct experiences, 2) suffering is a subjective experience, 3) the experience of suffering is characterized by a negative affective valence, and 4) disruption to one's sense of self is an integral part of suffering. A key outstanding challenge is that suffering is commonly viewed as a self-reflective and future-oriented process, which fails to validate many forms of suffering and marginalizes certain populations. Future research addressing different modes of suffering - with and without self-reflection - are discussed. Perspective This article offers a preliminary step toward operationalizing the construct of pain-related suffering and proposes priorities for future research. A robust operationalization of this construct is essential to developing clinical strategies that aim to better recognize and alleviate suffering among people living with pain.

THE CHRONIC DISEASE HELPLESSNESS SURVEY: DEVELOPING AND VALIDATING A BETTER MEASURE OF HELPLESSNESS FOR CHRONIC CONDITIONS

Lindsey R Yessick, Tim V Salomons. Pain Rep. 2022 Mar 14;7(2):e991. doi: 10.1097/PR9.0000000000000991. eCollection Mar-Apr 2022. PMID: 35311028 PMCID: PMC8923572.

[Free full article.](#)

Learned helplessness develops with prolonged exposure to uncontrollable stressors and is therefore germane to individuals living with pain or other poorly controlled chronic diseases. This study from Canada has

developed a helplessness scale for chronic conditions distinct from previous scales that blur the conceptualization of control constructs. Extant measures commonly examine controllability, not the three pillars of helplessness identified by Maier and Seligman (1976): cognitive, emotional, and motivational/motor deficits. Individuals who self-report a chronic pain condition (N = 350) responded to a Chronic Disease Helplessness Survey (CDHS) constructed to capture cognitive, motivational/motor, and emotion deficits. Exploratory factor analysis (EFA; N = 200) and confirmatory factor analysis (CFA; N = 150) were performed. The CDHS was assessed for convergent and discriminant validity. A three-factor solution corresponding to cognitive, emotional, and motivational/motor factors was identified by EFA. The solution exhibited sufficient model fit and each factor had a high degree of internal consistency. The CDHS was significantly associated with greater pain intensity and interference, PCS helplessness, lower perceived pain control, and lower general self-efficacy. Individuals with diabetes generally experience greater control strategies over daily symptoms (e.g., diet, oral medications, and insulin) than patients with chronic pain and in this study displayed significantly lower CDHS scores compared to individuals with chronic pain, demonstrating discriminant validity. This study provides preliminary evidence that the three-factor CDHS is a psychometrically sound measure of helplessness in individuals with chronic pain.

SJÖGREN'S SYNDROME

CURRENT AND FUTURE TREATMENT IN PRIMARY SJÖGREN'S SYNDROME - A STILL CHALLENGING DEVELOPMENT

Jacob Ritter, Yidan Chen, Luisa Stefanski, Thomas Dörner. Joint Bone Spine. 2022 May 7;105406. doi: 10.1016/j.jbspin.2022.105406. Online ahead of print. PMID: 35537697.

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by sicca symptoms, systemic manifestations and constitutional symptoms substantially diminishing patient's quality of life. In this review from Germany, Ritter and colleagues summarize recent recommendations for management of pSS patients and current clinical studies in pSS addressing unmet medical needs. Expanding knowledge about disease pathogenesis and the introduction of validated outcome measures, such as capturing disease activity (ESSDAI) and patient-reported outcomes (ESSPRI) have shaped recent developments. In contrast, lack of evidence for current treatment options remarkably limits the management of pSS patients as reflected by the 2019 updated EULAR recommendations for management of Sjögren's syndrome. In this context, symptomatic treatment is usually appropriate for sicca symptoms, whereas systemic treatment is reserved for moderate to severe organ manifestations including care by a multidisciplinary team in centers of expertise. Most promising targets for new treatment modalities are based on immunopathological insights and include direct B cell targeting strategies, targeting co-stimulation by CD40/CD40L blocking, inhibition of key cytokine activity (BLYS/BAFF, type I interferon) and intracellular signalling pathways.

FIBROMYALGIA

ADVANCES IN THE MANAGEMENT OF FIBROMYALGIA: WHAT IS THE STATE OF THE ART?

Roland Staud. Expert Opin Pharmacother. 2022 May 4;1-11. doi: 10.1080/14656566.2022.2071606. Online ahead of print. PMID: 35509228 DOI: 10.1080/14656566.2022.2071606

Fibromyalgia (FM) is a chronic pain syndrome associated with fatigue, insomnia, dyscognition, and emotional distress. Critical illness mechanisms include central sensitization to nociceptive and non-nociceptive stimuli often resulting in hypersensitivity to all sensory input. The clinical presentation of FM can vary widely and therefore requires therapies tailored to each patient's set of symptoms. This manuscript from the USA examines currently prescribed therapeutic approaches supported by empirical evidence as well as promising novel treatments. Although pharmacological therapy until now has been only moderately effective for FM symptoms, it represents a critical component of every treatment plan. Currently approved pharmacological therapies for FM symptoms have limited but proven effectiveness. Novel therapies with cannabinoids and naltrexone appear promising. Recent functional imaging studies of FM have discovered multiple brain network abnormalities that may provide novel targets for mechanism-based therapies. Future treatment approaches, however, need to improve more than clinical pain but also other FM domains like fatigue, insomnia, and distress.

PATIENT ENGAGEMENT

THE ADDED VALUE OF PATIENT ENGAGEMENT IN EARLY DIALOGUE AT EMA: SCIENTIFIC ADVICE AS A CASE STUDY

Aisling Murphy, Nathalie Bere, Spiros Vamvakas, Maria Mavris. Front Med (Lausanne). 2022 Jan 20;8:811855. doi: 10.3389/fmed.2021.811855. eCollection 2021. PMID: 35127766 PMCID: PMC8811124 DOI: 10.3389/fmed.2021.811855

Free full article

The European Medicines Agency provides Scientific Advice to medicines developers and patient input has been an integral part of this process for many years. As end users of medicines, patients bring their perspectives to many different processes along EMA's regulatory pathway, complementing the scientific expertise. While the value of including patients has been well-demonstrated over the years, requests for evidence of their impact continue. Using Scientific Advice as a case study, data was collected over a four-year period to assess the number of patients involved, where they contributed, as well as the impact and added value of their input. In this paper, the authors from the Netherlands and the United Kingdom show that patients' contributions have a tangible impact on the recommendations provided to developers and in over half of the cases, this led to further discussion on relevant patient perspectives. These data provide quantitative evidence of the value of patient input in medicines development and supports EMA's continued inclusion of their voice throughout the medicine's lifecycle.

The International Painful Bladder Foundation does not engage in the practice of medicine. It is not a medical authority nor does it claim to have medical knowledge. Information provided in IPBF emails, newsletters, patient information and website is not medical advice. The IPBF recommends patients to consult their own physician before undergoing any course of treatment or medication. While the IPBF endeavours to ensure that all information it provides is correct and accurate, it does not accept any liability for errors or inaccuracies.

If you do not wish to receive this IPBF e-newsletter or any other communications from the IPBF in future, please notify the International Painful Bladder Foundation: info@painful-bladder.org with "unsubscribe" in the subject bar.