

International Painful Bladder Foundation

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

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

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

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.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: OVERVIEW

CURRENT UNDERSTANDING OF THE PATHOPHYSIOLOGY AND NOVEL TREATMENTS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Jia-Fong Jhang, Yuan-Hong Jiang, Hann-Chorng Kuo. Biomedicines. 2022 Sep 23;10(10):2380. doi: 10.3390/biomedicines10102380. PMID: 36289642.

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The pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) is multifactorial. Identifying the clinical characteristics and cystoscopic findings of bladder-centered IC/BPS facilitates optimal treatment strategies targeting the diseased urinary bladder. Patients with Hunner's lesion (HIC) and without Hunner's lesion (NHIC) should be treated differently. Based on the histopathological findings, NHIC can be treated with intravesical instillation of urothelial protective agents, such as hyaluronic acid, to cover the urothelial defects. In non-responders, chronic inflammation and higher urothelial dysfunction can be treated with intravesical botulinum toxin A injection, platelet-rich plasma injection, or low-energy shock wave treatment to reduce inflammation, increase tissue regeneration, and improve the urothelial barrier. Patients with HIC should be treated with electrocauterization first; augmentation enterocystoplasty should only be used in end-stage HIC when the contracted bladder is refractory to other treatments. The antiviral agent, valacyclovir, can be used in patients with HIC, small bladder capacity, and high-grade glomerulations. In addition, behavioral modification is always recommended from the beginning of treatment. Treatment with cognitive behavioral therapy interventions in combination with bladder therapy can reduce anxiety and improve treatment outcomes. Herein, recent advances in the pathophysiology and novel treatments for IC/BPS are reviewed.

BROADEN HORIZONS: THE ADVANCEMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Jin Li, Xianyanling Yi, Jianzhong Ai. Int J Mol Sci. 2022 Nov 23;23(23):14594. doi: 10.3390/ijms232314594. PMID: 36498919.

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating disease that induces mental stress, lower urinary symptoms, and pelvic pain, therefore resulting in a decline in quality of life. The present diagnoses and treatments still lead to unsatisfactory outcomes, and novel diagnostic and therapeutic modalities are needed. Although our understanding of the etiology and pathophysiology of IC/BPS is growing, the altered permeability of the impaired urothelium, the sensitized nerves on the bladder wall, and the chronic or intermittent sensory pain with inaccurate location, as well as pathologic angiogenesis, fibrosis, and Hunner lesions, all act as barriers to better diagnoses and treatments. This study from Chengdu, China aimed to summarize the comprehensive information on IC/BPS research, thereby promoting the progress of IC/BPS in the aspects of diagnosis, treatment, and prognosis. According to diverse international guidelines, the etiology of IC/BPS is associated with multiple factors, while the presence of Hunner lesions could largely distinguish the pathology, diagnosis, and treatment of non-Hunner lesions in IC/BPS patients. On the basis of the diagnosis of exclusion, the diverse present diagnostic and therapeutic procedures are undergoing a transition from a single approach to multimodal strategies targeting different potential phenotypes recommended by different guidelines. Investigations into the mechanisms involved in urinary symptoms, pain sensation, and bladder fibrosis indicate the pathophysiology of IC/BPS for further potential strategies, both in diagnosis and treatment. An overview of IC/BPS in terms of epidemiology, etiology, pathology, diagnosis, treatment, and fundamental research is provided with the latest evidence. On the basis of shared decision-making, a multimodal strategy of diagnosis and treatment targeting potential phenotypes for individual patients with IC/BPS would be of great benefit for the entire process of management. The complexity and emerging evidence on IC/BPS elicit more relevant studies and research and could optimize the management of IC/BPS patients.

MANAGING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN FEMALE PATIENTS: CLINICAL RECIPES FOR SUCCESS.

Nickel JC. Can Urol Assoc J 2022;16(12):393-8. <http://dx.doi.org/10.5489/cuaj.8055> PMID: 36656690

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As one enters the twilight of their career, it is imperative to pass the wisdom of countless patient encounters to those who follow in their footsteps. Professor J Curtis Nickel explains that he has been asked by urologists many times over the decades how to treat a specific patient with interstitial cystitis/bladder pain syndrome (IC/BPS) and found that he gave a different answer to each query based on the individual patient's clinical characteristics or what some might call each patient's "clinical picture." Here he describes how he has managed his patients in the IC/BPS clinic at Queen's University in Kingston with useful recipes for instillations.

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

SENSORY RECEPTOR, INFLAMMATORY, AND APOPTOTIC PROTEIN EXPRESSION IN THE BLADDER UROTHELIUM OF PATIENTS WITH DIFFERENT SUBTYPES OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Yuan-Hong Jiang, Jia-Fong Jhang, Lori A Birder, Hann-Chorng Kuo. Int J Mol Sci. 2023 Jan 3;24(1):820. doi: 10.3390/ijms24010820. PMID: 36614264.

The aim of this study from Taiwan and the USA was to investigate the expression levels of sensory receptors, inflammatory proteins, and pro-apoptotic proteins in the urothelium of non-Hunner's interstitial cystitis (NHIC) bladders of patients with different clinical and cystoscopic phenotypes. The urothelia from the bladders of 52 NHIC patients were harvested. The expression of sensory receptors, including TRPV1, TRPV4, TRPA1, H1-receptors, and sigma-1 receptors; the inflammatory

proteins p38 and tryptase; and the pro-apoptotic proteins, such as caspase-3, BAD, and BAX in the urothelium, were investigated using immunohistochemistry and Western blotting. The authors compared the expression levels of these proteins in NHIC subtypes according to IC symptom scores, visual analog scores of bladder pain, maximal bladder capacity, glomerulation grades, and combined maximal bladder capacity and glomerulations after cystoscopic hydrodistention. The expression levels of TRPV1, TRPV4, sigma-1, P38, tryptase, caspase-3, and BAD were significantly increased in the urothelium of IC/BPS patients compared with the expression levels in the controls. TRPV1 was significantly associated with IC symptom severity. However, no significant differences in sensory receptor expression in the IC/BPS bladders with different bladder conditions were detected. Inflammatory and pro-apoptotic protein expression levels in the urothelium were similar among the IC/BPS subgroups. This study concluded that IC/BPS patients with frequency and bladder pain complaints have higher levels of urothelial sensory receptors, and inflammatory and pro-apoptotic proteins. The expression levels of these sensory receptors, inflammatory proteins, and pro-apoptotic proteins are not significantly different among IC/BPS bladders with different conditions.

CULTURED VERSUS FRESHLY ISOLATED ADIPOSE-DERIVED STEM CELLS IN IMPROVEMENT OF THE HISTOPATHOLOGICAL OUTCOMES IN HCL-INDUCED CYSTITIS IN A RAT MODEL

Hanan Hendawy, Elsayed Metwally, Ahmed Elfadadny, Tomohiko Yoshida, Danfu Ma, Kazumi Shimada, Lina Hamabe, Kenta Sasaki., Ryou Tanaka. *Biomed Pharmacother.* 2022 Sep;153:113422. doi: 10.1016/j.biopha.2022.113422. Epub 2022 Jul 19. PMID: 36076544.

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Interstitial cystitis (IC) is an incurable chronic disease. The etiology of IC is unclear, and no effective therapies have been established. Here, in a study from Egypt, China and Japan, using a hydrogen chloride (HCL)-induced IC in a rat model, the therapeutic potency of stromal vascular fraction (SVF) and Adipose-derived stem cells (ADSCs) was studied. Thirty-six female Sprague Dawley rats were divided into four groups: the sham, HCL, (HCL+SVF) group, and (HCL+ADSCs) group (9 for each). Cystitis was induced by transurethral instillation of HCL, while PBS was used for the sham group. A single dose of SVF or ADSCs was injected into the submucosa of the rat bladder in HCL-induced IC groups. The bladder tissues were analyzed for Toluidine Blue, Masson Trichrome, CD3, and CD34 to evaluate mast cell activation, fibrosis, inflammatory cells, and bladder regeneration, respectively. Compared to HCL-induced IC, SVF or ADSCs injection into IC bladder dramatically decreased mast cell infiltration, T-cell activation, and fibrosis. Taken together, administration of SVF cells or cultured ADSCs improves the histopathological outcomes of HCL-induced bladder injury in a time-dependent manner. Of note, SVF injection into the bladder submucosa was estimated to have the most potent therapeutic efficacy and may represent an essential component in future clinical applications.

URINARY ATP LEVELS ARE CONTROLLED BY NUCLEOTIDASES RELEASED FROM THE UROTHELIUM IN A REGULATED MANNER

Alejandro Gutierrez Cruz, Mafalda S L Aresta Branco, Brian A Perrino, Kenton M Sanders, Violeta N Mutafova-Yambolieva. *Metabolites.* 2022 Dec 24;13(1):30. doi: 10.3390/metabo13010030. PMID: 36676954.

Adenosine 5'-triphosphate (ATP) is released in the bladder lumen during filling. Urothelial ATP is presumed to regulate bladder excitability. Urinary ATP is suggested as a urinary biomarker of bladder dysfunctions since ATP is increased in the urine of patients with overactive bladder, interstitial cystitis or bladder pain syndrome. Altered urinary ATP might also be associated with voiding dysfunctions linked to disease states associated with metabolic syndrome. Extracellular ATP levels are determined by ATP release and ATP hydrolysis by membrane-bound and soluble nucleotidases (s-NTDs). It is currently unknown whether s-NTDs regulate urinary ATP. Using etheno-ATP substrate and HPLC-FLD detection techniques, the authors from the USA found that s-NTDs are released in the lumen of ex vivo mouse detrusor-free bladders. Capillary immunoelectrophoresis by ProteinSimple Wes determined that intraluminal solutions (ILS) collected at the end of filling contain

ENTPD3 > ENPP1 > ENPP3 ≥ ENTPD2 = NT5E = ALPL/TNAP. Activation of adenylyl cyclase with forskolin increased luminal s-NTDs release whereas the AC inhibitor SQ22536 had no effect. In contrast, forskolin reduced and SQ22536 increased s-NTDs release in the lamina propria. Adenosine enhanced s-NTDs release and accelerated ATP hydrolysis in ILS and lamina propria. Therefore, there is a regulated release of s-NTDs in the bladder lumen during filling. Aberrant release or functions of urothelial s-NTDs might cause elevated urinary ATP in conditions with abnormal bladder excitability.

SELECTIVE PHARMACOLOGICAL INHIBITION OF NOX2 BY GSK2795039 IMPROVES BLADDER DYSFUNCTION IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS IN MICE

Mariana G de Oliveira, Fabíola Z Monica, Gabriela R Passos, Jamaira A Victorio, Ana Paula Davel, Anna Lethicia Lima Oliveira, Carlos A Parada, Carlos A L D'Ancona, Warren G Hill, Edson Antunes. Antioxidants (Basel). 2022 Dec 30;12(1):92. doi: 10.3390/antiox12010092. PMID: 36670953.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic inflammatory disease without consistently effective treatment. Among the many mediators implicated in cystitis, the overproduction of reactive oxygen species (ROS) seems to play a key role, although the main source of ROS remains unclear. This study from Brazil aimed to investigate the contribution of NADPH oxidase (NOX) isoforms in ROS generation and the voiding dysfunction of cyclophosphamide (CYP, 300 mg/Kg, ip, 24 h)-induced cystitis in adult female mice, a well-recognized animal model to study IC/BPS, by using GKT137831 (5 mg/Kg, ip, three times in a 24 h period) or GSK2795039 (5 mg/Kg, ip, three times in a 24 h period) to inhibit NOX1/4 or NOX2, respectively. The results showed that treatment with GSK2795039 improved the dysfunctional voiding behavior induced by CYP, reduced bladder edema and inflammation, and preserved the urothelial barrier integrity and tight junction occludin expression, besides inhibiting the characteristic vesical pain and bladder superoxide anion generation. In contrast, the NOX1/4 inhibitor GKT137831 had no significant protective effects. Taken together, the authors believe that their in vivo and ex vivo data demonstrate that NOX2 is possibly the main source of ROS observed in cystitis-induced CYP in mice. Therefore, selective inhibition of NOX2 by GSK2795039 may be a promising target for future therapies for IC/BPS.

TRPV4 ACTIVATION PREVENTS LIPOPOLYSACCHARIDE-INDUCED PAINFUL BLADDER HYPERSENSITIVITY IN RATS BY REGULATING IMMUNE PATHWAYS

Masaru Yoshizumi, Naoya Tazawa, Chizuko Watanabe, Hirokazu Mizoguchi. Front Immunol. 2022 Dec 22;13:1080302. doi: 10.3389/fimmu.2022.1080302. eCollection 2022. PMID: 36618411.

Chronic inflammation in the urinary bladder is a potential risk factor for bladder dysfunction, including interstitial cystitis/bladder pain syndrome (IC/BPS). Although several studies have reported that activation of transient receptor potential vanilloid 4 (TRPV4) contributes to bladder pain and overactive bladder with a cardinal symptom of acute or chronic cystitis, others have reported its involvement in the protective response mediated by lipopolysaccharides (LPS) to secrete anti-inflammatory/pro-resolution cytokines. Therefore, the authors from Japan investigated the potential benefit of an intravesical TRPV4 agonist for painful bladder hypersensitivity in a rat model of LPS-induced cystitis and determined whether its effects modulate the LPS signal for inflammatory reaction, cytokine release, and macrophage phenotype change. Previously, they showed that repeated intravesical instillations of LPS induce long-lasting bladder inflammation, pain, and overactivity in rats. In the present study, concurrent instillation of the selective TRPV4 agonist GSK1016790A (GSK) with LPS into the rat bladder improved LPS-induced bladder inflammation and reduced the number of mast cells. Furthermore, co-instillation of GSK prevented an increase in bladder pain-related behaviour and voiding frequency caused by LPS. Cytokine profiling showed that LPS-stimulated inflammatory events, such as the production and secretion of pro-inflammatory cytokines (CXCL1, CXCL5, CXCL9, CXCL10, CCL3, CCL5, CCL20, and CX3CL1), are suppressed by GSK. Furthermore, TRPV4 activation switched LPS-stimulated pro-inflammatory M1-type macrophages to anti-inflammatory M2-type macrophages. These results suggest that TRPV4 activation in the bladder

negatively regulates the pro-inflammatory response induced by LPS and prevents bladder hypersensitivity. These TRPV4 functions may be promising therapeutic targets for refractory IC/BPS.

TRPV1 AND TRPM8 ANTAGONISTS REDUCE CYSTITIS-INDUCED BLADDER HYPERSENSITIVITY VIA INHIBITION OF DIFFERENT SENSITISED CLASSES OF BLADDER AFFERENTS IN GUINEA PIGS

Stewart Ramsay, Lauren Keightley, Simon Brookes, Vladimir Zagorodnyuk. Br J Pharmacol. 2022 Dec 22. doi: 10.1111/bph.16017. Online ahead of print. PMID: 36549668.

Interstitial cystitis (=painful bladder syndrome) is a chronic bladder syndrome characterised by pelvic and bladder pain, urinary frequency and urgency, and nocturia. Transient receptor potential (TRP) channels are an attractive target in reducing the pain associated with interstitial cystitis. The current study from Australia aims to determine the efficacy of combination of TRP vanilloid 1 (TRPV1) and TRP melastatin 8 (TRPM8) channel inhibition in reducing the pain associated with experimental cystitis in guinea pigs. A novel animal model of non-ulcerative interstitial cystitis has been developed using protamine sulfate/zymosan in female guinea pigs. Continuous voiding cystometry was performed in conscious guinea pigs. Ex vivo "close-to-target" single unit extracellular recordings were made from fine branches of pelvic nerves entering the guinea pig bladder. Visceromotor responses in vivo were used to determine the effects of TRP channel antagonists on cystitis-induced bladder hypersensitivity. Protamine sulfate/zymosan treatment evoked mild inflammation in the bladder and increased micturition frequency in conscious animals. In cystitis, high threshold muscular afferents were sensitised via up-regulation of TRPV1 channels, high threshold muscular-mucosal afferents were sensitised via TRPM8 channels, and mucosal afferents by both. Visceromotor responses evoked by noxious bladder distension were significantly enhanced in cystitis and were returned to control levels upon administration of combination of low doses of TRPV1 and TRPM8 antagonists. The data demonstrate the therapeutic promises of combination of TRPV1 and TRPM8 antagonists for treatment of bladder hypersensitivity in cystitis.

ACUTE INTRAVESICAL CAPSAICIN FOR THE STUDY OF TRPV1 IN THE LOWER URINARY TRACT: CLINICAL RELEVANCE AND POTENTIAL FOR INNOVATION

Karl-Erik Andersson, Delphine Behr-Roussel, Pierre Denys, Francois Giuliano. Med Sci (Basel). 2022 Sep 10;10(3):50. doi: 10.3390/medsci10030050. Med Sci (Basel). 2022 Sep 10;10(3):50.

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Capsaicin acts on sensory nerves via vanilloid receptors. TRPV1 has been extensively studied with respect to functional lower urinary tract (LUT) conditions in rodents and humans. In this study from the USA, Sweden and France, the authors aimed to (1) provide background information on capsaicin and TRPV1 and its mechanisms of action and basis for clinical use, (2) review the use of acute intravesical capsaicin instillation (AICI) in rodents to mimic various LUT disorders in which capsaicin sensitive C-fibers are involved and (3) discuss future innovative treatments. A comprehensive search of the major literature databases until June 2022 was conducted. Both capsaicin-sensitive and resistant unmyelinated bladder afferent C-fibers are involved in non-neurogenic overactive bladder/detrusor overactivity (OAB/DO). AICI is a suitable model to study afferent hyperactivity mimicking human OAB. Capsaicin-sensitive C-fibers are also involved in neurogenic DO (NDO) and potential targets for NDO treatment. AICI has been successfully tested for NDO treatment in humans. Capsaicin-sensitive bladder afferents are targets for NDO treatment. TRPV1-immunoreactive nerve fibers are involved in the pathogenesis of interstitial cystitis/painful bladder syndrome (IC/PBS). The AICI experimental model appears relevant for the preclinical study of treatments targeting bladder afferents for refractory IC/BPS. The activity of capsaicin-sensitive bladder afferents is increased in experimental bladder outlet obstruction (BOO). The AICI model may also be relevant for bladder disorders resulting from C-fiber hyperexcitabilities related to BOO. In conclusion, there is a rationale for the selective blockade of TRPV1 channels for various bladder disorders. The AICI model is clinically relevant for the investigation of pathophysiological conditions

in which bladder C-fiber afferents are overexcited and for assessing innovative treatments for bladder disorders based on their pathophysiology.

INHIBITION OF TRPM8 BY THE URINARY TRACT ANALGESIC DRUG PHENAZOPYRIDINE

Noémie Luyts, Jan Daniluk, Ana Freitas, Bahar Bazeli, Annelies Janssens, Marie Mulier, Wouter Everaerts, Thomas Voets. Eur J Pharmacol. 2023 Jan 16;175512. doi: 10.1016/j.ejphar.2023.175512. Online ahead of print. PMID: 36657655

Phenazopyridine (PAP) is an over-the-counter drug widely used to provide symptomatic relief of bladder pain in conditions such as cystitis or bladder pain syndrome (BPS). Whereas the analgesic effect of PAP has been attributed to a local effect on the mucosa of the lower urinary tract (LUT), the molecular targets of PAP remain unknown. The authors from Belgium investigated the effect of PAP on pain-related Transient Receptor Potential (TRP) channels expressed in sensory neurons that innervate the bladder wall. The effects of PAP on the relevant TRP channels (TRPV1, TRPA1, TRPM8, TRPM3) expressed in HEK293 or CHO cells were investigated using Fura-2-based calcium measurements and whole-cell patch-clamp recordings. Activity of PAP on TRPM8 was further analysed using Fura-2-based calcium imaging on sensory neurons isolated from lumbosacral dorsal root ganglia (DRG) of mice. PAP rapidly and reversibly inhibits responses of TRPM8 expressed in HEK293 cells to cold and menthol, with IC₅₀ values between 2 and 10 μ M. It acts by shifting the voltage dependence of channel activation towards positive potentials, opposite to the effect of menthol. PAP also inhibits TRPM8-mediated, menthol-evoked calcium responses in lumbosacral DRG neurons. At a concentration of 10 μ M, PAP did not significantly affect TRPA1, TRPV1, or TRPM3. PAP inhibits TRPM8 in a concentration range consistent with PAP levels in the urine of treated patients. Since TRPM8 is expressed in bladder afferent neurons and upregulated in patients with painful bladder disorders, TRPM8 inhibition may underlie the analgesic activity of PAP.

TRANSIENT RECEPTOR POTENTIAL VANILLOID TYPE 4 (TRPV4) IN URINARY BLADDER STRUCTURE AND FUNCTION

Megan Elizabeth Perkins, Margaret A Vizzard. Curr Top Membr. 2022;89:95-138. doi: 10.1016/bs.ctm.2022.06.002. Epub 2022 Jul 18. PMID: 36210154

Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a urologic, chronic pelvic pain syndrome characterized by pelvic pain, pressure, or discomfort with urinary symptoms. Symptom exacerbation (flare) is common with multiple, perceived triggers including stress. Multiple transient receptor potential (TRP) channels (TRPA1, TRPV1, TRPV4) expressed in the bladder have specific tissue distributions in the lower urinary tract (LUT) and are implicated in bladder disorders including overactive bladder (OAB) and BPS/IC. TRPV4 channels are strong candidates for mechanosensors in the urinary bladder and TRPV4 antagonists are promising therapeutic agents for OAB. In this perspective piece from the USA, the authors address the current knowledge of TRPV4 distribution and function in the LUT and its plasticity with injury or disease with an emphasis on BPS/IC. They review their studies that extend the knowledge of TRPV4 in urinary bladder function by focusing on (i) TRPV4 involvement in voiding dysfunction, pelvic pain, and non-voiding bladder contractions in NGF-OE mice; (ii) distention-induced luminal ATP release mechanisms and (iii) involvement of TRPV4 and vesicular release mechanisms. Finally, they review their lamina propria studies in postnatal rat studies that demonstrate: (i) the predominance of the TRPV4⁺ and PDGFR α ⁺ lamina propria cellular network in early postnatal rats; (ii) the ability of exogenous mediators (i.e., ATP, TRPV4 agonist) to activate and increase the number of lamina propria cells exhibiting active Ca²⁺ events; and (iii) the ability of ATP and TRPV4 agonist to increase the rate of integrated Ca²⁺ activity corresponding to coupled lamina propria network events and the formation of propagating wavefronts.

THE T-TYPE CALCIUM CHANNEL CA V 3.2 REGULATES BLADDER AFFERENT RESPONSES TO MECHANICAL STIMULI

Luke Grundy, Cindy Tay, Stewart Christie, Andrea M Harrington, Joel Castro, Fernanda C Cardoso, Richard J Lewis, Vladimir Zagorodnyuk, Stuart M Brierley. *Pain*. 2022 Oct 21. doi: 10.1097/j.pain.0000000000002795. Online ahead of print. PMID: 36279179.

The bladder wall is innervated by a complex network of afferent nerves that detect bladder stretch during filling. Sensory signals, generated in response to distension, are relayed to the spinal cord and brain to evoke physiological and painful sensations and regulate urine storage and voiding. Hyperexcitability of these sensory pathways is a key component in the development of chronic bladder hypersensitivity disorders including interstitial cystitis/bladder pain syndrome and overactive bladder syndrome. Despite this, the full array of ion channels that regulate bladder afferent responses to mechanical stimuli have yet to be determined. Here, the authors from Australia investigated the role of low-voltage-activated T-type calcium (Ca V 3) channels in regulating bladder afferent responses to distension. Using single-cell reverse-transcription polymerase chain reaction and immunofluorescence, the authors revealed ubiquitous expression of Ca V 3.2, but not Ca V 3.1 or Ca V 3.3, in individual bladder-innervating dorsal root ganglia neurons. Pharmacological inhibition of Ca V 3.2 with TTA-A2 and ABT-639, selective blockers of T-type calcium channels, dose-dependently attenuated ex-vivo bladder afferent responses to distension in the absence of changes to muscle compliance. Further evaluation revealed that Ca V 3.2 blockers significantly inhibited both low- and high-threshold afferents, decreasing peak responses to distension, and delayed activation thresholds, thereby attenuating bladder afferent responses to both physiological and noxious distension. Nocifensive visceromotor responses to noxious bladder distension in vivo were also significantly reduced by inhibition of Ca V 3 with TTA-A2. Together, these data provide evidence of a major role for Ca V 3.2 in regulating bladder afferent responses to bladder distension and nociceptive signalling to the spinal cord.

PATHOPHYSIOLOGY AND CLINICAL BIOMARKERS IN INTERSTITIAL CYSTITIS

John M Masterson, Peris R Castañeda, Jayoung Kim. *Urol Clin North Am*. 2023 Feb;50(1):39-52. doi: 10.1016/j.ucl.2022.09.006. PMID: 36424082.

Interstitial cystitis/bladder pain syndrome is a poorly understood yet prevalent condition accounting for a significant proportion of urology office visits. Identification of reliable biomarkers for disease remains an important yet challenging area of research given the heterogeneity of disease presentation and pathophysiology. A review of the literature by the authors from the USA revealed a handful of original investigations that revealed promising biomarkers within various physiologic processes or organ systems including immunity, inflammation, neural pathways, urothelial integrity, and anesthetic bladder capacity. Although no perfect biomarker has yet been identified for IC/BPS, research in this area has greatly expanded our understanding of disease.

IDENTIFICATION OF IMMUNE-RELATED GENES AND SMALL-MOLECULE DRUGS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME BASED ON THE INTEGRATIVE MACHINE LEARNING ALGORITHMS AND MOLECULAR DOCKING

Yiheng Jiang, Xinqing Zhu, Abdullah Y Al-Danakh, Qiwei Chen, Deyong Yang. *J Immunol Res*. 2022 Dec 28;2022:2069756. doi: 10.1155/2022/2069756. eCollection 2022. PMID: 36619718.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, severely distressing clinical syndrome characterized by bladder pain and pressure perceptions. The origin and pathophysiology of IC/BPS are currently unclear, making it difficult to diagnose and formulate successful treatments. This study from Dalian, China investigated the role of immune-related genes in the diagnosis, progression, and therapy of IC/BPS. The gene expression datasets GSE11783, GSE11839, GSE28242, and GSE57560 were retrieved from the GEO database for further analysis. Immune-related IC/BPS differentially expressed genes (DEGs) were identified by limma. Three distinct machine learning approaches, least absolute shrinkage and selection operator (LASSO), support vector machine-recursive feature elimination (SVM-RFE), and random forest (RF), were used to find the immune-related IC characteristic genes. Nomogram and receiving operator curves (ROC) were plotted to measure

characteristic effectiveness. Using the CMap database and the molecular docking approach, potential small-molecule medicines were found and verified. Consensus cluster analysis was also performed to separate the IC/BPS samples into immunological subtypes. A total of 24 immune-related IC/BPS-DEGs were identified. When compared to the normal control group, the IC/BPS cohort had significantly more immune cell infiltration. Integrative machine learning methods discovered 5 IC/BPS characteristic genes (RASGRP1, PPBP, RBP4, CR2, and PROS2) that may predict IC/BPS diagnosis and immune cell infiltration. Furthermore, two immunological subgroups with substantial variations in immune cell infiltration across IC/BPS samples were identified, which were named cluster1 and cluster2, with the hallmark genes having greater expression in cluster2. Finally, bumetanide was shown to have the potential to be a medication for the treatment of IC/BPS, and it performed well in terms of its molecular binding with RASGRP1. The authors found and validated 5 immune-related IC/BPS genes (RASGRP1, PPBP, RBP4, CR2, and PROS2) and 2 IC/BPS immune subtypes. In addition, bumetanide was discovered to be a potential drug for treating IC/BPS, which may provide new insight into the diagnosis and immune therapy of IC/BPS patients.

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

Andrew Schrepf, Chelsea Kaplan, Richard E Harris, David A Williams, Daniel J Clauw, Sawsan As-Sanie, Sara Till, J Quentin Clemens, Larissa V Rodriguez, Adrie Van Bokhoven, Richard Landis, Robert Gallop, Catherine Bradley, Bruce Naliboff, Mike Pontari, Michael O'Donnell, Yi Luo, Karl Kreder, Susan K Lutgendorf, Steven E Harte. Pain. 2022 Oct 19. doi: 10.1097/j.pain.0000000000002813. Online ahead of print. PMID: 36279178.

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

THE EFFICACY AND SAFETY OF A HUMAN PERIRENAL ADIPOSE TISSUE-DERIVED STROMAL VASCULAR FRACTION IN AN INTERSTITIAL CYSTITIS RAT MODEL

Ji Yong Ha, Eun Hye Lee, So Young Chun, Jun Nyung Lee, Yun-Sok Ha, Jae-Wook Chung, Bo Hyun Yoon, Minji Jeon, Hyun Tae Kim, Tae Gyun Kwon, Eun Sang Yoo, Bum Soo Kim. Tissue Eng Regen Med. 2023 Jan 4. doi: 10.1007/s13770-022-00505-w. Online ahead of print. PMID: 36600004.

Interstitial cystitis (IC) is a chronic and intractable disease that can severely deteriorate patients' quality of life. Recently, stem cell therapy has been introduced as a promising alternative treatment

for IC in animal models. This study from Korea aimed to verify the efficacy and safety of the human perirenal adipose tissue-derived stromal vascular fraction (SVF) in an IC rat model. From eight-week-old female rats, an IC rat model was established by subcutaneous injection of 200 µg of uroplakin3A. The SVF was injected into the bladder submucosal layer of IC rats, and pain scale analysis, awakening cytometry, and histological and gene analyses of the bladder were performed. For the in vivo safety analysis, genomic DNA purification and histological analysis were also performed to check tumorigenicity and thrombus formation. The mean pain scores in the SVF 20 µl group were significantly lower on days 7 and 14 than those in the control group, and bladder intercontraction intervals were significantly improved in the SVF groups in a dose-dependent manner. Regeneration of the bladder epithelium, basement membrane, and lamina propria was observed in the SVF group. In the SVF groups, however, bladder fibrosis and the expression of inflammatory markers were not significantly improved compared to those in the control group. This study demonstrated that a perirenal adipose tissue-derived SVF is a promising alternative for the management of IC in terms of improving bladder pain and overactivity.

IDENTIFICATION OF A POTENTIAL STRUCTURE-BASED GPCR DRUG FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: IN SILICO PROTEIN STRUCTURE ANALYSIS AND MOLECULAR DOCKING

Kuiqing Li, Cong Lai, Shangyan Hei, Cheng Liu, Zhuohang Li, Kewei Xu. Int Urogynecol J. 2022 Dec 28. doi: 10.1007/s00192-022-05424-x. Online ahead of print. PMID: 36576541.

There is currently no effective treatment for interstitial cystitis / bladder pain syndrome (IC/BPS) and thus seriously reduces the quality of life of patients. The purpose of this study from Guangzhou, China was to analyze the structure and function of G protein coupled receptors related to IC/BPS by integrating bioinformatics and provide basis for the development of new drugs for IC/BPS. The authors used ProtParam and DNAMAN to analyze the physical and chemical properties of GPR18 and GPR183 proteins. The secondary and tertiary structure, conservative domain, phosphorylation site of both proteins were predicted by ProtScale, PredictProtein, SWISS-MODEL and GPS5.0 respectively. Multiple sequence alignment of the proteins were carried out by DNAMAN and the phylogenetic tree was constructed by MEGA. Further, the molecular docking verification of cannabidiol and both proteins were carried out by using AutoDock Vin. GPR18 and GPR183 proteins were composed of 331 and 361 amino acids respectively. α -helix is the highest in the secondary structure of the two proteins. Both proteins contain seven transmembrane domains specific to G protein coupled receptors. And homology analysis showed that the two proteins had high homology. In terms of molecular docking, cannabidiol, a non-psychoactive component extracted from the cannabis, can form effective molecular binding with GPR18 and GPR183 proteins. The authors identified the structures of GPR18 and GPR183 proteins and their highly homologous evolutionary properties. Furthermore, both proteins can form effective binding with cannabidiol which provides new insights for the development of IC/BPS drugs by targeting G protein coupled receptors.

STRESS-INDUCED CHANGES IN TROPHIC FACTOR EXPRESSION IN THE RODENT URINARY BLADDER: POSSIBLE LINKS WITH ANGIOGENESIS

Mathijs M de Rijk, Amanda Wolf-Johnston, Aura F Kullmann, Katherine Maringer, Sunder Sims-Lucas, Gommert A van Koevinge, Larissa V Rodríguez, Lori A Birder. Int Neurourol J. 2022 Dec;26(4):299-307. doi: 10.5213/inj.2244118.059. Epub 2022 Dec 30. PMID: 36599338.

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Substantive evidence supports a role of chronic stress in the development, maintenance, and even enhancement of functional bladder disorders such as interstitial cystitis/bladder pain syndrome (IC/BPS). Increased urinary frequency and bladder hyperalgesia have been reported in rodents exposed to a chronic stress paradigm. Here, the authors from the USA and the Netherlands utilized a water avoidance stress (WAS) model in rodents to investigate the effect of chronic stress on vascular perfusion and angiogenesis. Female Wistar-Kyoto rats were exposed to WAS for 10 consecutive

days. Bladder neck tissues were analyzed by western immunoblot for vascular endothelial growth factor (VEGF) and nerve growth factor precursor (proNGF). Vascular perfusion was assessed by fluorescent microangiography followed by Hypoxyprobe testing to identify regions of tissue hypoxia. The expression of VEGF and proNGF in the bladder neck mucosa was significantly higher in the WAS rats than in the controls. There was a trend toward increased vascular perfusion, but without a statistically significant difference from the control group. The WAS rats displayed a 1.6-fold increase in perfusion. Additionally, a greater abundance of vessels was observed in the WAS rats, most notably in the microvasculature. The authors are of the opinion that these findings show that chronic psychological stress induces factors that can lead to increased microvasculature formation, especially around the bladder neck, the region that contains most nociceptive bladder afferents. These findings may indicate a link between angiogenesis and other inflammatory factors that contribute to structural changes and pain in IC/BPS.

DEHYDRATED HUMAN AMNION-CHORION MEMBRANE EXTRACTS CAN AMELIORATE INTERSTITIAL CYSTITIS IN RATS BY DOWN-REGULATING INFLAMMATORY CYTOKINES AND PROTEIN CODING GENES: A PRECLINICAL STUDY

Che-Hsueh Yang, Min-Che Tung, Yi-Sheng Lin, Chao-Yu Hsu, Ivan Akhrymuk, Kok-Tong Tan, Yen-Chuan Ou, Chi-Chien Lin. Life (Basel). 2022 Oct 25;12(11):1693. doi: 10.3390/life12111693. PMID: 36362848.

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This study from Taiwan aimed to investigate the therapeutic impact of intravesical instillation of dehydrated human amnion-chorion membrane (HACM) extracts based on the primary pathological feature of interstitial cystitis (IC). The authors divided 15 female Sprague-Dawley rats into three groups: sham control, IC, and treatment group. IC was induced by 400- μ L lipopolysaccharide (1 μ g/ μ L), and it was replaced with normal saline in the sham control group. After IC induction, 300 μ L dehydrated HACM extracts (3 mg/kg) were instilled into rats' urinary bladder weekly for 3 weeks. General histology, inflammatory cytokines, NF- κ B, oxidative markers, and western blots results were examined. The urothelial denudation, mast-cell infiltration, and tissues fibrosis were all ameliorated. The elevated TNF- α , IL-1 β , IL-6, IL-8, and NF- κ B were all down-regulated by dehydrated HACM extracts ($p < 0.05$). For reactive oxygen species, increased malondialdehyde, decreased superoxide dismutase, and decreased glutathione peroxidase were all reversed ($p < 0.05$). In apoptosis of IC, elevated Bax and suppressed Bcl-2 were improved ($p < 0.05$) after instillation. In fibrosis, dysregulated TGF β /R-Smads/Snail was corrected by the instillation of dehydrated HACM ($p < 0.05$). In conclusion, dehydrated HACM extracts could be a powerful remedy in treating IC by reconstructing the damaged urothelium, reducing mast-cell infiltration and inflammatory reactions, and ameliorating fibrotic changes.

[PLASMA ACID REPRODUCES OXIDATIVE AND NITROSATIVE STRESS IN BLADDER TISSUE IN VITRO: EXPERIMENTAL STUDY]

[Article in Russian]

E A Alekseeva, M A Firsov, N A Malinovskaya, A B Salmina, V V Salmin. Urologiia. 2022 Dec;(6):61-65. PMID: 36625615

The purpose of this study from Russia was to analyze some effects of plasma acid in vitro on the bladder tissue obtained from laboratory animals and to evaluate the possibility of its application for in vitro modeling of IC/BPS. The tissue samples of the bladder wall were obtained from female Wistar rats aged 3 months ($n=16$, weighing 180-200 g). The tissues were processed for 1 hour in the plasma acid prepared by spark discharge of water for injection in air. The immunohistochemical study of obtained samples was performed. The changes in the expression profile of bladder epithelial cells under the action of plasma acid in vitro were found indicating the development of oxidative, nitrosative and dicarbonyl stress, impaired expression of NADPH oxidase DUOX2 and VEGF, and a decrease in cell proliferative activity, which, in general, corresponds to the main

mechanisms of urothelial alterations specific for the IC/BPS. The revealed effects of plasma acid on bladder epithelial cells confirm the possibility of using it as an inducer of urothelial cell damage typical for IC/BPS in the in vitro models.

USEFULNESS OF URINARY BIOMARKERS FOR ASSESSING BLADDER CONDITION AND HISTOPATHOLOGY IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Yuan-Hong Jiang, Jia-Fong Jhang, Yuan-Hsiang Hsu, Hann-Chorng Kuo. *Int J Mol Sci.* 2022 Oct 10;23(19):12044. doi: 10.3390/ijms231912044. PMID: 36233356

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This study from Taiwan investigated the usefulness of urinary biomarkers for assessing bladder condition and histopathology in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Jiang and colleagues retrospectively enrolled 315 patients (267 women and 48 men) diagnosed with IC/BPS and 30 controls. Data on clinical and urodynamic characteristics (visual analog scale (VAS) score and bladder capacity) and cystoscopic hydrodistention findings (Hunner's lesion, glomerulation grade, and maximal bladder capacity (MBC)) were recorded. Urine samples were utilized to assay inflammatory, neurogenic, and oxidative stress biomarkers, including interleukin (IL)-8, C-X-C motif chemokine ligand 10 (CXCL10), monocyte chemoattractant protein-1 (MCP-1), brain-derived neurotrophic factor (BDNF), eotaxin, IL-6, macrophage inflammatory protein 1 beta (MIP-1 β), regulated on activation, normal T cell expressed and secreted (RANTES), tumor necrosis factor-alpha (TNF- α), prostaglandin E2 (PGE2), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and 8-isoprostane, and total antioxidant capacity. Further, specific histopathological findings were identified via bladder biopsy. The associations between urinary biomarker levels and bladder conditions and histopathological findings were evaluated. The results reveal that patients with IC/BPS had significantly higher urinary MCP-1, eotaxin, TNF- α , PGE2, 8-OHdG, and 8-isoprostane levels than controls. Patients with Hunner's IC (HIC) had significantly higher IL-8, CXCL10, BDNF, eotaxin, IL-6, MIP-1 β , and RANTES levels than those with non-Hunner's IC (NHIC). Patients with NHIC who had an MBC of \leq 760 mL had significantly high urinary CXCL10, MCP-1, eotaxin, IL-6, MIP-1 β , RANTES, PGE2, and 8-isoprostane levels and total antioxidant capacity. Patients with NHIC who had a higher glomerulation grade had significantly high urinary MCP-1, IL-6, RANTES, 8-OHdG, and 8-isoprostane levels. A significant association was observed between urinary biomarkers and glomerulation grade, MBC, VAS score, and bladder sensation. However, bladder-specific histopathological findings were not well correlated with urinary biomarker levels. The urinary biomarker levels can be useful for identifying HIC and different NHIC subtypes. Higher urinary inflammatory and oxidative stress biomarker levels are associated with IC/BPS. Most urinary biomarkers are not correlated with specific bladder histopathological findings; nevertheless, they are more important in the assessment of bladder condition than bladder histopathology.

DIMETHYL SULFOXIDE (DMSO): A SOLVENT THAT MAY SOLVE SELECTED CUTANEOUS CLINICAL CHALLENGES

Maria Karim, Robert S Boikess, Robert A Schwartz, Philip J Cohen. *Arch Dermatol Res.* 2022 Dec 2. doi: 10.1007/s00403-022-02494-1. Online ahead of print. PMID: 36459193.

Dimethyl sulfoxide (DMSO) is a clear, odorless liquid, inexpensively produced as a by-product of the wood pulp industry. DMSO's unique chemical properties allow for its broad applications in a wide variety of cutaneous challenges. Widely available in the USA as a solvent, DMSO is FDA-approved only for the treatment of interstitial cystitis and for use as a preservative for organ transplant. DMSO readily penetrates and diffuses through biological membranes. At low concentrations, DMSO exhibits anti-inflammatory, analgesic, diuretic, vasodilator, anti-platelet aggregation, radioprotective, and muscle-relaxing properties. DMSO is also a vigorous scavenger of hydroxyl free radicals, which may explain its observed beneficial effects on skin rejuvenation and recovery from thermal injury. DMSO has a relatively low level of toxicity. DMSO has shown promise in the off-label treatment of basal cell carcinoma, pressure ulcers, scleroderma, herpes simplex, cutaneous fungal

infections, and amyloidosis. The potential of DMSO to serve as an independent or adjuvant topical treatment for these conditions is explored in this review from the USA.

EFFICACY OF INTRAVESICAL COCKTAIL THERAPY WITH OR WITHOUT DIMETHYL SULPHOXIDE IN INTERSTITIAL CYSTITIS.

Emrullah Sogutdelen, Burak Citamak. Cent European J Urol. 2022;75(3):299-304. doi: 10.5173/ceju.2022.129. Epub 2022 Sep 24. PMID: 36381159.

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Interstitial cystitis (IC) is a chronic bladder inflammation with unknown etiologies that impairs the quality of life of patients. The authors from Turkey aimed to investigate the efficacy of dimethyl sulphoxide (DMSO) use in the cocktail therapy in IC patients. Patients treated with intravesical cocktail therapy which contained a mixture of 10 mL of bupivacaine, 1 mL of heparin, and 9 mL of sodium bicarbonate, was introduced to Group 1, and, 25 mL of DMSO was added to this cocktail and introduced to Group 2. Statistical analyses between groups were assessed by Turkish validated O'Leary Sant score composed of IC Symptom Index (ICSI) and IC Problem Index (ICPI), visual analog scale (VAS) score, and short form-36 (SF-36) questionnaire in the baseline versus post-instillation week 6, month 6, and month 12, comparatively. A total of 62 patients (58 women and 4 men) with a median age of 52 (28-76) years were included. Baseline versus post-instillation 6th week of ICSI and ICPI scores were 15 ± 3.4 vs 7.4 ± 2.9 and 12.6 ± 2.8 vs 6.1 ± 2.7 , respectively ($p < 0.001$ and < 0.001 , respectively). VAS scores of Group 2 were statistically significantly lower than that of Group 1 in the post-instillation month 6 ($p = 0.03$) whereas, the baseline of VAS scores were similar. Intravesical cocktail therapy is an effective and reliable treatment method and can be safely applied with or without DMSO. Adding DMSO to cocktail therapy provides a further decrease in VAS score in the post-instillation month 6.

EFFECT OF INTRATRIGONAL BOTULINUM TOXIN IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A LONG-TERM, SINGLE-CENTER STUDY IN REAL-LIFE CONDITIONS

Pedro Abreu-Mendes, António Ferrão-Mendes, Francisco Botelho, Francisco Cruz, Rui Pinto. Toxins (Basel). 2022 Nov 10;14(11):775. doi: 10.3390/toxins14110775. PMID: 36356025.

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The high percentage of treatment failures seen in patients with bladder pain syndrome/interstitial cystitis (BPS/IC) managed conservatively frequently demands invasive treatment options. The authors from Portugal aimed to evaluate the long-term efficacy and adverse events of intratrigoal botulinum toxin injection in such circumstances, as well as to determine possible predictors of response to toxin treatment. A retrospective cohort study included 47 female BPS/IC patients treated with onabotulinum toxin A (OnabotA) in a tertiary hospital between the years 2009 and 2022. All patients received 100 U of OnabotA in ten injections limited to the trigonal area. Patients were divided into three groups based on their treatment response as responders, non-responders and lost to follow-up due to non-medical reasons. The clinical and surgical records of the individuals were retrieved, including the 10-point visual analogue scale (VAS), the number of treatments, the time between injections, and the age at the first injection. A total of 25 patients (>50% of the cohort) were long-term responders, but none of the evaluated parameters was a predictor for this circumstance: age, pain intensity, or duration of improvement following the injection. The time between injections was stable (around 1 year). No severe adverse events were registered. The intratrigoal injection of botulinum toxin in patients with BPS/IC was an effective and safe long-term treatment for patients' refractory to conservative forms of treatment. Age, basal pain intensity, and time to injection request did not predict long-term response to OnaBotA.

CHINESE BOTULINUM TOXIN A FOR THE TREATMENT OF LOWER URINARY TRACT DYSFUNCTION: IT WORKS JUST AS WELL

Fan Zhang, Qinggang Liu, Limin Liao, Xiaojuan Li, Xueping Zhang. Bladder (San Franc). 2022 Sep 14;9(1):e47. doi: 10.14440/bladder.2022.847. eCollection 2022. PMID: 36425077.

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The botulinum neurotoxin type A (BoNT/A) is a neurotoxin produced by *Clostridium botulinum*. It causes botulism and represents the most powerful natural poison. In urological practice, the indications for BoNT/A therapy include neurogenic detrusor overactivity (NDO), idiopathic overactive bladder (OAB) or idiopathic detrusor overactivity (IDO), detrusor-sphincter dyssynergia (DSD), interstitial cystitis/bladder pain syndrome (IC/BPS), urinary tract infections (UTI), benign prostatic hyperplasia (BPH), and, more recently, chronic prostatic pain (CPP). BoNT/A is not only conducive to the treatment of muscle spasticity but also effectively works on hyperalgesia associated with various disorders of the lower urinary tract, thanks to its anti-nociceptive properties. While Botox® (Allergan Inc., Irvine, CA) is currently being used across the globe, the authors from Beijing and Shandong, China have been using Chinese BoNT/A for many years for the treatment of DSD, NDO, idiopathic OAB, IC/BPS, BPH and UTI. Their experience has shown that Chinese BoNT/A was as good as other BoNT/A products in terms of efficacy, safety, and tolerability. In this study, they explored the current and potential applications of Chinese BoNT/A in urology and reviewed the background information regarding the toxin.

LIPOSOME-ENCAPSULATED BOTULINUM TOXIN A IN TREATMENT OF FUNCTIONAL BLADDER DISORDERS

Fan-Ching Hung, Hann-Chorng Kuo. Toxins (Basel). 2022 Dec 1;14(12):838. doi: 10.3390/toxins14120838. PMID: 36548734.

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Botulinum toxin A (BoNT-A) intravesical injections have been used to treat patients with refractory functional bladder disorders such as overactive bladder (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS), but the risk of adverse events and the need for repeated injections continue to prevent widespread application of this treatment. Liposomes are vesicles that comprise concentric phospholipid layers and an aqueous core; their flexible compositions enable them to adsorb and fuse with cell membranes and to deliver drugs or proteins into cells. Therefore, liposomes have been considered as promising vehicles for the less invasive delivery of BoNT-A. In previous placebo-controlled trials including patients with OAB refractory to medical treatment, it was shown that liposomal BoNT-A could significantly decrease the frequency and urgency of urination. In patients with IC/BPS, it was shown that liposomal BoNT-A could also improve bladder pain, but the therapeutic efficacy was not superior to that of the placebo. As the therapeutic mechanisms of BoNT-A include the decreased expression of nerve growth factors, P2X3 receptors, and vanilloid receptors on C-fibers, liposomal BoNT-A might play a more promising role in the treatment of bladder oversensitivity. This article from Taiwan features the contemporary literature regarding BoNT-A, liposomes, and liposomal BoNT-A treatment for functional bladder disorders and potential clinical applications in the future.

TREATMENT OUTCOMES OF INTRAVESICAL BOTULINUM TOXIN A INJECTIONS ON PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Wan-Ru Yu, Yuan-Hong Jiang, Jia-Fong Jhang, Wei-Chuan Chang, Hann-Chorng Kuo. Toxins (Basel). 2022 Dec 11;14(12):871. doi: 10.3390/toxins14120871. PMID: 36548768.

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Botulinum toxin A (BoNT-A) is effective in reducing bladder hypersensitivity and increasing capacity through the effects of anti-inflammation in the bladder urothelium; however, studies on the treatment outcome of interstitial cystitis/bladder pain syndrome (IC/BPS) are lacking. The authors from Taiwan investigated the treatment outcome in IC/BPS patients receiving intravesical BoNT-A

injections. This retrospective study included IC/BPS patients who had 100U BoNT-A intravesical injections in the past 20 years. The treatment outcomes at 6 months following the BoNT-A treatment were evaluated using the global response assessment (GRA) scale. The treatment outcomes according to the GRA scale include clinical symptoms, urodynamic parameters, cystoscopic characteristics, and urinary biomarkers, and it was these predictive factors for achieving satisfactory outcomes which were investigated. Among the 220 enrolled patients (180 women, 40 men) receiving BoNT-A injections, only 87 (40%) had significantly satisfactory treatment outcomes. The satisfactory group showed significantly larger voided volumes, and lower levels of both the urinary inflammatory protein MCP-1 and the oxidative stress biomarker 8-isoprostane in comparison to the unsatisfactory group. The IC severity and detrusor pressure are predictive factors of BoNT-A treatment outcomes. IC/BPS patients with less bladder inflammation showed satisfactory outcomes with intravesical BoNT-A injections. Patients with severe bladder inflammation might require more intravesical BoNT-A injections to achieve a satisfactory outcome.

PRELIMINARY EXPLORATION OF A NEW THERAPY FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: BOTULINUM TOXIN A COMBINED WITH SAPYLIN

Wenshuang Li, Zhenming Zheng, Kaiqun Ma, Caixia Zhang, Kuiqing Li, Paierhati Tayier, Yousheng Yao. Toxins (Basel). 2022 Nov 30;14(12):832. doi: 10.3390/toxins14120832. PMID: 36548729.

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is an intractable disease without long-term effective therapy. This study from China aims to evaluate the efficacy and safety of botulinum toxin A (BoNT/A) plus Sapylin, which might modulate the immune response of the bladder in the treatment of IC/BPS patients. The authors retrospectively investigated the clinical outcomes among 34 patients who accepted repeated Sapylin instillations after 200 U of BoNT/A submucosally injected into bladder walls (Mix group) and 28 patients who received BoNT/A alone (Control group). Each of the bladder walls (left, right, anterior and posterior) was injected six times with 8 U of BoNT/A per injection. The primary outcome measure was the global response assessment. The results showed that at 6 months post-injection, the response rate in the Mix group was remarkably higher than that in the Control group (58.8% vs. 28.6%, $p < 0.05$). The mean effective duration of the responders in the Mix group was apparently better than that in the Control group (27.5 (range 0-89) vs. 4.9 (range 0-11) months, $p < 0.05$). None of the patients experienced serious adverse events. In conclusion, repeated intravesical instillations of Sapylin after BoNT/A injection can produce significantly better clinical outcomes than BoNT/A alone in IC/PBS patients.

EVALUATION OF PAIN AND QUALITY OF LIFE AFTER HYALURONIC ACID INSTILLATION IN ADDITION TO BOTULINUM TOXIN-A INJECTION IN WOMEN WITH REFRACTORY INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: A PILOT STUDY

Ahmed Fayez Ghaith, Mohamed Hasan Radwan, Mohamed Rashed Taha, Mohamed Ahmed Elbendary, Mahmoud Elsayed Al Damhogy, Ayman Mohamed Hagra. Arch Ital Urol Androl. 2022 Dec 27;94(4):447-450. doi: 10.4081/aiua.2022.4.447. PMID: 36576459.

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The aim of this study from Egypt was to assess changes in quality of life and pain alleviation in women with refractory Interstitial Cystitis/Painful Bladder syndrome following a combined intravesical injection of Botulinum Toxin-A and Hyaluronic Acid instillation versus Hyaluronic acid instillation alone. Two groups of women with painful bladder syndrome/interstitial cystitis were randomly divided (one to one randomization). Intravesical injections of botulinum toxin-A and intravesical Hyaluronic acid were given to Group (I). Only Hyaluronic acid was instilled intravesically in Group II. Patients were given voiding diaries, a visual analogue scale for pelvic pain, the International Cystitis Symptom Index and Problem Index, the Pelvic Pain Urgency/Frequency Patient Symptom Scale, and the Patient Health Questionnaire-9 to assess the candidates' quality of life. The Student t-test and mean and standard deviation were used in statistical analysis, with $p < 0.05$

considered as significant (IBM SPSS statistics) Results: Thirty-four women were included in this study. The pain severity (VAS) of group (I) cases dropped dramatically from 8.5 ± 1.5 at the start to 3.9 ± 2.4 after three months and 2.9 ± 2.1 after six months. Among group (II) cases, the pain score reduced dramatically from 8.6 ± 1.3 to 5.8 ± 1.4 to 4.3 ± 2.6 . In patients with refractory Interstitial Cystitis/Bladder Discomfort Syndrome, Botulinum Toxin-A injection combined with Hyaluronic Acid instillation improves pelvic pain and improves quality of life.

VAGINAL HORMONE THERAPY FOR CONDITIONS OF THE LOWER URINARY TRACT

Amy Nemirovsky, Natalia Arias Villela, J Christine Yuan, Rohit Patil, Rena D Malik. Curr Urol Rep. 2022 Dec 1. doi: 10.1007/s11934-022-01132-7. Online ahead of print. PMID: 36454371.

Up to half of postmenopausal women experience genitourinary symptoms secondary to hormone deficiency, and there is little consensus on the use of vaginal hormone therapy (VHT) for lower urinary tract symptoms (LUTS) in these patients. This is a review from the USA of the scientific literature in the last decade evaluating the use of VHT for disorders of the lower urinary tract including overactive bladder (OAB), stress urinary incontinence (SUI), recurrent urinary tract infections (UTI), and interstitial cystitis/bladder pain syndrome (ICS/BPS). Vaginal estrogen therapy improves OAB symptoms in postmenopausal women, but results are mixed when VHT is used in combination with other treatments. There is inconclusive or limited data for the use of VHT to treat SUI and IC/BPS. Vaginal estrogen and prasterone (DHEA) therapies have demonstrated efficacy as treatment modalities for patients who experience recurrent UTIs. VHT preparations show efficacy for the treatment of certain LUTS and can be considered in carefully selected patients when clinically indicated.

SILODOSIN IMPROVES PAIN AND URINARY FREQUENCY IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS PATIENTS

Pedro Abreu-Mendes, Beatriz Araújo-Silva, Ana Charrua, Francisco Cruz, Rui Pinto. J Clin Med. 2022 Sep 26;11(19):5659. doi: 10.3390/jcm11195659. PMID: 36233527.

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Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) is a bladder-related chronic inflammatory disease. Data indicate that stress enhances the excitability of bladder nociceptors through the stimulation of alpha1A-adrenoceptors. Stress is known to play a crucial role in BPS/IC patients. The authors aimed to assess the efficacy and safety of daily silodosin in refractory BPS/IC female patients and its correlation with stress coping. An open-label trial was conducted in Portugal with 20 refractory BPS/IC patients. Evaluations occurred at baseline and the 8th and 12th weeks. Primary endpoint was bladder pain evaluated by visual analogue scale (VAS). Secondary endpoints included daily frequency, nocturia and maximum voided volume obtained from a 3-day bladder diary, the O'Leary-Sant Symptom Score, and two questions accessing stress coping. Patients initiated daily doses of 8 mg silodosin, which could be titrated to 16 mg. Median values with percentiles 25 and 75 (25; 75) were used. Wilcoxon signed-rank test was used for comparisons. A minimally important difference of 3 points for pain was established to define clinically relevant improvement. Median age was 56 years. Median pain score decreased from 8.00 (6.00; 8.00) at baseline to 4.00 (2.00; 5.50) ($p < 0.001$), meaning that the primary endpoint was reached. Total urinary frequency decreased from 14.00 (13.00; 21.00) to 9.00 (7.50; 11.00) ($p < 0.05$), and all the other secondary endpoints also showed a statistically significant improvement. Eleven patients improved by ≥ 3 pain points in VAS, meaning that 65% of patients that ended the study protocol achieved clinically significant improvement or, in the full analysis set, that 55% of the 20 initial patients improved significantly. Fourteen (82%) decreased by ≥ 2 micturitions/day. Overall, the cohort's stress coping was low. It was concluded that Silodosin can be an effective and well-tolerated treatment for refractory BPS/IC female patients.

EFFICACY OF TRANSCUTANEOUS TIBIAL NERVE STIMULATION IN THE TREATMENT OF BLADDER PAIN SYNDROME

Okan Alkis, Bekir Aras, Mehmet Sevim, İbrahim Güven Kartal, Oğuzhan Yusuf Sönmez, Halil İbrahim İvelik. Curr Urol. 2022 Jun;16(2):83-87. doi: 10.1097/CU9.000000000000082. Epub 2022 Jan 27. PMID: 36570363.

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This study from Turkey aimed to demonstrate the effectiveness of transcutaneous tibial nerve stimulation (TTNS) in the treatment of bladder pain syndrome (BPS). The data of 16 female patients, diagnosed with BPS in their clinic between 2019 and 2021 and had TTNS twice a week for 12 weeks, were retrospectively analyzed. The mean age of the patients was 46.00 ± 13.11 years, and the mean body mass index was 26.43 ± 3.07 kg/m². After the treatment, the median day time frequency of the patients decreased from 13.37 (3.69) to 10.25 (4.56) ($p < 0.001$). Nocturia also decreased after treatment from 4.37 (1.81) to 3.00 (1.94) ($p = 0.001$). The median voiding volume increased by 26.5 mL ($p = 0.001$). The median of the patients' visual analog scale scores decreased after treatment (median of visual analog scale score changed from interquartile range 8 [1] to 7 [4]) ($p = 0.001$). In addition, the median interquartile range interstitial cystitis symptom index scores decreased from 17 (4) to 15 (10) ($p = 0.002$). In this study it was demonstrated that TTNS is an alternative method that can be successfully applied before invasive methods in the treatment of BPS.

[EFFECT OF ELECTROACUPUNCTURE ON THE EXPRESSIONS OF TRPV1, P2X3 RECEPTORS IN BLADDER OF RATS WITH INTERSTITIAL CYSTITIS]

[Article in Chinese]

Zhi-Hao Li, Xue-Dan Zhao, Wen Li, Wen-Jun Han. Zhongguo Zhen Jiu. 2022 Nov 12;42(11):1263-8. doi: 10.13703/j.0255-2930.20211028-k0002. PMID: 36397224.

The purpose of this study from Shanghai, China was to observe the effect of electroacupuncture (EA) at "Ciliao" (BL 32) and "Huiyang" (BL 35) on the pain, urodynamic and the expressions of transient receptor potential vanilloid 1 (TRPV1) and P2X3 receptors in bladder of rats with interstitial bladder (IC), and to explore the possible mechanism on EA for IC. A total of 24 Wistar female rats were randomly divided into a blank group, a model group and an EA group, 8 rats in each group. In the model group and the EA group, IC model was established by intraperitoneal injection of cyclophosphamide by 150 mg/kg at once. EA was applied at "Ciliao" (BL 32) and "Huiyang" (BL 35) in the EA group for 20 min, with continuous wave, 30 Hz in frequency, once a day for 3 consecutive days. Mechanical pain threshold of bladder and urodynamic indexes (first urination time, bladder effective volume and urination pressure) were observed after model establishment and after intervention, the expressions of TRPV1 and P2X3 receptors in the bladder were detected by Western blot. After model establishment, the mechanical pain threshold of bladder was decreased in the model group and the EA group compared with that in the blank group ($P < 0.01$). After intervention, the mechanical pain threshold of bladder in the model group was lower than the blank group ($P < 0.01$), and that in the EA group was higher than the model group ($P < 0.01$). The urodynamic of the rats in the blank group was normal, obvious abnormal contraction during the filling period of bladder was found in the rats of the model group, while no abnormal contraction during the filling period was found in the rats of the EA group. After model establishment, in the model group and the EA group, the first urination time was earlier than the blank group ($P < 0.01$), while bladder effective volume and urination pressure were lower than the blank group ($P < 0.01$). After intervention, in the model group, the first urination time was earlier than the blank group ($P < 0.01$), while bladder effective volume and urination pressure were lower than the blank group ($P < 0.05$); in the EA group, the first urination time was later than the model group ($P < 0.05$), while bladder effective volume and urination pressure were higher than the model group ($P < 0.05$). Compared with the blank group, the protein expressions of TRPV1 and P2X3 receptors in bladder were up-regulated in the model group ($P < 0.01$); compared with the model group, the protein expressions of TRPV1 and P2X3 receptors in bladder were down-regulated in the EA group ($P < 0.05$). It was concluded that EA can relieve bladder

pain and improve urodynamic in IC rats. The mechanism may be related to the down-regulation on the expressions of TRPV1 and P2X3 receptors and the further inhibition on the abnormal input of bladder signal.

USE OF LOW-INTENSITY EXTRACORPOREAL SHOCK WAVE THERAPY IN THE MANAGEMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS: A THIRTY CASE STUDY IN A TERTIARY MEDICAL CENTER

Lan-Sin Jhang, Wu-Chiao Hsieh, Ting-Xuan Huang, Yi-Chun Chou, Tsia-Shu Lo, Ching-Chung Liang, Yi-Hao Lin. Neurourol Urodyn. 2023 Jan;42(1):65-72. doi: 10.1002/nau.25027. Epub 2022 Sep 30. PMID: 36177673

Low-energy extracorporeal shock wave therapy (LiESWT) is a new potential treatment for intractable interstitial cystitis/bladder pain syndrome (IC/BPS), and this paper from Taiwan evaluates its therapeutic effects on IC/BPS. This prospective clinical trial enrolled 30 women who have been diagnosed with IC/PBS to receive LiESWT treatment at an intensity of 0.25 mJ/mm² and a frequency of 3 pulses/second, for a total of 3000 pulses within 8 weeks. The authors assessed questionnaires (including O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI)), 3-day voiding diary, and urodynamic study at the following intervals: 4 weeks of LiESWT (W4), 8 weeks of LiESWT (W8), 1-month follow-up (F1), 3-month follow-up (F3) after LiESWT, and 1 year follow-up (F12). The primary outcome of questionnaires showed significant improvement of symptoms compared to baseline (W0), especially on ICSI (12.87 ± 3.44 before treatment and 7.87 ± 5.27 at F12, *p* < 0.05). 3-day voiding diary also revealed significant decrease in daytime voiding frequency (15.57 ± 5.22 times before treatment and 10.70 ± 4.21 times at F1, *p* < 0.05) and significant increase on average voiding volume (95.85 ± 35.30 mL before treatment and 161.27 ± 74.21 mL at F1, *p* < 0.05). However, there were no significant differences in all parameters of the urodynamic study. It was concluded that LiESWT can mitigate pain and lower urinary tract symptoms and improve the quality of life in IC/PBS patients, but does not increase the maximal cystometric capacity.

CURRENT ROLE OF NEUROMODULATION IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Bárbara Padilla-Fernández, David Hernández-Hernández, David M Castro-Díaz.

Ther Adv Urol. 2022 Nov 21;14:17562872221135941. doi: 10.1177/17562872221135941. eCollection 2022 Jan-Dec. PMID: 36438605.

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Neuromodulation is recommended by major international guidelines as a fourth-line treatment in bladder pain syndrome/interstitial cystitis (BPS/IC) patients after failure of behavioural, oral and intravesical pharmacological treatments, including hydrodistension. A non-systematic review of studies identified by electronic search of MEDLINE was performed in Spain with no time limitation. A narrative synthesis of the existing evidence regarding the results of sacral, tibial and pudendal nerve stimulation in the management of BPS/IC was developed. Neuromodulation in pelvic chronic pain disorders, including BPS/IC, is a useful tool for refractory patients to conventional treatments. Sacral neuromodulation may be effective in patients with BPS without Hunner's lesions, and the effect seems to be maintained in the mid- and long-term. Posterior tibial nerve stimulation can be offered to patients with BPS/IC in the context of a multidisciplinary approach. When pudendal neuralgia is suspected, selective pudendal nerve stimulation has a high response rate. The aetiology of the pain can influence the outcomes in the mid- and long-term of the different neuromodulation approaches, thus careful diagnosis is recommended.

SACRAL NEUROMODULATION TREATMENT FOR URINARY VOIDING DYSFUNCTIONS: RESULTS OF TREATMENT WITH THE LARGEST SINGLE-CENTER SERIES IN A TERTIARY REFERRAL CENTER IN TURKEY

Mehmet Umut Kütükoğlu, Türker Altuntaş, Bahadır Şahin, Ahmet Rahmi Onur Turk J Med Sci. 2022 Mar 19. doi: 10.55730/sag-2107-132. Online ahead of print. PMID: 36453628

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

[TRANSVAGINAL PHOTOBIO-MODULATION IMPROVES PAIN IN WOMEN WITH PELVIC MUSCLE TENDERNESS AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PRELIMINARY OBSERVATIONAL STUDY](#)

Charles W Butrick, Georgine Lamvu. *Urology*. 2022 Dec;170:14-20. doi: 10.1016/j.urology.2022.08.036. Epub 2022 Sep 15. PMID: 36116559.

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Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS) is characterized by pelvic/bladder pain, associated with pelvic muscle tenderness, urgency, frequency, and dysuria. Prior studies show that transvaginal photobiomodulation (TV-PBM) reduces pain in women with chronic pelvic pain (CPP). The objective of this study from the USA was to obtain preliminary data on treatment effect and adherence, in women with IC/BPS who selected TV-PBM therapy for management of pelvic pain. In this before-and-after observational cohort study of women with IC/BPS who received TV-PBM in 17 US practices, pain was measured using a 0-10 numeric rating scale (NRS). The primary outcome was a minimal clinical important difference (MCID); reduction of overall pelvic pain severity by ≥ 2 NRS points from baseline compared to after 8 treatments. Cohen d coefficient measured effect size (low effect size $d < 0.2$, medium $0.2 < d < 0.8$, and high $d > 0.8$). Of 140 patients with IC/BPS who self-selected to start TV-PBM therapy, 89.3% ($n=125$) completed 4 treatments and 59.3% ($n=83$) completed 8. Improvement ≥ 1 NRS point was reported by 73.5% ($n=61$) and meaningful improvement (≥ 2 points) was reported by 63.9% ($n=53$) after 8 treatments. In this group, patients with severe / moderate pain decreased from 83.1% ($n=44$) to 38.5% ($n=20$); $p < 0.001$. Pain levels decreased as follows: overall pelvic pain MCID=-2.7, $d=1.07$, pain with urination MCID=-2.6, $d=1.0$; pain with exercise MCID=-2.6, $d=0.91$, pain with intercourse MCID=-2.5, $d=0.82$. In conclusion, in real-world clinical settings, 2/3 women with IC/BPS who opted to undergo TV-PBM therapy reported significant decrease in pelvic pain and dysuria. While these findings are promising, controlled studies are needed.

[EFFECTIVENESS OF INTRAVESICAL OZONE IN INTERSTITIAL CYSTITIS BY THE O'LEARY-SANT SYMPTOM INDEX](#)

Maria Verônica Pires, Carlos José de Lima, Henrique Cunha Carvalho, Lívia Helena Moreira, Adriana Barrinha Fernandes. *Int Urogynecol J*. 2022 Oct 15;1-10. doi: 10.1007/s00192-022-05383-3. Online ahead of print. PMID: 36242631.

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Introduction and hypothesis: A prospective clinical, preliminary study was performed in patients with interstitial cystitis/bladder pain syndrome (IC/BPS) who were non-responders to conventional treatment and received intravesical ozone as a therapeutic alternative. Sixteen patients received six applications of intravesical ozone at a concentration of 41 µg/mL. The authors evaluated therapeutic efficacy by the percentage reduction of Interstitial Cystitis Symptom and Problem Index scores (ICSI/ICPI-the O'Leary-Sant symptom index), recurrence rate, nonresponse, and side effects in scores collected on admission (pre-treatment), at the end of the therapeutic protocol (post-treatment), and 180 days (follow-up) after the last ozone application. The mean age of women was 52.9 years (SD: 15.5), and the duration of symptoms was 5.7 years (SD: 7.1). The median ICSI on admission was 17 (IQR: 14.25-19.5) and at follow-up was 0.5 (IQR: 0-2), with a reduction of 97.5% (CI: 85.7-100). The median ICSI/ICPI on admission was 31.5 (IQR: 29-35.2) and at follow-up was 2.0 (IQR: 0-3.75), with a reduction of 92.3% (CI: 88.8-100). The recurrence rate was only 6.25%, and no patients were non-responders to the treatment. The application of intravesical ozone was effective in the treatment of patients with IC/BPS who were non-responders to conventional therapy, showing a progressive and safe effect, at least in the short term.

[IS ERBIUM/NEODYMIUM LASER COMBINATION THERAPY AN EFFECTIVE TREATMENT OPTION FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH VULVODYNIA?](#)

Nobuo Okui, Machiko Okui, Marco Gambacciani. Cureus. 2022 Nov 8;14(11):e31228. doi: 10.7759/cureus.31228. eCollection 2022 Nov. PMID: 36505169.

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is often associated with vulvodynia and poor vaginal health. IC/BPS causes pelvic and bladder pain and urinary symptoms, which considerably reduce the quality of life. To date, this condition has no definitive cure. Local estrogen therapy (LET) has been proposed as a treatment for vulvodynia and poor vaginal health to improve the symptoms of IC/BPS. However, chronic LET could be contraindicated or not desired in some patients. The present study from Japan and Italy reports the case of a 55-year-old postmenopausal woman with IC/BPS who was successfully treated with combined vaginal erbium (VEL)/neodymium (Nd:YAG) laser (VEL+Nd:YAG) therapy. The patient presented with a five-year history of pelvic pain and urinary frequency. Direct approaches for the bladder (such as hydrodistension, anticholinergic drugs, and transurethral Hunner lesion ablation/cauterization) were conducted with inconsistent results. Immediately prior to the patient's presentation, LET was administered for 12 weeks; however, this therapy resulted in mild improvement and poor patient satisfaction. After presentation, VEL+Nd:YAG therapy was conducted once a month for three months. The patient reported considerable decrease in pain during urination. The improved symptoms were maintained for six months after the last therapy session. These results suggest that VEL+Nd:YAG therapy is an effective method for improving symptoms in patients with IC/BPS.

[CHRONIC SPONTANEOUS URTICARIA IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: INSIGHTS FROM BIG DATA ANALYSES](#)

Omer Anis, Khalaf Kridin, Arnon Dov Cohen, Miriam Levmore, Shlomit Yaron, Yuliya Valdman-Grinshpoun, Tali Czarnowicki. Urology. 2023 Jan;171:83-87. doi: 10.1016/j.urology.2022.10.017. Epub 2022 Nov 5. PMID: 36343865.

The purpose of this study from Israel was to examine the association between chronic spontaneous urticaria (CSU) and interstitial cystitis/bladder pain syndrome (IC/BPS). A population-based retrospective cross-sectional study was performed using the Clalit Health Services medical database. The prevalence of CSU was compared between patients diagnosed with IC/BPS and age- and gender-matched controls. Univariate analysis was performed using Chi-square and Student t test and a multivariable analysis was performed using a logistic regression model. The study included 681 patients with IC/BPS and 3376 demographically matched controls. The mean age of IC/BPS patients

was 60 years old. The prevalence of CSU among patients with IC/BPS was higher as compared to the control group (20% vs 13.7%; $P < .001$). The adjusted OR for CSU in patients with IC/BPS was 1.58 (95% CI 1.28-1.97). Female gender and Jewish ethnicity were associated with the coexistence of these disorders (OR 1.7 95% CI 1.36-2.13, and 1.6 95% CI 1.28-2, respectively). A significant association was found between IC/BPS and CSU. This finding may support the presence of allergic/immune components in the pathogenesis of IC/BPS.

PELVIC FLOOR MYOFASCIAL PAIN MIGHT INFLUENCE TREATMENT OUTCOME OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PROSPECTIVE STUDY

Wan-Ru Yu, Fei-Chi Chuang, Wei-Chuan Chang, Hann-Chorng Kuo. *Pain Physician*. 2022 Nov;25(8):E1315-E1322. PMID: 36375205

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In patients with interstitial cystitis or bladder pain syndrome (IC/BPS), 85% were found to have pelvic floor myofascial pain (PFMP) and hypertonicity (PFH). However, they physicians are not typically trained to consider or assess PFMP as a contributing factor to patients' IC/BPS symptoms. This prospective study from Hualien, Taiwan aimed to explore the relationship between PFMP and treatment outcomes in women with IC/BPS. Patients with IC/BPS who received any type of treatment were prospectively enrolled. They underwent vaginal digital examination at baseline. PFMP severity was quantified on the visual analog scale (VAS). Subject assessment items included O'Leary-Sant symptom score (OSS), Global Response Assessment (GRA), and Beck's anxiety inventory. Object assessment items included bladder computed tomography (CT), urodynamic parameters, maximum bladder capacity, and grade of glomerulation. A total of 65 women with IC/BPS (mean age, 57.1 ± 11.3 years) were enrolled in the study. Patients with more severe PFMP had significantly higher rate of dyspareunia ($P = 0.031$); more comorbidities ($P = 0.010$); higher number of PFMP sites ($P < 0.001$); and higher OSS ($P = 0.012$). PFMP severity was not significantly correlated with bladder conditions, whether subjective or objective. Moreover, PFMP severity (VAS) was significantly negatively associated with the GRA score. Limitations included the fact that there was a small sample size and short follow-up duration, the patients in this study are all women, and the applicability to other populations is uncertain. It was concluded that PFMP might affect the subjective results of IC/BPS treatment but not the bladder condition. Therefore, in the future treatment of patients with IC/BPS, digital vaginal examinations of pelvic floor muscles should be performed and focused more on the PFM-related conditions, and necessary PFM treatments, such as the vaginal pelvic floor muscle message, should be scheduled.

CHOREITO, A KAMPO MEDICINE ATTENUATES DETRUSOR OVERACTIVITY AND BLADDER PAIN SYMPTOMS IN RAT TRANILAST-INDUCED INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME-LIKE MODEL

Yohei Tokita, Kimio Sugaya, Saori Nishijima, Naoko Tsuchiya, Marie Hamaguchi, Hideyuki Yamamoto. *Neurourol Urodyn*. 2023 Jan;42(1):56-64. doi: 10.1002/nau.25095. Epub 2022 Nov 15. PMID: 36378833.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic inflammatory condition of the bladder. However, there are only a few medicines that are of pharmaceutical grade and reliably effective for IC/BPS symptoms. Choreito (CRT) is a pharmaceutical-grade Kampo medicine and has been widely prescribed for patients of lower urinary tract symptoms (LUTS) and BPS in Japan. In this study from Japan, the authors investigated the effects of CRT on the IC/BPS-like symptoms induced by tranilast. The rat IC/BPS-like model was induced by feeding administration with 0.4% tranilast. The rats were divided into the three following treatment groups: normal diet (Normal), tranilast treatment (Control), and the groups of 1% CRT (CRT) treatment for IC/BPS-like model. After 4 weeks, continuous cystometry, locomotor, and vascular permeability was assessed. Furthermore, the cytokine levels in bladder were analyzed by the Bio-Plex suspension array system and plasma monoamine were measured. Control group exhibited 14.3% decrease of locomotor activity in the

dark period, and which were 20.3% increase by 1%CRT treatment. The voiding interval was shorter in control than in other groups. 1%CRT suppressed the shortening of voiding interval. Evans blue leakage of bladder wall observed 44.8% higher in control group than in the normal group. The leakage of 1%CRT group was 33.3% less than in the control group. The cytokine level of IFN γ and VEGF were elevated in the control, and CRT treatment suppressed the elevation of IFN γ in the bladder. Plasma noradrenaline was significantly reduced by CRT treatment compared normal group. These results suggest that CRT can be an effective therapeutic agent for the treatment of IC/BPS-like symptoms.

UROPROTECTIVE AND HEPATOPROTECTIVE POTENTIAL OF ANAGALLIS ARVENSIS AGAINST THE EXPERIMENTAL ANIMAL MODEL

Ushna Shabbir, Irfan Anjum, Muhammad Naveed Mushtaq, Muhammad Nasir Hayat Malik, Sana Ismail, Joham Javed, Saeeda Noreen, Ayesha Pervaiz, Anika Tariq, Misbah Wazir, Zeenat Islam, Muhammad Majid, Sehrish Mansha, Zaka Ur Rehman. J Trop Med. 2022 Sep 26;2022:7241121. doi: 10.1155/2022/7241121. eCollection 2022. PMID: 36199432

Anagallis arvensis (*A. arvensis*) belonging to the family Primulaceae is traditionally used for liver and kidney diseases. The aim of this study from Pakistan was to evaluate the uroprotective and hepatoprotective potentials of *A. arvensis* in cyclophosphamide-induced interstitial cystitis and paracetamol-induced hepatotoxicity rat model, respectively. Nociception, bladder weight, vesical vascular permeability, Gray's criteria for edema and hemorrhage, and levels of nitric oxide, catalase, and glutathione were estimated and studied in the cystitis model. Liver function test, lipid profile, and histopathological evaluation were carried out in the hepatoprotective activity. Oral administration of methanol extract of *A. arvensis* significantly reduced bladder weight, vesical vascular permeability, edema, hemorrhage, nitric oxide, IL-6, and TNF- α , while the level of catalase and glutathione peroxide was increased. In hepatoprotective activity, pretreatment with *A. arvensis* significantly decreased the level of liver markers (Bilirubin, ALT, AST, and ALP) and lipid profile (cholesterol, TG, LDL, and VLDL). Histopathological studies confirmed the biochemical findings of both studies. GC-MS analysis presented the presence of antioxidant phytoconstituents. Thus, it was concluded that *A. arvensis* might act as uroprotective and hepatoprotective due to the presence of antioxidant phytochemicals in the rodent model. Isolation and identification of phytochemicals present in the methanol extract of *A. arvensis* and evaluation of their exact mechanism of action become mandatory in future studies.

EFFECT OF INTRAVESICAL TARANTULA CUBENSIS EXTRACT (THERANEKRON) ON INFLAMMATION IN AN INTERSTITIAL CYSTITIS RAT MODEL

Akdağ Abdullah, Yenisey Çiğdem, Epikmen E Tuğrul, Ateş Erhan. Low Urin Tract Symptoms. 2022 Dec 7. doi: 10.1111/luts.12470. Online ahead of print. PMID: 36478083

The purpose of this study from Turkey was to reveal the histopathological and immunological outcomes of intravesical treatment with tarantula cubensis extract (TCE) in a rat model of interstitial cystitis. A total of 30 female Wistar albino rats were divided into three groups: group 1 (control group), group 2 (disease group), and group 3 (treatment group). The rat model of interstitial cystitis was created by biweekly intraperitoneal administration of cyclophosphamide (CYP). In group 3, TCE (a venom extracted from a brown spider known as tarantula cubensis) was administered intravesically after the model had been created. Urothelial degeneration, necrosis, ulcer, bleeding, edema, inflammation and mast cell count, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), myeloperoxidase (MPO), and hydroxyproline parameters were evaluated. Statistical analysis was performed using one-way analysis of variance, chi-square tests, and Kruskal-Wallis tests. All parameters were found to be lower in the rats in group 1 than in the other groups, and IL-6 and MPO values were found to be higher in group 2 ($p < .001$). The mean TNF-alpha value was highest in group 2 ($p = .078$). No difference was found between all groups regarding ulcer ($p = .087$). Urothelial degeneration, necrosis, edema, inflammation, hemorrhage and fibroblast proliferations, and

hydroxyproline values were higher in group 3 ($p < .001$). Intravesical TCE instillation produces an anti-inflammatory effect by reducing the levels of inflammatory parameters such as IL-6, TNF-alpha, and MPO in bladder tissue. It also accelerates tissue healing by increasing hydroxyproline and fibroblast proliferation.

BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS RESPONSE TO NERVE BLOCKS AND TRIGGER POINT INJECTIONS

Soha Patil, Gabrielle Daniel, Yogita Tailor, Marjorie Mamsaang, Janaki Natarajan, Erika Moody, Neha James, Rakhi Vyas, Allyson Shrikhande. BJUI Compass. 2022 Jun 18;3(6):450-457. doi: 10.1002/bco2.176. eCollection 2022 Nov. PMID: 36267200

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Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a debilitating condition characterised by bladder/pelvic pain and pressure as well as persistent or recurrent urinary symptoms in the absence of an identifiable cause. It is hypothesised that in addition to organ specific visceral hypersensitivity, contributions of the hypertonic pelvic floor, peripheral sensitisation, and central sensitisation exacerbate this condition. The aim of this paper from the USA is to investigate outcomes of treating underlying neuromuscular dysfunction and neuro-plastic mechanisms in BPS/IC patients. A retrospective chart review of 84 patients referred to an outpatient pelvic rehabilitation centre with a diagnosis of BPS/IC given to them by a urologist. All 84 patients failed to progress after completing 6 weeks of pelvic floor physical therapy and underwent an institutional review board approved protocol (IRB# 17-0761) consisting of external ultrasound-guided trigger point injections to the pelvic floor musculature, peripheral nerve blocks of the pudendal and posterior femoral cutaneous nerves and continued pelvic floor physical therapy once weekly for 6 weeks. Pelvic pain intensity and functionality were measured pretreatment and 3 months posttreatment using Visual Analogue Scale (VAS) and Functional Pelvic Pain Scale (FPPS). Pretreatment, mean VAS was 6.23 ± 2.68 (95% CI 5.65 to 6.80). Posttreatment mean VAS was 3.90 ± 2.63 (95% CI 3.07-4.74). Mean FPPS before treatment was 11.98 ± 6.28 (95% CI 10.63 to 13.32). Posttreatment mean FPPS was 7.68 ± 5.73 (95% CI 6.45-8.90). Analysis of subcategories within FPPS indicated highest statistically significant improvement in the categories of bladder, intercourse and working. Analysis suggests the treatment was effective at ameliorating bladder pain and function including urinary urgency, frequency, and burning in BPS/IC patients.

MULTIMODAL TREATMENT WITH COGNITIVE BEHAVIORAL THERAPEUTIC INTERVENTION PLUS BLADDER TREATMENT IS MORE EFFECTIVE THAN MONOTHERAPY FOR PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME-A RANDOMIZED CLINICAL TRIAL

Wan-Ru Yu, Jia-Fong Jhang, Bai-Yueh Chen, Syuan-Ru Ou, Hao-Ming Li, Hann-Chorng Kuo. J Clin Med. 2022 Oct 21;11(20):6221. doi: 10.3390/jcm11206221. PMID: 36294541.

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Interstitial cystitis/bladder pain syndrome (IC/BPS) not only induces physiological damage but also greatly affects psychological stress. Multidisciplinary therapy has been recommended for IC/BPS treatment, but clinical trial data of combined bladder therapy and cognitive behavioral therapy (CBT) are lacking. This study from Taiwan evaluated CBT efficacy in patients with IC/BPS. Patients with IC/BPS were randomized to the bladder monotherapy (BT) or combined CBT (CBT) group. The primary endpoint was the self-reported outcome by global response assessment (GRA). Secondary endpoints included IC symptoms and problem index, bladder pain score, Beck's anxiety inventory (BAI), and depression inventory, and objective parameters were also compared. A total of 30 patients receiving BT and 30 receiving CBT therapy were enrolled. Significant improvement of the BAI at 8 ($p = 0.045$) and 12 weeks ($p = 0.02$) post-treatment was observed in the CBT group, with significantly greater GRA scores at 12 weeks ($p \leq 0.001$). Repeated measures analysis of variance showed a significant effect within the CBT group on IC/BPS patients' self-reported treatment outcomes ($p = 0.001$) and anxiety severity BAI scores ($p = 0.033$). A multimodal treatment of CBT

combined with suitable bladder treatment more effectively improves anxiety severity and treatment outcomes in patients with IC/BPS.

[COMPENSATORY COPING AND DEPRESSION IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME](#)

Susanna Sutherland, Anna Grace Kelly, Anna Ryden, Roger R Dmochowski, William S Reynolds, Lindsey C McKernan. NeuroUrol Urodyn. 2023 Jan;42(1):322-329. doi: 10.1002/nau.25089. Epub 2022 Nov 15. PMID: 36378850.

Women with genitourinary pain, a hallmark symptom of interstitial cystitis/bladder pain syndrome (IC/BPS), are at a two- to four-fold risk for depression as compared to women without genitourinary pain. Despite the pervasive impact of IC/BPS on psychological health, there is a paucity of empirical research on understanding the relation between IC/BPS and psychological distress. It has been previously reported that women with overactive bladder use increased compensatory coping and these behaviors are associated with heightened anxiety and stress. However, it is unknown whether a similar pattern emerges in IC/BPS populations, as IC/BPS and OAB share many similar urinary symptoms. The current study from the USA examined the relationship between compensatory coping behaviors and symptoms of psychological distress in a sample of women with IC/BPS to inform understanding of risk and potential mechanisms for intervention. This was a secondary analysis of an observational cohort of women with bladder symptoms. Fifty-five adult women with IC/BPS completed validated assessments of genitourinary symptoms, emotional distress, and bladder coping behaviors. Five compensatory coping behaviors were summed to create a total Bladder Coping Score. Linear regression examined associations between individual coping behaviors, total compensatory coping scores, and other risk variables. Most (93%) participants reported use of at least one compensatory coping behavior. Age, education level, history of vaginal birth, and symptom severity were all associated with greater compensatory coping scores, and anxiety was not. Beyond the influence of symptom severity, higher levels of depression were significantly associated with higher compensatory coping scores. Greater compensatory coping was associated with increased depression but not anxiety, suggesting different profiles of coping and psychological distress may exist among different types of bladder dysfunction.

[DEVELOPMENT OF THE INTERSTITIAL CYSTITIS SELF-HELP AND MEDICAL RESOURCES SCALE \(ICSR\) FOR WOMEN WITH INTERSTITIAL CYSTITIS](#)

Hui-Chun Chen, Lee-Ing Tsao, Chun-Hou Liao, Chieh-Yu Liu. Medicina (Kaunas). 2022 Aug 30;58(9):1183. doi: 10.3390/medicina58091183. PMID: 36143860

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Women with interstitial cystitis (IC) suffer from spontaneous serious bladder pain symptoms without immediate resolution. Women with IC may lack knowledge of how to help themselves. Therefore, a measurement of IC self-help and medical-resource-seeking for women with IC is needed. This study from Taiwan recruited 100 women with IC from a teaching hospital in Northern Taiwan. The reliability and validity of the Interstitial Cystitis Self-Help and Medical Resources Scale (ICSR) were assessed using expert validity, confirmatory factor analysis (CFA) to test the construct validity, composite reliability to evaluate the internal consistency, and item analysis to test the discrimination validity of each item. The results showed that the ICSR had accurate goodness-of-fit indices and the component reliability ranged from 0.42 to 0.83, indicating good reliability and validity. The authors concluded that the ICSR is recommended for screening the self-help and medical-resource-seeking abilities of women with IC to aid in diagnosing IC and providing more precise medical treatments.

[DEVELOPMENT OF A PATIENT-CENTERED TEXT MESSAGE-BASED PLATFORM FOR THE SELF-MANAGEMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME SYMPTOMS](#)

Edward K Kim, Lily A Brown, Emily K Seltzer, Denise Hartzell-Leggin, Yelizaveta L Borodyanskaya, Uduak U Andy, Roy M Rosin, Kristene E Whitmore, Diane K Newman, Lily A Arya. Neurourol Urodyn. 2022 Dec 15. doi: 10.1002/nau.25115. Online ahead of print. PMID: 36519701.

The purpose of this study from the USA was to develop a patient-centered text message-based platform that promotes self-management of symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). Adult women with IC/BPS interested in initiating a first- or second-line treatments per American Urological Association guidelines (recategorized as "behavioral/non-pharmacologic treatments" and "oral medicines" in the 2022 version) participated in rapid cycle innovation consisting of iterative cycles of contextual inquiry, prototype design and development. The authors delivered treatment modules and supportive messages using an algorithm-driven interactive messaging prototype through a HIPAA-compliant texting platform. Patients provided feedback through narrative text messages and an exit interview. Feedback was analyzed qualitatively and used to iteratively revise the platform until engagement $\geq 85\%$ and accuracy $\geq 80\%$ were achieved. The final version consisted of four treatment module categories (patient education and behavioral modification, cognitive behavioral therapy, pelvic floor physical therapy, and guided mindfulness practices) and supportive messages delivered through an automated algorithm over 6 weeks. Thirty IC/BPS patients with moderate symptom bother (median IC Problem Index score 9, range 6-12) participated in five cycles of contextual inquiry. Qualitative analysis identified three overarching concepts that informed the development of the platform: preference for patient centered terms, desire to gain self-efficacy in managing symptoms, and need for provider support. Patients preferred the term "interstitial cystitis" to "bladder pain syndrome" which carried the stigma of chronic pain. Patients reported greater self-efficacy in managing symptoms through improved access to mind-body and behavioral treatment modules that helped them to gain insight into their motivations and behaviors. The concept of provider support was informed by shared decision making (patients could choose preferred treatment modules) and reduced sense of isolation (weekly check in messages to check on symptom bother). A patient centered text message-based platform may be clinically useful in the self-management of IC/BPS symptoms.

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

Jeffrey C Loh-Doyle, Alisa J Stephens-Shields, Renee Rolston, Craig Newcomb, Bayley Taple, Siobhan Sutcliffe, Claire C Yang, Henry Lai, Larissa V Rodriguez. 2022 Dec;19(12):1804-1812. doi: 10.1016/j.jsxm.2022.08.196. Epub 2022 Sep 28. PMID: 36180370.

Sexual dysfunction (SD), including erectile (ED) and ejaculatory dysfunction, is associated with diminished quality of life (QoL) in men with UCPPS (chronic prostatitis/chronic pelvic pain syndrome (CP/ CPPS) and/or interstitial cystitis/bladder pain syndrome (IC/BPS)). The authors in this MAPP study sought to compare SD among male patients with UCPPS, other chronic pain conditions (positive controls, PC), and healthy controls (HC) without chronic pain, and to evaluate the association of comorbidities, psychosocial factors, and urologic factors of SD in all 3 groups. Baseline data from male UCPPS participants, PC (irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia) and HC enrolled in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Epidemiology and Phenotyping Study were included in the analysis. Sexual function was assessed using the International Index of Erectile Function-Erectile Function Domain (IIEFEF) and Ejaculatory Function Scale (EFS). Male ED was defined as a composite IIEF-EF score < 21 . Higher EFS score indicated worse sexual dysfunction; no threshold to define SD was identified for the EFS. Multivariable logistic and linear regression was used to investigate associations of comorbidities, psychosocial factors, and urologic factors with ED and ejaculatory, respectively. Comorbidities, genital pain, and psychosocial factors are associated with SD across the study population and male patients with UCPPS had a high prevalence of ED and greater ejaculatory

dysfunction. There were 191 males with UCPPS; 44 PC; and 182 HC. Males with UCPPS had worse SD compared to PC and HC including lower mean IIEF-EF scores, greater degree of ejaculatory dysfunction, and lower quality of sexual relationships. Among all 3 cohorts, depression, stress, and pain were associated with ED in univariable and multivariable analysis, as was diabetes mellitus. Pain in the genitalia, severity of urinary symptoms, depression, stress, and history of childhood sexual trauma were associated with ejaculatory dysfunction in univariable and multivariable analysis. Therefore, a multidisciplinary approach that addresses the identified risk factors for SD may improve overall QoL in males with UCPPS. This study is strengthened by its use of validated, patient-reported questionnaires and inclusion of healthy and positive controls. Understanding of the role of IC in this study is limited because only 1 patient in the study had IC/BPS as a sole diagnosis. When compared to healthy controls and patients with other chronic pain conditions, males with UCPPS experience higher degrees of SD, including erectile and ejaculatory dysfunction.

ASSOCIATIONS BETWEEN UROLOGIC CHRONIC PELVIC PAIN SYNDROME SYMPTOM FLARES, ILLNESS IMPACT, AND HEALTH CARE SEEKING ACTIVITY: FINDINGS FROM THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN SYMPTOM PATTERNS STUDY

Siobhan Sutcliffe, Craig Newcomb, Catherine S Bradley, J Quentin Clemens, Bradley Erickson, Priyanka Gupta, H Henry Lai, Bruce Naliboff, Eric Strachan, Alisa Stephens-Shields. J Urol. 2023 Jan 11;101097JU0000000000003155. doi: 10.1097/JU.0000000000003155. Online ahead of print. PMID: 36630590.

Most studies on interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome use typical or average levels of pelvic pain or urologic symptom intensity as their outcome, as both are associated with reduced quality of life (QOL). Symptom exacerbations or "flares" have also been found to be associated with reduced QOL, but no studies, as far as the authors are aware, have investigated whether these associations are independent of typical pelvic pain levels and thus might be useful additional outcome measures (or stated differently, whether reducing flare frequency even without reducing mean pain intensity may be important to patients). The authors used screening visit and weekly run-in period data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Symptom Patterns Study to investigate associations between flare frequency and multiple measures of illness impact and health care seeking activity, independent of typical non-flare and overall pelvic pain levels. Among the 613 eligible participants, greater flare frequency was associated with worse condition-specific illness impact (standardized β coefficients=0.11-0.68, p-trends <0.0001) and health care seeking activity (odds ratios=1.52-3.94, p-trends=0.0039-<0.0001) in analyses adjusted for typical non-flare and overall pelvic pain levels. Experiencing ≥ 1 /day was also independently associated with worse general illness impact (standardized β coefficients=0.11-0.25). This MAPP team concluded that their findings suggest that flare frequency and possibly other flare characteristics may be worth considering as additional outcome measures in UCPPS research to support the development of new preventive and therapeutic flare strategies.

HUNNER LESION

A SHARED B-CELL CLONOTYPE IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PRESENTING WITH HUNNER LESIONS

Inna Tabansky, Robert M. Moldwin, Min Liu, Souhel Najjar, Derin B. Keskin, Vishaan Nursey, Micheline Laurent, Lori A. Birder, Vladimir Brusic, Guanglan Zhang, Joel N.H. Stern.

Continence Reports, Volume 4, 100015, ISSN 2772-9745,

<https://doi.org/10.1016/j.cont.2022.100015>.

(<https://www.sciencedirect.com/science/article/pii/S2772974522000096>)

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Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is characterized by bladder pain and lower urinary tract symptoms without obvious causes. A subset of patients with IC/BPS present with

Hunner lesions (HL), which are focal regions of gross inflammation on the bladder wall. It has been previously proposed that cell populations within HL are enriched in B- and T-cells, suggesting that this form of IC/BPS may be caused by reaction to a specific antigen within the lesions. Alternatively, B-cell enrichment in the HL might be caused by generalized inflammatory processes. Here, the authors distinguished between these hypotheses by using single-cell sequencing to identify B-cell clonotypes in the HL and the bladder of IC/BPS patients. They identified a clonotype that is shared in two patients with IC/BPS and that represented a significant subpopulation of total immune cells within the lesions. This finding is strong evidence that B-cells in the patients' bladders are reacting to a specific antigen. Further studies of this specific B-cell clonotype can identify the antigen, helping to define the pathophysiology for IC/BPS with HL.

EBV INFECTION MEDIATED BDNF EXPRESSION IS ASSOCIATED WITH BLADDER INFLAMMATION IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH HUNNER'S LESION

Jia-Fong Jhang, Cheng-Der Liu, Yung-Hsiang Hsu, Chien-Chin Chen, Hsiang-Chin Chen, Yuan-Hong Jiang, Wan-Chen Wu, Chih-Wen Peng, Hann-Chorng Kuo. J Pathol. 2022 Nov 28. doi: 10.1002/path.6040. Online ahead of print. PMID: 36441149.

Interstitial cystitis/bladder pain syndrome with Hunner's lesion (HIC) is characterized by chronic inflammation and nerve hyperplasia; however, the pathogenesis of HIC remains a mystery. In this study from Taiwan, the authors detected both Epstein-Barr virus (EBV) latency infection genes EBNA-1 and LMP-1 and EBV lytic infection BZLF-1 and BRLF-1 expression in the HIC bladders, indicating the coexistence of EBV persistence and reactivation in the B cells in HIC bladders. Upregulation of EBV-associated inflammatory genes in HIC bladders, such as TNF- α and IL-6, suggests EBV infection is implicated in the pathogenesis of bladder inflammation. Nerve hyperplasia and upregulation of brain-derived neurotrophic factor (BDNF) were noted in the HIC bladders. Double immunohistochemical staining and flow cytometry revealed the origin of BDNF to be EBV-infected B cells. Inducible BDNF expression was noted in B cells upon EBV infection, but not in the T cells. A chromatin immunoprecipitation study revealed BDNF transcription could be promoted by cooperation between EBV nuclear antigens, chromatin modifiers, and B-cell-specific transcription. Knockdown of BDNF in EBV-infected B cells resulted in the inhibition of cell proliferation and viability. Downregulation of phosphorylated SMAD2 and STAT3 after BDNF knockdown may play a role in the mechanism. Implantation of latent EBV-infected B cells into rat bladder walls resulted in a higher expression level of CD45 and PGP9.5, suggesting tissue inflammation and nerve hyperplasia. In contrast, implantation of BDNF depleted EBV-infected B cells abrogated these effects. This is the first study to provide insights into the mechanisms underlying the involvement of EBV-infected B cells in HIC pathogenesis.

SAFETY OF HUMAN EMBRYONIC STEM CELL-DERIVED MESENCHYMAL STEM CELLS FOR TREATING INTERSTITIAL CYSTITIS: A PHASE I STUDY

Jung Hyun Shin, Chae-Min Ryu, Hwan Yeul Yu, Juhyun Park, Ah Reum Kang, Jeong Min Shin, Ki-Sung Hong, Eun Young Kim, Hyung-Min Chung, Dong-Myung Shin, Myung-Soo Choo. Stem Cells Transl Med. 2022 Oct 21;11(10):1010-1020. doi: 10.1093/stcltm/szac065. PMID: 36069837.

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There are still no definite treatment modalities for interstitial cystitis (IC). Meanwhile, stem cell therapy is rising as potential alternative for various chronic diseases. This study from Korea aimed to investigate the safety of the clinical-grade mesenchymal stem cells (MSCs) derived from human embryonic stem cells (hESCs), code name MR-MC-01 (SNU42-MMSCs), in IC patients. Three female IC patients with (1) symptom duration ≥ 6 months, (2) visual pain analog scale (VAS) ≥ 4 , and (3) one or two Hunner lesions ≥ 2 cm in-office cystoscopy within 1 month were included. Under general anesthesia, participants received cystoscopic submucosal injection of SNU42-MMSCs (2.0 \times 10⁷/5 mL) at the center or margin of Hunner lesions and other parts of the bladder wall except trigone with each injection volume of 1 mL. Follow-up was 1, 3, 6, 9, and 12 months postoperatively.

Patients underwent scheduled follow-ups, and symptoms were evaluated with validated questionnaires at each visit. No SNU42-MMSCs-related adverse events including immune reaction and abnormalities on laboratory tests and image examinations were reported up to 12-month follow-up. VAS pain was temporarily improved in all subjects. No de novo Hunner lesions were observed and one lesion of the first subject was not identifiable on 12-month cystoscopy. This study reports the first clinical application of transurethral hESC-derived MSC injection in three patients with IC. hESC-based therapeutics was safe and proved to have potential therapeutic efficacy in IC patients. Stem cell therapy could be a potential therapeutic option for treating IC.

LETTERS TO EDITOR

[REPLY TO "INTERSTITIAL CYSTITIS - A CONSEQUENCE OF WEAKENED UTEROSACRAL LIGAMENTS FAILING TO SUPPORT VISCERAL PLEXUSES AND BLADDER STRETCH RECEPTORS AND THEREFORE POTENTIALLY CURABLE?"](#)

Tomohiro Ueda. *Int Neurourol J.* 2022 Dec;26(4):352. doi: 10.5213/inj.2142204.102. Epub 2022 Dec 30. PMID: 36599345.

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To the editor,

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a heterogeneous disease consisting of distinct subgroups of patients who have different underlying pathophysiology. Thus, the proposal by Prof. Petros that loose or damaged uterosacral ligaments (USLs) may be an important etiology outside the bladder to induce or worsen the symptoms of IC/BPS due to altered urothelial receptor sensitivity is interesting. However, for the proper diagnosis and treatment of IC/BPS, it is necessary to first identify bladder-centric pathophysiology including Hunner lesions by using cystoscopy and also prove that identified bladder mucosal abnormalities are the causes of bladder pain, for example, as shown by pain reduction following intravesical lidocaine instillation in the recent dimethyl sulfoxide clinical trial in IC/BPS patients [1,2]. Then, in the case that bladdercentric pathophysiology is less likely to be involved in IC/BPS symptoms, outside-bladder etiology such as the lax USL discussed here should be considered as a cause of bladder symptoms in IC/BPS patients. There will be no bright future for IC/ BPS without the following 3 steps: (1) understanding the symptoms, (2) detecting abnormal findings in or outside the bladder, and (3) verifying that the abnormality is the cause of the symptoms.

[INTERSTITIAL CYSTITIS: A CONSEQUENCE OF WEAKENED UTEROSACRAL LIGAMENTS FAILING TO SUPPORT VISCERAL PLEXUSES AND BLADDER STRETCH RECEPTORS, AND THEREFORE POTENTIALLY CURABLE?](#)

Peter Petros. *Int Neurourol J.* 2022 Dec;26(4):349-351. doi: 10.5213/inj.2142366.183. Epub 2022 Dec 30. PMID: 36599344.

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To the editor,

I read the state-of-the-art review of interstitial cystitis/bladder pain syndrome (IC/BPS) by Ueda et al. [1] with great interest. An erudite, scholarly paper, it states there is a crisis as regards IC—namely, there has been no progress for 25 years. The authors concluded [1], “Thus, there can be no bright future for IC/BPS without these 3 steps: (1) understanding the symptoms, (2) detecting abnormal findings in or outside the bladder, and (3) verifying that the abnormality is the cause of the symptoms” [1]. This commentary aims to address their statements, first by introducing an important discovery to International Neurourology Journal readers, Dr. Scheffler’s histologically validated cure of IC/BPS with Hunner ulcer (nonulcerating) [2], and then by discussing its implications relevant to those 3 statements [1].

[See more- click on title](#)

INTRAVESICAL DRUG DELIVERY

[NANO-FORMULATION BASED INTRAVESICAL DRUG DELIVERY SYSTEMS: AN OVERVIEW OF VERSATILE APPROACHES TO IMPROVE URINARY BLADDER DISEASES](#)

Muhammad Sarfraz, Shaista Qamar, Masood Ur Rehman, Muhammad Azam Tahir, Muhammad Ijaz, Anam Ahsan, Mulazim Hussain Asim, Imran Nazir. *Pharmaceutics*. 2022 Sep 8;14(9):1909. doi: 10.3390/pharmaceutics14091909. PMID: 36145657.

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Intravesical drug delivery is a direct drug delivery approach for the treatment of various bladder diseases. The human urinary bladder has distinctive anatomy, making it an effective barrier against any toxic agent seeking entry into the bloodstream. This screening function of the bladder derives from the structure of the urothelium, which acts as a semi-permeable barrier. However, various diseases related to the urinary bladder, such as hyperactive bladder syndrome, interstitial cystitis, cancer, urinary obstructions, or urinary tract infections, can alter the bladder's natural function. Consequently, the intravesical route of drug delivery can effectively treat such diseases as it offers site-specific drug action with minimum side effects. Intravesical drug delivery is the direct instillation of medicinal drugs into the urinary bladder via a urethral catheter. However, there are some limitations to this method of drug delivery, including the risk of washout of the therapeutic agents with frequent urination. Moreover, due to the limited permeability of the urinary bladder walls, the therapeutic agents are diluted before the process of permeation, and consequently, their efficiency is compromised. Therefore, various types of nanomaterial-based delivery systems are being employed in intravesical drug delivery to enhance the drug penetration and retention at the targeted site. This review article from the United Arab Emirates, Pakistan and China covers the various nanomaterials used for intravesical drug delivery and future aspects of these nanomaterials for intravesical drug delivery.

CHRONIC UTI, MICROBIOTA

[THE CLINICAL IMPLICATIONS OF BACTERIAL PATHOGENESIS AND MUCOSAL IMMUNITY IN CHRONIC URINARY TRACT INFECTION](#)

Catherine C Y Chieng, Qingyang Kong, Natasha S Y Liou, Rajvinder Khasriya, Harry Horsley. *Mucosal Immunol*. 2023 Jan 12;S1933-0219(22)01768-8. doi: 10.1016/j.mucimm.2022.12.003. Online ahead of print. PMID: 36642381.

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Urinary tract infections (UTIs) exert a significant health and economic cost globally. Approximately one in four people with a previous history of UTI continue to develop recurrent or chronic infections. Research on UTI has primarily concentrated on pathogen behavior, with the focus gradually shifting to encompass the host immune response. However, these are centered on mouse models of *Escherichia coli* infection, which may not fully recapitulate the infective etiology and immune responses seen in humans. The emerging field of the urobiome also inadvertently confounds the discrimination of true UTI-causing pathogens from commensals. This review from the United Kingdom aims to present a novel perspective on chronic UTI by linking microbiology with immunology, which are commonly divergent in this field of research. It also describes the challenges in understanding chronic UTI pathogenesis and the human bladder immune response, largely conjectured from murine studies. Lastly, it outlines the shortcomings of current diagnostic methods in identifying individuals with chronic UTI and consequently treating them, potentially aggravating their disease due to mismanagement of prior episodes. This discourse highlights the need to consider these knowledge gaps and encourages more relevant studies of UTI in humans.

DETECTION OF BACTERIA IN BLADDER MUCOSA OF ADULT FEMALES

Alan J Wolfe, David J Rademacher, Carine R Mores, Robert J Evans, Tyler Overholt, Thomas Halverson, Roberto Limeira, Catherine Matthews, Gopal Badlani, Linda Brubaker, Stephen J Walker. J Urol. 2023 Jan 19;101097JU00000000000003189. doi: 10.1097/JU.00000000000003189. Online ahead of print. PMID: 36657058.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic urological condition diagnosed in nearly 8 million females in the United States. Whether urinary microbiota play an etiologic role remains controversial. Most studies assessed the microbiota of IC/BPS patients with voided or catheterized urine as a proxy for bladder urothelium; however, urine may not be a true reflection of the bladder microbiota. Bladder biopsy tissue may provide a more accurate, and thus more clinically relevant, picture of bladder microbiota. In this study from the USA, bladder biopsy tissues were obtained from: (a) 30 females with IC/BPS (18-80 y/o) via cystoscopically guided cold-cup biopsy following therapeutic bladder hydrodistension, and (b) 10 non-IC/BPS females undergoing pelvic organ prolapse repair. To detect bacteria, technical duplicates of each RNA later-preserved biopsy were subjected to 16S rRNA gene sequencing. To visualize bacteria, paraformaldehyde-fixed, paraffin-embedded biopsies were subjected to a combined multiplexed fluorescence in situ hybridization (FISH) and fluorescence immunohistochemistry (IHC) assay and confocal microscopy. Bacteria were detected by 16S rRNA gene sequencing in at least one technical duplicate of most biopsies. The most abundant genus was *Staphylococcus* followed by *Lactobacillus*; *Escherichia* was common but not abundant. There was no significant difference between IC/BPS patients and controls ($P > .05$). Combined FISH and IHC reproducibly detected 16S rRNA in epithelial cells and shed cells in the urothelium and lesioned areas and capillary walls in the lamina propria of human bladder biopsy tissue. The authors concluded that urothelial and urinary microbiota are similar but not identical in adult females.

KETAMINE CYSTITIS

KETAMINE-INDUCED CYSTITIS: A COMPREHENSIVE REVIEW OF THE UROLOGIC EFFECTS OF THIS PSYCHOACTIVE DRUG

Danyon J Anderson, Jessica Zhou, David Cao, Matthew McDonald, Maya Guenther, Jamal Hasoon, Omar Viswanath, Alan D Kaye, Ivan Urits. Health Psychol Res. 2022 Sep 15;10(3):38247. doi: 10.52965/001c.38247. eCollection 2022. PMID: 36118982.

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Ketamine is a common medical anesthetic and analgesic but is becoming more widely used as a recreational drug. Significant side effects on the urinary tract are associated with frequent recreational ketamine use most notably ketamine-induced cystitis (KIC). Regular ketamine consumption has been shown to increase the risk of cystitis symptoms by 3- to 4-fold, and cessation of ketamine use is usually associated with improvement of symptoms. Common KIC-related problems are urinary pain and discomfort, bladder epithelial barrier damage, reduced bladder storage and increased pressure, ureter stenosis, and kidney failure, all of which significantly impact patients' quality of life. Furthermore, it becomes a vicious cycle when KIC patients attempt to manage their urinary pain with increased ketamine use. The precise pathophysiology of KIC is still unknown but several theories exist, most of which highlight the inflammatory signaling pathways leading to bladder epithelium damage due to presence of ketamine in the urine. Empirical treatment options for KIC are available and consist of ketamine cessation, noninvasive therapies, and surgery, and should be decided upon based on the time course and severity of the disease. Of note, cessation of use is strongly recommended for all KIC patients, and should be supplemented with motivational interviews and psychological and social support. It is crucial for clinicians to be familiar with KIC diagnosis and treatment, and to be prepared to have informed discussions with ketamine-using patients about the potential health consequences of ketamine.

SYSTEMATIC REVIEW AND META-ANALYSIS OF KETAMINE-ASSOCIATED UROPATHY

E O T Chan, V W S Chan, T S T Tang, V Cheung, M C S Wong, C H Yee, C F Ng, J Y C Teoh. Hong Kong Med J. 2022 Dec;28(6):466-474. doi: 10.12809/hkmj209194. Epub 2022 Dec 5. PMID: 36464318

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This systematic review and meta-analysis from Hong Kong and the United Kingdom focused on the literature regarding ketamine-associated uropathy to summarise its clinical manifestations, the results of urological assessments, and current management. A literature search was conducted using keywords and MeSH terms related to ketamine abuse, urinary tracts, and urological examinations. Databases including Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials were searched up to 26 June 2020. In total, 1365 articles were retrieved; 45 articles (4921 patients) were included in the analysis of patient demographics, clinical manifestations, examination results, and treatments. Frequency was the most common manifestation (pooled prevalence 77.1%, 95% confidence interval [CI]=56.9%-92.2%), followed by urgency (69.9%, 95% CI=48.8%-87.3%) and suprapubic pain (60.4%, 95% CI=35.3%-82.9%). Upper urinary tract involvement was less common; the pooled prevalence of hydronephrosis was 30.2% (95% CI=22.0%-39.2%). Further workup revealed a pooled functional bladder capacity of 95.23 mL (95% CI=63.57-126.88 mL), pooled voided volume of 113.31 mL (95% CI=59.44- 167.19 mL), and pooled maximum urine flow rate of 8.69 mL/s (95% CI=5.54-11.83 mL/s). Cystoscopic examinations and bladder biopsy revealed frequent urothelial denudation, inflammatory changes, and inflammatory cell infiltration. Treatments included oral medications for symptomatic relief, intravesical therapy, and surgery (eg, hydrodistension and bladder reconstruction), but ketamine abstinence was necessary for improvement. Ketamine-associated uropathy frequently involves frequency, urgency, and suprapubic pain; upper urinary tract involvement is less common. Affected patients showed reductions in bladder capacity and urine flow rate. Endoscopic and histological analyses often revealed cystitis. Despite variations in treatment, ketamine abstinence is important for all patients with ketamine-associated uropathy.

URINARY TRACT ENDOMETRIOSIS

A REVIEW OF URINARY TRACT ENDOMETRIOSIS

Amanda K Sherman, Lara S MacLachlan. Curr Urol Rep. 2022 Oct;23(10):219-223. doi: 10.1007/s11934-022-01107-8. Epub 2022 Sep 1. PMID: 36048338.

The purpose of this study from the USA was to describe the presenting signs and symptoms of patients with urinary tract endometriosis (UTE), appropriate workup, and to review medical and surgical therapies for symptom palliation and definitive management. UTE is a condition that clinicians should maintain a high index of suspicion for, as symptoms can be easily misdiagnosed from other causes. Surgical resection of implants appears to offer safe and durable symptom relief. Urinary tract endometriosis may present with symptoms overlapping with interstitial cystitis, nephrolithiasis, bladder overactivity, or recurrent urinary tract infections, and may or may not be cyclical in nature. Cyclical gross hematuria is considered pathognomonic, though final diagnosis must be made after a pathologic review. Without proper diagnosis and treatment, consequences such as silent renal loss from asymptomatic obstruction may result. After the diagnosis is made, initial therapy can be undertaken with hormonal treatment to palliate symptoms (most commonly in the form of combined oral contraceptives), followed by surgical resection for a definitive treatment option.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

TYPE 3 MACULAR NEOVASCULARIZATION IN A PATIENT WITH PENTOSAN POLYSULFATE MACULOPATHY

Elodie Bousquet, Brian A Lee, Ahmad Santina, Srinivas Satta, David Sarraf. Am J Ophthalmol Case Rep. 2022 Dec 5;29:101771. doi: 10.1016/j.ajoc.2022.101771. eCollection 2023 Mar. PMID: 36561881.

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The purpose of this paper from the USA is to report the development of type 3 macular neovascularization (MNV) in a patient with pentosan polysulfate sodium (PPS) maculopathy one year after PPS cessation. A 72-year-old woman presented for decreased visual acuity in the left eye. Medical history was significant for interstitial cystitis treated with PPS for 11 years (cumulative dose of 1205 g) and PPS maculopathy. PPS was discontinued 1 year prior to presentation. Blue-light fundus autofluorescence and spectral domain optical coherence tomography confirmed the diagnosis of bilateral PPS maculopathy. OCT-angiography illustrated the development of type 3 MNV with intraretinal fluid in the left eye. Intravitreal injections of aflibercept were initiated with a good visual and anatomical response. This report describes the development of type 3 MNV in a patient with PPS macular toxicity one year after PPS cessation. This complication emphasizes the need for regular retinal surveillance even after discontinuation of the inciting drug.

BLADDER AND BOWEL

BLADDER-COLON CHRONIC CROSS-SENSITIZATION INVOLVES NEURO-GLIAL PATHWAYS IN MALE MICE

Karim Atmani, Fabien Wuestenberghs, Maximilien Baron, Illona Bouleté, Charlène Guérin, Wafa Bahlouli, David Vaudry, Jean Claude do Rego, Jean-Nicolas Cornu, Anne-Marie Leroi, Moïse Coëffier, Mathieu Meleine, Guillaume Gourcerol. World J Gastroenterol. 2022 Dec 28;28(48):6935-6949. doi: 10.3748/wjg.v28.i48.6935. PMID: 36632316.

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Irritable bowel syndrome and bladder pain syndrome often overlap and are both characterized by visceral hypersensitivity. Since pelvic organs share common sensory pathways, it is likely that those syndromes involve a cross-sensitization of the bladder and the colon. The precise pathophysiology remains poorly understood. The purpose of this study from France was to develop a model of chronic bladder-colon cross-sensitization and to investigate the mechanisms involved. Chronic cross-organ visceral sensitization was obtained in C57BL/6 mice using ultrasound-guided intravesical injections of acetic acid under brief isoflurane anesthesia. Colorectal sensitivity was assessed in conscious mice by measuring intracolonic pressure during isobaric colorectal distensions. Myeloperoxidase, used as a marker of colorectal inflammation, was measured in the colon, and colorectal permeability was measured using chambers. c-Fos protein expression, used as a marker of neuronal activation, was assessed in the spinal cord (L6-S1 level) using immunohistochemistry. Green fluorescent protein on the fractalkine receptor-positive mice were used to identify and count microglia cells in the L6-S1 dorsal horn of the spinal cord. The expression of NK1 receptors and MAPK-p38 were quantified in the spinal cord using western blot. Visceral hypersensitivity to colorectal distension was observed after the intravesical injection of acetic acid vs saline ($P < 0.0001$). This effect started 1 h post-injection and lasted up to 7 d post-injection. No increased permeability or inflammation was shown in the bladder or colon 7 d post-injection. Visceral hypersensitivity was associated with the increased expression of c-Fos protein in the spinal cord ($P < 0.0001$). In green fluorescent protein on the fractalkine receptor-positive mice, intravesical acetic acid injection resulted in an increased number of microglia cells in the L6-S1 dorsal horn of the spinal cord ($P < 0.0001$). NK1 receptor and MAPK-p38 levels were increased in the spinal cord up to 7 d after injection ($P = 0.007$ and 0.023 respectively). Colorectal sensitization was prevented by intrathecal or intracerebroventricular injections of minocycline, a microglia inhibitor, by intracerebroventricular injection of CP-99994 dihydrochloride, a NK1 antagonist, and by intracerebroventricular injection of SB203580, a MAPK-p38 inhibitor. The authors describe a new model of cross-organ visceral sensitization between the bladder and the colon in mice. Intravesical

injections of acetic acid induced a long-lasting colorectal hypersensitivity to distension, mediated by neuroglial interactions, MAPK-p38 phosphorylation and the NK1 receptor.

NOCTURIA AND SLEEP DISORDERS

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

Thomas F Monaghan, Jeffrey P Weiss, Alan J Wein, Syed N Rahman, Jason M Lazar, Donald L Bliwise, Karel Everaert, Gary E Lemack, Jean-Nicolas Cornu, Marcus J Drake, Christopher R Chapple, Hashim Hashim, Jerry G Blaivas, Roger R Dmochowski. NeuroUrol Urodyn. 2023 Jan 19. doi: 10.1002/nau.25128. Online ahead of print. PMID: 36655726

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

AUTOIMMUNE DISEASES

INFLUENCE OF X CHROMOSOME IN SEX-BIASED AUTOIMMUNE DISEASES

Charles-Henry Miquel, Berenice Faz-Lopez, Jean-Charles Guéry. J Autoimmun. 2023 Jan 12;102992. doi: 10.1016/j.jaut.2023.102992. Online ahead of print. PMID: 36641351

Females have better ability to resolve infections, compared to males, but also, a greater susceptibility to develop autoimmunity. Besides the initial interest on the contribution of sex-steroid hormone signaling, the role of genetic factors linked to X chromosome has recently focused much attention. In human and mouse, the number of X chromosomes, rather than sex-steroid hormones, have been found associated with higher risk or susceptibility to develop autoimmunity, particularly rheumatic diseases, such as SLE, Sjögren's syndrome or Scleroderma. For all of these diseases, the Toll-like receptor TLR7 and TLR8, encoded on the same locus in the human Xp, have been demonstrated to be causal in disease development through gene dosage effect or gain of function mutations. During embryonic development in female mammals, one X chromosome is stochastically inactivated to balance X-linked gene expression between males and females, a process known as X chromosome inactivation (XCI). Nevertheless, some genes including immune related genes can

escape XCI to variable degree and penetrance, resulting in a bi-allelic expression in some immune cells, such as TLR7. Because tight regulation of TLR expression is necessary for a healthy, self-tolerant immune environment, XCI escape has been proposed as a mechanism contributing to this sexual dimorphism. In this review from France, the authors summarize general mechanisms of XCI, and describe the known escapee's genes in immune cells, the cellular diversity created by such mechanisms and its potential implication in autoimmune diseases, with a particular focus on the X-linked genes and immune cell populations involved in SLE. Whether dysregulated expression of X-linked genes could contribute to the enhanced susceptibility of females to develop such diseases remains to be proven. Shedding lights onto the X-linked genetic mechanisms contributing to modulation of immune cell functions will undoubtedly provide new insights into the intricate mechanisms underlying sex differences in immunity and autoimmunity.

VULVODYNIA/VULVAR PAIN

VULVODYNIA: PAIN MANAGEMENT STRATEGIES

Lucia Merlino, Luca Titi, Francesco Pugliese, Giulia D'Ovidio, Roberto Senatori, Carlo Della Rocca, Maria Grazia Piccioni. Pharmaceuticals (Basel). 2022 Dec 5;15(12):1514. doi: 10.3390/ph15121514. PMID: 36558965.

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Vulvodynia is defined in this international consensus as persistent vulvar pain that occurs for >3 months without an identifiable cause and with several potential associated factors. At present there is no univocal consensus in the therapeutic treatment of vulvodynia. The methods of intervention are based on various aspects including, above all, the management of painful symptoms. In this study from Italy, research into scientific databases such as "Pubmed", "Medline Plus", "Medscape" was conducted, using the words "women's genital pain" and "vulvodynia" for the review of the scientific evidence on the assessment and treatment of women's genital pain. Among the drugs with pain-relieving action, the most effective in the treatment of vulvodynia would seem to be those with antidepressant and anticonvulsant action, even if their mechanisms of action are not known and there are still insufficient studies able to demonstrate their real validity. Among the least effective are non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. However, the ideal would seem to use a combined treatment with multiple types of drugs. Future studies are needed to draw up a unique therapeutic action plan that considers the stratification of patients with vulvodynia and the variability of the symptom.

EVALUATION AND TREATMENT OF VULVODYNIA: STATE OF THE SCIENCE

Judith M Schlaeger, Jennifer E Glayzer, Michelle Villegas-Downs, Hongjin Li, Edward J Glayzer, Ying He, Miho Takayama, Hiroyoshi Yajima, Nobuaki Takakura, William H Kobak, Barbara L McFarlin. J Midwifery Womens Health. 2022 Dec 19. doi: 10.1111/jmwh.13456. Online ahead of print. PMID: 36533637.

Vulvodynia affects 7% of American women, yet clinicians often lack awareness of its presentation. It is underdiagnosed and often misdiagnosed as vaginitis. The etiology of vulvodynia remains unknown, making it difficult to identify or develop effective treatment methods. The purpose of this article from the USA is to (1) review the presentation and evaluation of vulvodynia, (2) review the research on vulvodynia treatments, and (3) aid the clinician in the selection of vulvodynia treatment methods. The level of evidence to support vulvodynia treatment varies from case series to randomized controlled trials (RCTs). Oral desipramine with 5% lidocaine cream, intravaginal diazepam tablets with intravaginal transcutaneous electric nerve stimulation (TENS), botulinum toxin type A 50 units, enoxaparin sodium subcutaneous injections, intravaginal TENS (as a single therapy), multimodal physical therapy, overnight 5% lidocaine ointment, and acupuncture had the highest level of evidence with at least one RCT or comparative effectiveness trial. Pre to post-test reduction in vulvar pain and/or dyspareunia in non-RCT studies included studies of gabapentin cream,

amitriptyline cream, amitriptyline with baclofen cream, up to 6 weeks' oral itraconazole therapy, multimodal physical therapy, vaginal dilators, electromyography biofeedback, hypnotherapy, cognitive behavioral therapy, cold knife vestibulectomy, and laser therapy. There is a lack of rigorous RCTs with large sample sizes for the treatment of vulvodynia, rendering it difficult to determine efficacy of most treatment methods. Clinicians will be guided in the selection of best treatments for vulvodynia that have the highest level of evidence and are least invasive.

CHRONIC UROGENITAL PELVIC PAIN, PELVIC DYSFUNCTION

NURSES' ROLE IN THE MANAGEMENT OF PERSONS WITH CHRONIC UROGENITAL PELVIC PAIN SYNDROMES: A SCOPING REVIEW

Stefano Terzoni, Paolo Ferrara, Mauro Parozzi, Federica Colombani, Cristina Mora, Silvia Cilluffo, Jeannette Verkerk-Geelhoed, Anne Destrebecq, Barbara Pinna, Maura Lusignani, Chiara Sighinolfi, Giorgia Gaia, Bernardo Rocco. Neurourol Urodyn. 2023 Jan;42(1):13-22. doi: 10.1002/nau.25053. Epub 2022 Oct 2. PMID: 36183384.

Pelvic pain has cognitive, behavioral, sexual, and emotional consequences. Nurses involved in pelvic floor rehabilitation clinics have contacts with patients reporting chronic pain and should know the most appropriate service for patient referral, to submit the problem to professionals capable of correctly assessing and managing the condition. Furthermore, in some countries nurses can use conservative methods to treat the painful symptoms inside a multidisciplinary team such as breathing retraining, biofeedback, and noninvasive neuromodulation. This paper from Italy and the Netherlands aims to provide an overview of the literature regarding the role of rehabilitation nurses in dealing with patients suffering from chronic urogenital pelvic pain or urogenital painful syndromes, inside a multidisciplinary team. This was a scoping review on Pubmed, CINAHL, Embase, Scopus, Web of Science including trials, reviews, case studies or series, and other descriptive studies regarding the role of nurses inside the multidisciplinary team in the management of males and females presenting chronic pelvic pain (CPP) or chronic pelvic pain syndrome (CPPS). The 36 papers included in this review allowed answering research questions in four areas of nursing: collecting basic information, referring the person to appropriate services, evidence-based nursing interventions for CPP and CPPS, and proper documentation. Clinical history and assessment of breathing pattern, Muscular assessment and research of trigger points are the main points of data collection. Techniques for muscular relaxation and breathing retraining are important aspects of treatment, as well as biofeedback and noninvasive neuromodulation where the law allows nurses to practice such techniques. The McGill pain questionnaire and the pain inventory of the International Pain Society allow systematic data collection and handover. It was concluded that rehabilitation nurses work inside multidisciplinary teams when dealing with persons suffering from pelvic pain. Further research is needed as comprehension of the underlying pathophysiological mechanisms of CPP and CPPS evolve.

COMPREHENSIVE PELVIC MUSCLE ASSESSMENT: DEVELOPING AND TESTING A DUAL E-LEARNING AND SIMULATION-BASED TRAINING PROGRAM

Diane K Newman, Jerry L Lowder, Melanie Meister, Lisa K Low, Colleen M Fitzgerald, Cynthia S Fok, Julia Geynisman-Tan, Emily S Lukacz, Alayne Markland, Sara Putnam, Kyle Rudser, Ariana L Smith, Janis M Miller; Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium. Neurourol Urodyn. 2023 Jan 10. doi: 10.1002/nau.25125. Online ahead of print. PMID: 36626146 .

The Prevention of Lower Urinary Tract Symptoms (PLUS) research consortium launched the RISE FOR HEALTH (RISE) national study of women's bladder health which includes annual surveys and an in-person visit. For the in-person exam, a standardized, replicable approach to conducting a pelvic muscle (PM) assessment was necessary. The process used to develop the training, the products, and group testing results from the education and training are described. A comprehensive pelvic muscle assessment (CPMA) program was informed by literature view and expert opinion. Training materials

were prepared for use on an electronic Learning (e-Learning) platform. An in-person hands-on simulation and certification session was then designed. It included a performance checklist assessment for use by Clinical Trainers, who in collaboration with a gynecology teaching assistant, provided an audit and feedback process to determine Trainee competency. Five discrete components for CPMA training were developed as e-Learning modules. These were: (1) overview of all the clinical measures and PM anatomy and examination assessments, (2) visual assessment for pronounced pelvic organ prolapse, (3) palpatory assessment of the pubovisceral muscle to estimate muscle integrity, (4) digital vaginal assessment to estimate strength, duration, symmetry during PM contraction, and (5) pressure palpation of both myofascial structures and PMs to assess for self-report of pain. Seventeen Trainees completed the full CPMA training, all successfully meeting the a priori certification required pass rate of 85% on checklist assessment. The RISE CPMA training program was successfully conducted to assure standardization of the PM assessment across the PLUS multicenter research sites. This approach can be used by researchers and healthcare professionals who desire a standardized approach to assess competency when performing this CPMA in the clinical or research setting.

FIBROMYALGIA

[IDENTIFICATION OF THE INVOLVEMENT OF POTASSIUM CHANNELS IN FIBROMYALGIA](#)

Kim Lawson. *Front Biosci (Schol Ed)*. 2022 Oct 17;14(4):29. doi: 10.31083/j.fbs1404029. PMID: 36575839.

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Fibromyalgia is a central sensitivity syndrome that presents with chronic pain, fatigue, cognitive dysfunction, and disordered sleep. The pathophysiology which due to multisensory hypersensitivity of the central nervous system involves neuronal excitability leading to central sensitization. Treatments of the challenges associated with the complexities of fibromyalgia involve combinations of pharmacological and non-pharmacological therapeutic approaches which often offer limited benefit. Potassium (K⁺) channels play a fundamental role in establishing and maintaining stability of neuronal activity. The large molecular diversity and distribution of K⁺ channels support involvement in a broad range of physiological functions. In nociceptive pathways, neuronal hyperexcitability leading to pain sensation has been associated with reduced function of K⁺ channels and loss of cellular control. This article from Sheffield, United Kingdom reviews the evidence of involvement of K⁺ channels in fibromyalgia. A potential role both in the pathophysiological processes responsible for the symptoms of fibromyalgia and as therapeutic targets for the management of the condition is considered.

COVID IMPACT

[GENITOURINARY TRACT SYMPTOMS IN PATIENTS ADMITTED WITH COVID-19: EXPLORING CHANGES IN FREQUENCY BY DETERMINANTS AND PANDEMIC WAVES](#)

Vanessa Viegas Madrid, Adrián Peláez Laderas, Joan B. Soriano, Rosa Girón Moreno, Maria Celeste Marcos, Ana Sánchez Ramírez, Julio Ancochea Bermúdez, Carlos Olivier Gómez, Luis López-Fando Lavalle. *Continence*, Volume 5, March 2023, 100572

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Journal homepage: <http://www.elsevier.com/locate/cont>

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Urothelial cells exhibit increased expression of angiotensin-converting enzyme-2 receptor, which is the binding site of severe acute respiratory syndrome coronavirus 2 to cells. The frequency and distribution of genitourinary tract symptoms in patients diagnosed with coronavirus disease 2019 (COVID-19) is unknown. The authors from Madrid, Spain explored trends in genitourinary tract symptoms by gender and each of six pandemic waves in patients admitted for COVID-19, and related them with severity, death and length of hospitalization. A retrospective study took place of COVID-

19 patients admitted to their institution. Only patients with RT-PCR or antigen test confirmed SARS-CoV-2 infection were included. Demographic, clinical, and genitourinary symptoms were explored. COVID-19 patients with genitourinary tract symptoms were compared with those without. Statistical comparisons were conducted by parametric and nonparametric tests for quantitative variables, and test for qualitative variables. Out of a total of 4,661 COVID-19 patients, genitourinary symptoms were found in 21.1%. These symptoms were more frequent in patients admitted for longer than 30 days, except for urinary incontinence (UI) and erectile dysfunction (ED). Acute kidney injury (AKI) and urinary tract infections (UTI) had a higher presence in the 5th (16.7%; 12.8% respectively) and 3rd wave (13.3%; 12.6% respectively). Genitourinary symptoms were higher for those patients admitted in critical care units. Frequency of AKI, UI, UTI and acute urinary retention (AUR) were higher for patients who were finally deceased (26.2%; 3.5%; 13.6% and 3.6% respectively). A high frequency of genitourinary symptoms in patients admitted for COVID-19 was observed, whose frequency and distribution varied according to pandemic waves. Specific genitourinary conditions were associated with worse outcomes and poorer prognosis.

ASSOCIATIONS OF UNSPECIFIED PAIN, IDIOPATHIC PAIN AND COVID-19 IN SOUTH KOREA: A NATIONWIDE COHORT STUDY

Namwo Kim, Jeewuan Kim, Bo Ram Yang, Bong-Jin Hahm. Korean J Pain. 2022 Oct 1;35(4):458-467. doi: 10.3344/kjp.2022.35.4.458. PMID: 36175345.

Few studies have investigated unspecified or idiopathic pain associated with COVID-19. This study from South Korea aimed to provide the incidence rates of unspecified pain and idiopathic pain in patients with COVID-19 for 90 days after COVID-19 diagnosis. A propensity score matched cohort was used, including all patients with COVID-19 in South Korea, and analyzed their electronic medical records. The control group consisted of those who had not had tests for COVID-19 at all. Unspecified pain diagnoses consisted of diagnoses related to pain included in the ICD-10 Chapter XVIII. Idiopathic pain disorders included fibromyalgia, temporomandibular joint disorders, headaches, chronic prostatitis, complex regional pain syndrome, atypical facial pain, irritable bowel syndrome, and interstitial cystitis. After matching, the number of participants in each group was 7,911. For most unspecified pain, the incidences were higher in the COVID-19 group (11.7%; 95% confidence interval [CI], 11.0-12.5) than in the control group (6.5%; 95% CI, 6.0-7.1). For idiopathic pain, only the headaches had a significantly higher incidence in the COVID-19 group (6.6%; 95% CI, 6.1-7.2) than in the control group (3.7%; 95% CI, 3.3-4.1). However, using a different control group that included only patients who visited a hospital at least once for any reasons, the incidences of most unspecified and idiopathic pain were higher in the control group than in the COVID-19 group. Patients with COVID-19 might therefore be at a higher risk of experiencing unspecified pain in the acute phase or after recovery compared with individuals who had not had tests for COVID-19.

A COMPARISON OF PAIN, FATIGUE, AND FUNCTION BETWEEN POST-COVID-19 CONDITION, FIBROMYALGIA, AND CHRONIC FATIGUE SYNDROME: A SURVEY STUDY

Saman Haider, Adam J Janowski, Joseph B Lesnak, Kazuhiro Hayashi, Dana L Dailey, Ruth Chimenti, Laura A Frey-Law, Kathleen A Sluka, Giovanni Berardi. Pain. 2023 Feb 1;164(2):385-401. doi: 10.1097/j.pain.0000000000002711. Epub 2022 Jun 29. PMID: 36006296

A growing number of individuals report prolonged symptoms following acute Coronavirus-19 (COVID-19) infection, known as post-COVID-19 condition (post-COVID-19). While studies have emerged investigating the symptom sequelae of post-COVID-19, there has been limited investigation into the characterization of pain, fatigue, and function in these individuals, despite initial reports of a clinical phenotype similar to fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME). This study from the USA aimed to characterize multiple symptom domains in individuals reporting post-COVID-19 and compare its clinical phenotype with those with FMS and CFS. A total of 707 individuals with a single or comorbid diagnosis of post-COVID-19, FMS, and/or CFS completed multiple surveys assessing self-reported pain, fatigue,

physical and cognitive function, catastrophizing, kinesiophobia, anxiety, depression, dyspnea, and sleep quality. In all 3 diagnoses, elevated pain, fatigue, anxiety, depression, catastrophizing, and kinesiophobia were reported. Physical and cognitive function were similarly impacted among individuals with post-COVID-19, FMS, and CFS; however, individuals with post-COVID-19 reported lower pain and fatigue than FMS and CFS. The comorbid diagnosis of post-COVID-19 with FMS and/or CFS further exacerbated pain, fatigue, and psychological domains when compared with post-COVID-19 alone. In summary, individuals with post-COVID-19 report a symptom phenotype similar to FMS and CFS, negatively impacting cognitive and physical function, but with less severe pain and fatigue overall. These findings may help direct future investigations of the benefit of a biopsychosocial approach to the clinical management of post-COVID-19.

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