

International Painful Bladder Foundation

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

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

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

- Adapting to the impact of COVID-19
- Information about COVID-19 and online resources
- Patient support groups and country contacts update
- Upcoming meetings
- Publications
- Research Update
- Donations & Sponsoring

ADAPTING TO THE IMPACT OF COVID-19

Due to the COVID-19 pandemic, most scientific and patient conferences have been either cancelled, postponed or transformed into online, virtual conferences. Details of these are given further down in this Newsletter. These virtual conferences are in fact giving many people the opportunity to “attend” who would not normally have been able to do so. There are also numerous webinars and virtual lectures to keep you informed and participating while in lockdown. All of this means that we have no meeting reviews for you in this IPBF Newsletter.

The patient organizations are now greatly benefiting from the efforts they have put into developing websites and social media contacts for their members and patients worldwide in recent years. COVID-19 lockdown situations mean that many patient meetings have had to be cancelled and everything moved online. IC India (icindiaorg@gmail.com) for example has been organizing a series of online Question & Answer webinar sessions for IC patients who can put their questions to Indian doctors in this field who kindly offered their services. A great initiative.

INFORMATION ABOUT COVID-19 AND ONLINE RESOURCES

While just 2 months ago we could scarcely find any information about COVID-19 or “Coronavirus”, we are now inundated with it and it is becoming very difficult to see the wood for the trees. A few links below may be useful and will probably lead you to more. Some provide basic patient information, others detailed research. Information and insights change almost daily as more is learnt about the disease and how it is affecting different people.

IC/BPS patients are not specifically at risk as such. However, patients with associated disorders (comorbidities) and/or patients prescribed immunosuppressants may be more at risk.

The International Alliance of Patients’ Organizations (IAPO) has put together a COVID-19 resources hub at <https://www.iapo.org.uk/covid-19-resources-hub> which patients and their support groups may find useful.

Some useful suggestions for IC/BPS patients can be found at:

<https://bladderhealthuk.org/news/article/coronavirus--a-statement-from-bhuk> (Bladder Health UK)
<https://www.ichelp.org/covid-19-a-letter-to-the-ica-community> (Interstitial Cystitis Association)

IC/BPS Patients who also have Sjogren's syndrome may find the COVID-19 information of the website of the Sjogren's Foundation (USA) useful. <https://www.sjogrens.org/news/2020/coronavirus-and-the-sjogrens-foundation-updates>.

Latest research information is available from the National Institutes of Health (NIH) at <https://www.nih.gov/health-information/coronavirus> while newly published COVID-19 articles can be found on PubMed <https://www.ncbi.nlm.nih.gov/pubmed>

The United Kingdom National Health Service (NHS) also has a portal with a variety of information: <https://www.nhs.uk/conditions/coronavirus-covid-19/>

For speakers of Dutch, Dr Joop P. van de Merwe in the Netherlands is continually updating a very interesting and highly informative article about COVID-19 (in Dutch).

The introductory page with links can be found at: <https://www.jpvandemerwe.nl/corona>

Direct link to the article: <https://www.jpvandemerwe.nl/corona/pdf/coronapaper.pdf>

GLOBAL PATIENT SUPPORT GROUPS AND COUNTRY CONTACTS UPDATE

The IPBF is endeavouring to update its list of global IC/BPS support groups and country contacts. If your group is not included in the list, please contact the IPBF at info@painful-bladder.org providing details. [Click here](#) to view the online list.

UPCOMING MEETINGS

The unprecedented situation surrounding COVID-19 has led to mass cancellation or postponement of conferences, some replaced by virtual e-conferences online. The list below is continually subject to change.

- EAU 2020

This EAU 2020 congress was first postponed, then cancelled and has now been replaced by a virtual online congress [17-21 July 2020](#). Further information on how to participate:

<https://eaucongress.uroweb.org/the-congress>

- IAPO 9TH GLOBAL PATIENTS CONGRESS:

The IAPO 9th Global Patients Congress date has been changed to 16-18 September 2020, to be held in London UK. GPC2020 will also be reimaged online. The organisers are now in the process of designing a digital offering to support and connect those who may not be able to attend in person on the new dates.

www.globalpatientscongress.org

AUA (AMERICAN UROLOGICAL ASSOCIATION) 2020

The AUA 2020 meeting has been cancelled.

Abstracts are available online with open access at:

<https://www.auajournals.org/toc/juro/203/Supplement+4?pageStart=3&pageSize=100>

The AUA website now has a new section on AUA Virtual Education: <https://www.aanet.org/aua-virtual-experience>

More information: <https://www.aa2020.org/>

EULAR: EUROPEAN CONGRESS OF RHEUMATOLOGY 2020

The 2020 meeting has been cancelled and replaced by a virtual e-conference experience, starting from Wednesday 3 June 2020 and accessible on demand over a time frame of several months

<https://www.congress.eular.org/registration.cfm>

50th INTERNATIONAL CONTINENCE SOCIETY ANNUAL MEETING 2020

This meeting has been postponed to 18-21 November 2020, Rio Convention Centre, Las Vegas,

Please also note that the 7th International Consultation on Incontinence (ICI) will now take place at ICS 2021 in Melbourne. In the upcoming weeks, the website will be updated with new programme details and additional information. Registration will also re-open soon with a new Early Bird deadline of 29 July.

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

GIBS 2020 (GLOBAL INTERSTITIAL CYSTITIS BLADDER PAIN SOCIETY)

Annual Congress on IC/BPS. 5-6 September 2020, Mumbai India

<https://gibsociety.com/featured-image/#>

PUBLICATIONS

MORE PUBLICATIONS ON POSSIBLE LINK BETWEEN ORAL PENTOSAN POLYSULFATE AND PIGMENTARY MACULOPATHY

In the research update, you will find new ophthalmic publications on a possible link between long-term oral pentosan polysulfate and pigmentary maculopathy. While it should be emphasized that this is still under investigation and needs further much bigger studies, it would be wise for patients already taking oral PPS to have an annual eye check, and for patients contemplating taking this oral PPS treatment to have their eyes checked before starting. It goes without saying that any patient who has been taking oral PPS for several years and is experiencing vision problems should immediately undergo ophthalmic screening.

RESEARCH UPDATE

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

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

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

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

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

[CORRELATES OF 1-YEAR CHANGE IN QUALITY OF LIFE IN PATIENTS WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROME: FINDINGS FROM THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN \(MAPP\) RESEARCH NETWORK.](#)

Clemens JQ, Stephens-Shields AJ, Newcomb C, Rodriguez LV, Lai HH, Bradley CS, Naliboff BD, Griffith JW, Taple BJ, Gupta P, Afari N, Harte SE, Strachan E, Guo W, Landis JR. J Urol. 2020 Apr 14:101097JU0000000000001080. doi: 10.1097/JU.0000000000001080. [Epub ahead of print] PMID: 32294397

The purpose of this MAPP study was to evaluate and identify baseline factors associated with change in health-related quality of life (HRQOL) among patients with interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). A total of 191 men and 233 women with IC/BPS or CP/CPPS (collectively referred to as urologic chronic pelvic pain syndrome, or UCPPS) were followed for 12 months with bimonthly completion of the Short Form 12 (SF-12) to assess general mental and physical HRQOL, and with biweekly assessment of condition-specific HRQOL using the Genitourinary Pain Index. A functional clustering algorithm was used to classify participants as improved, stable, or worsened for each HRQOL measure. Ordinal logistic regression was used to determine baseline factors associated with change. Physical HRQOL improved in 22% of the participants, mental HRQOL improved in 25%, and condition-specific HRQOL improved in 47%. Better baseline physical HRQOL, older age, and the presence of non-urologic symptoms were associated with lower likelihood of improvement in physical HRQOL. Better baseline mental HRQOL, female sex, and greater baseline depression and stress were associated with lower likelihood of improvement in mental HRQOL. Better baseline condition-specific HRQOL and more severe baseline UCPPS pain symptoms were associated with lower

likelihood of improvement in condition-specific HRQOL. While several non-UCPPS factors influenced the trajectory of general HRQOL over time, only condition-specific baseline HRQOL and UCPPS symptoms were associated with UCPPS-specific HRQOL change. Significant differences in how UCPPS impacts various aspects of HRQOL suggest a multidisciplinary approach to assessment and treatment of these patients.

VOLUNTARY EXERCISE IMPROVES VOIDING FUNCTION AND BLADDER HYPERALGESIA IN AN ANIMAL MODEL OF STRESS-INDUCED VISCERAL HYPERSENSITIVITY: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME RESEARCH NETWORK STUDY.

Sanford MT, Yeh JC, Mao JJ, Guo Y, Wang Z, Zhang R, Holschneider DP, Rodriguez LV. Neurourol Urodyn. 2020 Feb;39(2):603-612. doi: 10.1002/nau.24270. Epub 2020 Jan 13. PMID: 31944369

Physical activity has shown beneficial effects on individuals suffering from chronic pain. Anxiety-prone rats exposed to water avoidance stress (WAS) develop urinary frequency and lower bladder sensory thresholds with high face and construct validity for the study of IC/BPS. The aim of this study was to evaluate the role of chronic voluntary exercise on urinary frequency, voiding function, and hyperalgesia in animals exposed to WAS. Twenty-six female Wistar-Kyoto rats were exposed to WAS and thereafter randomized to either voluntary exercise for 3 weeks or sedentary groups. Voiding parameters were assessed at baseline, post-WAS, and weekly for 3 weeks. Before euthanasia, the animals underwent cystometrogram (CMG), external urinary sphincter electromyography, and assessment of visceromotor response (VMR) to isotonic bladder distension (IBD). WAS exposure resulted in adverse changes in voiding parameters. Compared with sedentary animals, animals in the voluntary exercise group had improved voiding parameters during metabolic cage and CMG testing, as well as improved bladder sensory thresholds as determined by VMR during IBD. Voluntary exercise in an animal model of chronic stress leads to improvement in voiding function and visceral bladder hyperalgesia.

LOWER URINARY TRACT SYMPTOMS: ADVANCES IN WOMEN'S UROLOGIC HEALTH FROM MAPP AND LURN.

Yang CC, Clemens JQ. Urology. 2020 Apr 21. pii: S0090-4295(20)30404-0. doi: 10.1016/j.urology.2020.04.024. [Epub ahead of print] PMID: 32330529

Urinary tract conditions causing urinary symptoms, including pain and discomfort, are common in women of all ages. Lower urinary tract symptoms (LUTS) are highly prevalent with 59.2% of women exhibiting storage symptoms; 19.5% exhibiting voiding symptoms; and 14.2% exhibiting post-micturition symptoms and the prevalence of symptoms increases with age. Lower urinary tract pain, in particular, appears to be a problem more common in women than men. Unfortunately, many patients who seek care for LUTS experience neither total nor permanent resolution of their symptoms with current management approaches. The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the US National Institutes of Health (NIH) has been sponsoring multi-site research networks to investigate the causes and improve the treatment of patients suffering from lower urinary tract symptoms. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network and the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN), were both convened to examine these conditions from a perspective of phenotyping, whereby subgroups of patients having distinct underlying pathological mechanisms would be identified. MAPP focuses on urologic chronic pelvic pain syndromes (UCPPS) including interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/male chronic pelvic pain syndrome (CP/PPS). LURN focuses on non-painful urinary symptoms not arising from neurogenic, overtly infectious, or other identifiable causes.

HUNNER LESION

HUNNER LESION DISEASE DIFFERS IN DIAGNOSIS, TREATMENT AND OUTCOME FROM BLADDER PAIN SYNDROME: AN ESSIC WORKING GROUP REPORT.

Fall M, Nordling J, Cervigni M, Dinis Oliveira P, Fariello J, Hanno P, Kåbjörn-Gustafsson C, Logadottir Y, Meijlink J, Mishra N, Moldwin R, Nasta L, Quaghebeur J, Ratner V, Sairanen J, Taneja R, Tomoe H, Ueda T, Wennevik G, Whitmore K, Wyndaele JJ, Zaitcev A. Scand J Urol. 2020 Feb 28:1-8. doi: 10.1080/21681805.2020.1730948. [Epub ahead of print] PMID: 32107957

There is confusion about the terms of bladder pain syndrome (BPS) and Interstitial Cystitis (IC). The European Society for the Study of IC (ESSIC) classified these according to objective findings [9]. One phenotype, Hunner lesion disease (HLD or ESSIC 3C) differs markedly from other presentations. Therefore, the question was raised as to whether this is a separate condition or BPS subtype. An evaluation was made to explore if HLD differs from other BPS presentations regarding symptomatology, physical examination findings, laboratory tests, endoscopy, histopathology, natural history, epidemiology, prognosis and treatment outcomes. Cystoscopy is the method of choice to identify Hunner lesions, histopathology the method to confirm it. You cannot distinguish between main

forms of BPS by means of symptoms, physical examination or laboratory tests. Epidemiologic data are incomplete. HLD seems relatively uncommon, although more frequent in older patients than non-HLD. No indication has been presented of BPS and HLD as a continuum of conditions, one developing into the other. A paradigm shift in the understanding of BPS/IC is urgent. A highly topical issue is to separate HLD and BPS: treatment results and prognoses differ substantially. Since historically IC was tantamount to Hunner lesions and interstitial inflammation in the bladder wall, still a valid definition, the term IC should preferably be reserved for HLD patients. BPS is a symptom syndrome without specific objective findings and should be used for other patients fulfilling the ESSIC definitions.

[EDITORIAL: IT IS PREMATURE TO CATEGORIZE HUNNER LESION INTERSTITIAL CYSTITIS AS A DISTINCT DISEASE ENTITY.](#)

Nickel JC. *Scand J Urol.* 2020 Mar 27;1-2. doi: 10.1080/21681805.2020.1744714. [Epub ahead of print] PMID: 32216505

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

[COMPARISON OF THE EFFICACY BETWEEN TRANSURETHRAL COAGULATION AND TRANSURETHRAL RESECTION OF HUNNER LESION IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL.](#)

Ko KJ, Cho WJ, Lee YS, Choi J, Byun HJ, Lee KS. *Eur Urol.* 2020 Jan 17. pii: S0302-2838(20)30002-6. doi: 10.1016/j.eururo.2020.01.002. [Epub ahead of print]. PMID: 31959549

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition characterized by chronic pelvic pain related to the bladder with no effective treatment options. The purpose of this study from Korea was to evaluate the efficacy and safety of transurethral resection (TUR) and transurethral coagulation (TUC) as treatments for Hunner lesion (HL) in IC/BPS. A single-center, prospective, randomized controlled trial involving 126 patients with HL in IC/BPS. Primary outcome was recurrence-free time after surgery. Secondary outcomes included change of the number of frequency, nocturia, urgency episodes in voiding diaries, O'Leary-Sant Interstitial Cystitis Symptom Index (ICSi) and Interstitial Cystitis Problem Index (ICPI), pelvic pain and urgency/frequency (PUF) symptom scale, and visual analog scale (VAS) for pain and risk factors for recurrence. There were no differences in the recurrence-free time between treatment groups, a difference of 12.2 mo (95% confidence interval [CI], 11.1-17.6) for TUR, and a difference of 11.5 mo (95% CI, 9.03-16.1; p=0.735) for TUC. No difference was found in decreased mean daytime frequency, nocturia, urgency episodes, ICSi, ICPI, PUF symptom scale, and VAS for pain between both groups over 12 mo. Regardless of treatment types, there were significant improvements in all symptom questionnaires and pain compared with baseline (all, p < 0.05). Treatment type (TUR or TUC), age, sex, previous history of hydrodistension, and number of HLs did not affect recurrence. Incidence of bladder injury was higher in the TUR group (7.9%) than in the TUC group (3.4%). The authors concluded that there was no difference in the recurrence-free time and effect on urinary symptoms, including pain between TUC and TUR, for HL. Taking into account procedure-related complications, the surgeon can choose the method with which he/she is most familiar and comfortable.

PATIENT SUMMARY: In patients with bladder pain syndrome with Hunner lesions, both endoscopic resection and coagulation of the lesions are effective treatments.

[HUNNER LESION PHENOTYPE IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS.](#)

Lai HH, Pickersgill NA, Vetter JM. *J Urol.* 2020 Mar 30;101097JU0000000000001031. doi: 10.1097/JU.0000000000001031. [Epub ahead of print] PMID: 32223699

The purpose of this study from the US was to compare demographics, clinical presentation, comorbidities, urinary profiles, and treatment responses between interstitial cystitis/bladder pain syndrome (IC/BPS) patients with and without Hunner lesions (HL). Lai and colleagues performed a systematic review of literature in PubMed® in February 2019. Publications were included if they compared data between IC/BPS patients with and without HL, yielding 59 articles. Meta-analysis was performed on a subset of clinical characteristics. Meta-analysis showed that IC/BPS patients with HL were significantly older, reported higher urinary frequency, nocturia, and IC Symptom Index, but lower cystometric bladder capacity compared to IC/BPS patients without HL. There were no differences in pain scores, symptom duration, or sex between the two groups. While some studies reported higher rates of comorbid pain syndromes (e.g., fibromyalgia) among patients without HL, overall results were conflicting. Patients with HL had higher urinary levels of pro-inflammatory cytokines/chemokines (CXCL10, NGF, IL-6, IL-8, MIF), luminal nitric oxide (NO), and responded well to endoscopic treatment of the Hunner lesions (e.g. fulguration or triamcinolone injection). In comparative studies, IC/BPS

patients with HL responded better to oral cyclosporine A than those without HL. It was concluded that systematic review and meta-analysis demonstrated significant differences in demographics, clinical presentation, urinary marker profiles, and treatment responses between patients with and without HL, suggesting that they may represent two distinct clinical phenotypes. Studies are needed to investigate their mechanistic differences.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: THE EVOLVING LANDSCAPE, ANIMAL MODELS AND FUTURE PERSPECTIVES.

Akiyama Y, Luo Y, Hanno PM, Maeda D, Homma Y. Int J Urol. 2020 Apr 4. doi: 10.1111/iju.14229. [Epub ahead of print] PMID: 32246572

Interstitial cystitis/bladder pain syndrome is a debilitating condition of unknown etiology characterized by persistent pelvic pain with lower urinary tract symptoms and comprises a wide variety of potentially clinically useful phenotypes with different possible etiologies. Current clinicopathological and genomic evidence suggests that interstitial cystitis/bladder pain syndrome should be categorized by the presence or absence of Hunner lesions, rather than by clinical phenotyping based on symptomatology. The Hunner lesion subtype is a distinct inflammatory disease with proven bladder etiology characterized by epithelial denudation and enhanced immune responses frequently accompanied by clonal expansion of infiltrating B cells, with potential engagement of infection. Meanwhile, the non-Hunner lesion subtype is a non-inflammatory disorder with little evidence of bladder etiology. It is potentially associated with urothelial malfunction and neurophysiological dysfunction, and frequently presents with somatic and/or psychological symptoms, that commonly result in central nervous sensitization. Animal models of autoimmune cystitis and neurogenic sensitization might serve as disease models for the Hunner lesion and non-Hunner lesion subtypes, respectively. Here, we revisit the taxonomy of interstitial cystitis/bladder pain syndrome according to current research and discuss its potential pathophysiology and representative animal models. Categorization of interstitial cystitis/bladder pain syndrome based on cystoscopy is mandatory to design optimized treatment and research strategies for each subtype. A tailored approach that specifically targets the characteristic inflammation and epithelial denudation for the Hunner lesion subtype, or the urothelial malfunction, sensitized/altered nervous system and psychosocial problems for the non-Hunner lesion subtype, is essential for better clinical management and research progress in this complex condition.

THE ROLE OF GLYCOSAMINOGLYCANS IN THE MANAGEMENT OF CHRONIC PELVIC PAIN: A SYSTEMATIC REVIEW.

Iacovelli V, Bianchi D, Pletto S, Pacini P, Fede Spicchiale C, Finazzi Agrò E. Minerva Urol Nefrol. 2020 Mar 16. doi: 10.23736/S0393-2249.20.03672-3. [Epub ahead of print] PMID: 32182229

Glycosaminoglycans (GAGs) are involved in the pathogenesis of several urologic chronic diseases. Thus, GAGs replenishment therapy is widely reported as a therapeutic tool for chronic pelvic pain (CPP) conditions such as interstitial cystitis/bladder pain syndrome (IC/BPS) and prostate pain syndrome/chronic prostatitis. In this article we reviewed the current status of evidence on the clinic applications of glycosaminoglycans (GAGs) in the CPP. A literature search from inception was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement to identify clinical trials, randomized controlled trials, meta-analyses, and guidelines. A total of 29 papers were identified regarding the use of GAGs in CPP. GAGs replenishment therapy results are encouraging in chronic forms of pelvic pain even though well-powered randomized clinical trials are needed to better comprehend the exact role of this treatment.

SMALL FIBER POLYNEUROPATHY IN HUNNER LESION AND NON-HUNNER LESION INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Han E, Killinger KA, Turner KM, Gilleran J, Tenney D, Peters KM. Female Pelvic Med Reconstr Surg. 2020 Jan 25. doi: 10.1097/SPV.0000000000000824. [Epub ahead of print] PMID: 32217920

This study aimed to determine whether small fiber polyneuropathy (SFPN) diagnosis differs between Hunner lesion interstitial cystitis/bladder pain syndrome (HL IC/BPS) and non-Hunner lesion IC/BPS (NHL IC/BPS). This was a pilot study of 20 women with IC/BPS. Results from baseline questionnaires, such as Genitourinary Pain Index, Interstitial Cystitis Symptom Index/Interstitial Cystitis Problem Index (ICSI/ICPI), Patient Health Questionnaire-2, were collected. Two punch biopsies were performed on each patient: distal leg and thigh. The samples were evaluated for intraepidermal nerve fiber density. One intraepidermal nerve fiber density less than the fifth percentile, regardless of site, indicated a positive SFPN diagnosis. Twenty patients were enrolled: 10 HL IC/BPS and 10 NHL IC/BPS. The HL IC/BPS group was found to be significantly older than the NHL IC/BPS group. No significant differences were found in employment or relationship statuses, or in levels of education or

comorbidities between the 2 groups. Sixty percent (6/10) of patients had SFPN in the NHL IC/BPS group compared with 40% (4/10) in the HL IC/BPS group. No significant differences were seen in SFPN positivity or Genitourinary Pain Index, Patient Health Questionnaire-2, or Interstitial Cystitis Symptom Index/Interstitial Cystitis Problem Index scores between the NHL and HL IC/BPS groups. Similar to previously published studies, 60% of NHL IC/BPS patients in this cohort were positive for SFPN compared with only 40% of the HL IC/BPS patients. Larger studies may be needed to realize the full impact of SFPN in IC/BPS.

ASSESSING BLADDER HYPER-PERMEABILITY BIOMARKERS IN VIVO USING MOLECULARLY-TARGETED MRI.

Towner RA, Smith N, Saunders D1, Lerner M, Greenwood-Van Meerveld B, Hurst RE. Am J Nucl Med Mol Imaging. 2020 Feb 25;10(1):57-65. eCollection 2020. PMID: 32211219

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

The objective was to investigate if some of the key molecular players associated with bladder hyper-permeability in interstitial cystitis/bladder pain syndrome (IC/BPS) could be visualized with molecularly-targeted magnetic resonance imaging (mt-MRI) in vivo. IC/BPS is a chronic, painful condition of the bladder that affects primarily women. It has been demonstrated over the past several decades that permeability plays a substantial role in IC/BPS. There are several key molecular markers that have been associated with permeability, including glycosaminoglycan (GAG), biglycan, chondroitin sulfate, decorin, E-cadherin, keratin 20, uroplakin, vascular endothelial growth factor receptor 1 (VEGF-R1), claudin-2 and zonula occludens-1 (ZO-1). Towner and colleagues used in vivo molecularly-targeted MRI (mt-MRI) to assess specific urothelial biomarkers (decorin, VEGF-R1, and claudin-2) associated with bladder hyper-permeability in a protamine sulfate (PS)-induced rat model. The mt-MRI probes consisted of an antibody against either VEGF-R1, decorin or claudin-2 conjugated to albumin that had also Gd-DTPA (gadolinium diethylene triamine penta acetic acid) and biotin attached. mt-MRI- and histologically-detectable levels of decorin and VEGF-R1 were both found to decrease following PS-induced bladder urothelial hyper-permeability, whereas claudin-2, was found to increase in the rat PS model. Verification of the presence of the mt-MRI probes were done by targeting the biotin moiety for each respective probe with streptavidin-horse radish peroxidase (HRP). Levels of protein expression for VEGF-R1, decorin and claudin-2 were confirmed with immunohistochemistry. In vivo molecularly-targeted MRI (mt-MRI) was found to successfully detect alterations in the expression of decorin, VEGFR1 and claudin-2 in a PS-induced rat bladder permeability model. This in vivo molecularly-targeted imaging approach has the potential to provide invaluable information to enhance our understanding of bladder urothelium hyper-permeability in IC/BPS patients, and perhaps be used to assist in developing novel therapeutic strategies.

QUESTIONNAIRE-GUIDED EVALUATION OF THE EFFECTIVENESS OF LONG-TERM INTRAVESICAL 0.2% CHONDROITIN SULFATE THERAPY IN INTERSTITIAL CYSTITIS.

Kocatürk H, Atasoy N, Bedir F, Altay MS, Demirdöğen ŞO, Koç E, Yilmaz S. Int Urogynecol J. 2020 Feb 11. doi: 10.1007/s00192-020-04245-0. [Epub ahead of print] PMID: 32047969

The purpose of this study from Turkey was to investigate the long-term feasibility, safety and effectiveness of intravesical chondroitin sulfate therapy in patients with one or more forms of chronic cystitis. The study included 62 female patients with interstitial cystitis/painful bladder syndrome (IC/PBS) who received intravesical chondroitin sulfate (40 ml/80 mg) therapy between 2014 and 2018. A total of 15 doses of intravesical treatment were applied, once weekly in the first month and once monthly from the second month onward. A 3-day voiding diary, a visual analog scale (VAS), the O'Leary Sant Indexes (ICSI/ICPI), the Pelvic Pain and Urgency/Frequency Symptom (PPUFS) Scale and PPUF Bother scores were recorded and evaluated through prospective comparison before treatment and at the first month and first year. Patients were also assessed using the Global Response Assessment (GRA) at the end of the first month and first year to assess the effectiveness of responses to treatment. In the first month of treatment, 0.2% chondroitin sulfate was ineffective in 22.5% of patients, with mild improvement observed in 40.0% and moderate-good improvement in 37.0%. Evaluation at the end of the first year revealed mild improvement in 21.0% of patients and moderate-good improvement in 79.0%. Statistically significant improvements were observed in all scoring systems at 1 and 12 months compared with pre-treatment values. The authors concluded that long-term intravesical chondroitin sulfate therapy is a safe and highly successful therapeutic modality that produces significant improvement in patients' quality of life and symptoms in the treatment of IC/PBS.

IMPROVING THE BARRIER FUNCTION OF DAMAGED CULTURED UROTHELIUM USING CHONDROITIN SULFATE.

Rozenberg BB, Janssen DAW, Jansen CFJ, Schalken JA, Heesakkers JPFA. NeuroUrol Urodyn. 2020 Feb;39(2):558-564. doi: 10.1002/nau.24240. Epub 2019 Nov 27. PMID: 31774209

The purpose of this study from the Netherlands was to determine whether glycosaminoglycan (GAG) replenishment is able to improve recovery of a deficient urothelial barrier, chondroitin sulfate (CS) instillations were tested using an in vitro model. Porcine urothelial cells (Ucells) were terminally differentiated in culture conditions to construct a urothelial layer with a functional barrier. This layer was damaged to compromise barrier function to simulate a key characteristic of bladder pain syndrome/interstitial cystitis. The functional effect of subsequent treatment with CS was evaluated. Primary porcine Ucells were isolated and cultured on inserts. Differentiation of cells was evaluated with immunohistochemical analysis for the presence of umbrella cells, tight junctions and CS. Transepithelial electrical resistance (TEER) measurements were performed to evaluate barrier function. Protamine was used to simulate mild urothelial damage. CS 0.2% (vol/vol), a GAG, was subsequently instilled in the treatment group. The recovery of barrier function was further evaluated with TEER measurements. The Student t test was used for the analysis of results. After induction of differentiation, the Ucells expressed barrier markers and a functional barrier was established (measured by high TEER). TEER decreased significantly after instillation with protamine. CS instillation improved recovery of TEER significantly measured after 7 hours (84% vs 22% in controls). After 24 hours; however, the TEER was comparable in both experimental groups. CS instillation improves the recovery of the urothelial barrier after damage in vitro. This functional experiment shows that CS improves recovery of damaged urothelial function, which supports the hypothesis behind the mechanism of action of GAG-replenishment therapy.

URINARY MICROBIOME IN UNCOMPLICATED AND INTERSTITIAL CYSTITIS: IS THERE ANY SIMILARITY?

Yildirim S, Shoskes D, Kulkarni S, Laguna P. World J Urol. 2020 Jan 31. doi: 10.1007/s00345-020-03099-x. [Epub ahead of print] PMID: 32006175

Acute/uncomplicated cystitis is the most common bacterial infection causing inflammation in the bladder tissues and predominantly diagnosed in women. Interstitial cystitis may too, cause inflammation in the bladder but its etiology has been elusive. Even though the site and symptoms of both diseases are largely shared, state of the urinary microbiome in these disorders have not been comparatively evaluated before. The purpose of this review is to assess and qualitatively compare structure and composition of the urinary microbiome in acute/uncomplicated cystitis and interstitial cystitis. The available literature in MEDLINE were extensively searched using keywords and screened. Pertinent evidence is carefully assessed and synthesized. Yildirim and colleagues included the original studies with a cohort of medically stable, non-pregnant women with otherwise functionally normal urinary tract and excluded the original articles if the infection in a patient's cohort is accompanied by urinary syndromes such as incontinence and overactive bladder syndrome. A total of six original papers reporting on the urinary microbiome in acute cystitis and nine papers on the interstitial cystitis met the selection criteria. The evidence they have gleaned from the literature on the urinary microbiome associated with the acute and interstitial cystitis does not point to convergence of microbiome similarities between the two diseases. More studies with direct sampling of the bladder tissues besides sampling bladder surfaces are warranted for accurate comparison of microbiome similarity between the two conditions. Future research on interstitial cystitis microbiome should include stratified cohorts with prospective design.

CLINICAL EFFICACY OF SUBMUCOSAL INJECTION OF TRIAMCINOLONE ACETONIDE IN THE TREATMENT OF TYPE II/III INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Jiang T, Zhou X, Chen Z, Xiong T, Fu J1, Liu Z, Yan D, Zhou Z, Shen W. BMC Urol. 2020 Mar 30;20(1):36. doi: 10.1186/s12894-020-00597-3. PMID: 32228552

The purpose of this study from China was to evaluate the efficacy of submucosal injection of triamcinolone acetonide for the treatment of type II/III interstitial cystitis/bladder pain syndrome. A retrospective analysis of the clinical data of type II/III interstitial cystitis/bladder pain syndrome patients treated in their department from April 2016 to August 2018 was conducted, and changes in International Prostate Symptom Scores and the Pelvic Pain and Urgency/Frequency symptom scale after surgery were evaluated to explore factors that may affect patient outcomes. A total of 27 female patients and 8 male patients were enrolled, with type II patients accounting for 62.9% of the sample, and the median follow-up duration was 31 months (range: 12-40 months). Twenty-two patients (74.3%) had significantly improved questionnaire scores at 4 weeks postoperatively. Treatment efficacy was sustained for at least 1 year in 15 patients, and persistent effectiveness was noted in 10 (28.6%) patients. Patients with an advanced age, high pain scores, and higher International Prostate Symptom Scores and Pelvic Pain and Urgency/Frequency symptom scale scores were more likely to benefit from submucosal injection of triamcinolone acetonide. Gender, disease duration, and the presence of Hunner's lesions had no predictive value for treatment outcomes. It was concluded that submucosal injection of triamcinolone acetonide can improve the clinical symptoms and quality of life in both men and women with type

II/III interstitial cystitis/bladder pain syndrome. Patients with an advanced age and more severe interstitial cystitis/bladder pain syndrome related symptoms may benefit more from triamcinolone acetonide injection.

COMPARISON OF URODYNAMIC RESULTS AND QUALITY OF LIFE BETWEEN WOMEN WITH INTERSTITIAL CYSTITIS AND OVERACTIVE BLADDER.

Hsu CC, Liang CC, Chang SD, Chien CW, Hsieh WC. Taiwan J Obstet Gynecol. 2020 Jan;59(1):39-42. doi: 10.1016/j.tjog.2019.11.005. PMID: 32039798

Some symptoms of overactive bladder overlap with those of interstitial cystitis. This study was conducted to compare the urodynamic results and quality of life of patients with the two conditions. Urodynamic data were retrospectively analyzed in 55 females with interstitial cystitis and 171 females with overactive bladder between 2012 and 2016. Females with overactive bladder were divided into detrusor overactivity group and non-detrusor overactivity group based on urodynamic results. All recruited patients completed validated questionnaires including incontinence impact questionnaire (IIQ-7), urogenital distress inventory (UDI-6), and short form 12 health survey (SF-12). Patient demographics, total scores of questionnaires, and urodynamic results were compared among interstitial cystitis, detrusor overactivity, and non-detrusor overactivity groups. The age and body mass index of interstitial cystitis patients were significantly lower than that of overactive bladder patients. The severity of urinary symptoms was higher in interstitial cystitis group than in non-detrusor overactivity group from questionnaire, but similar as detrusor overactivity group. Interstitial cystitis group had lower maximum flow rate, lower residual urine volume, lower maximum cystometric capacity, and higher maximal urethral closure pressure compared with non-detrusor overactivity group. However, there was no significant difference in urodynamic parameters between interstitial cystitis and detrusor overactivity groups. It was concluded that interstitial cystitis and overactive bladder have a negative impact on quality of life, but urodynamic studies are not effective in distinguishing between interstitial cystitis and detrusor overactivity.

THE CLINICAL EFFECT OF TRADITIONAL CHINESE MEDICINE ON MIDDLE-AGED WOMEN WITH INTERSTITIAL CYSTITIS: PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL.

Liu Y, Zhang P, Liu M, Liu X, Liu R, Yu X, Deng S, Si H, Sun B. Medicine (Baltimore). 2020 Apr;99(14):e19673. doi: 10.1097/MD.00000000000019673. PMID: 32243402

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Interstitial cystitis (IC) has caused great harm to the patient's physical and psychological well-being. Traditional Chinese medicine (TCM) is characterized by overall concepts and dialectical treatment. It provides clinicians with safer and more reliable alternatives in terms of clinical prescriptions and prepared medicines, and also improves the quality of life of patients with IC. Therefore, in this study from China, Liu and colleagues use the research method of randomized controlled trials to explore the effects of TCM combined with western medicine on renal function and urine metabolism on middle-aged women with IC.

CULTIVABLE BACTERIA IN URINE OF WOMEN WITH INTERSTITIAL CYSTITIS: (NOT) WHAT WE EXPECTED.

Jacobs KM, Price TK, Thomas-White K, Halverson T, Davies A, Myers DL, Wolfe AJ. Female Pelvic Med Reconstr Surg. 2020 Apr 6. doi: 10.1097/SPV.0000000000000854. [Epub ahead of print] PMID: 32265402

Multiple studies show cultivatable bacteria in urine of most women. The existence of these bacteria challenges interstitial cystitis (IC)/painful bladder syndrome (PBS) diagnosis, which presumes a sterile bladder. The aims of this study were (1) to compare the female bladder microbiomes in women with IC/PBS and unaffected controls and (2) to correlate baseline bladder microbiome composition with symptoms. This cross-sectional study enrolled 49 IC/PBS and 40 controls. All provided catheterized urine samples and completed validated questionnaires. A subset of the IC/PBS cohort provided voided and catheterized urine samples. All samples from both cohorts were assessed by the expanded quantitative urine culture (EQUC) protocol; a subset was assessed by 16S rRNA gene sequencing. Of the IC/PBS cohort, 49.0% (24/49) were EQUC positive; in these EQUC-positive samples, the most common urotypes were Lactobacillus (45.8%) and Streptococcus (33.3%). Of the controls, 40.0% were EQUC positive; of these EQUC-positive samples, the most common urotype was Lactobacillus (50.0%). The urotype distribution was significantly different ($P < 0.05$), as 16% of the IC/PBS cohort, but 0% of controls, were Streptococcus urotype. Symptom-free IC/PBS participants were less likely to be EQUC positive (12.5%) than IC/PBS participants with moderate or severe symptoms and the control cohort. It was concluded that lactobacillus was the most common urotype. However, the presence of Lactobacillus did not differ between cohorts, and it did not impact IC/PBS symptom severity. Bacteria were not isolated from most participants with active IC/PBS symptoms. These findings suggest that bacteria may not be an etiology for IC/PBS.

APPLICATION OF ADULT AND PLURIPOTENT STEM CELLS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME THERAPY: METHODS AND PERSPECTIVES.

Dayem AA, Kim K, Lee SB, Kim A2 Cho SG. *J Clin Med.* 2020 Mar 12;9(3). pii: E766. doi: 10.3390/jcm9030766. PMID: 32178321

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a multifactorial, chronic disease without definite etiology characterized by bladder-related pelvic pain. IC/BPS is associated with pain that negatively affects the quality of life. There are various therapeutic approaches against IC/BPS. However, no efficient therapeutic agent against IC/BPS has been discovered yet. Urothelium dysfunction is one of the key factors of IC/BPS-related pathogenicity. Stem cells, including adult stem cells (ASCs) and pluripotent stem cells (PSCs), such as embryonic stem cells (ESCs) and induced PSCs (iPSCs), possess the abilities of self-renewal, proliferation, and differentiation into various cell types, including urothelial and other bladder cells. Therefore, stem cells are considered robust candidates for bladder regeneration. This review provides a brief overview of the etiology, pathophysiology, diagnosis, and treatment of IC/BPS as well as a summary of ASCs and PSCs. The potential of ASCs and PSCs in bladder regeneration via differentiation into bladder cells or direct transplantation into the bladder and the possible applications in IC/BPS therapy are described in detail. A better understanding of current studies on stem cells and bladder regeneration will allow further improvement in the approaches of stem cell applications for highly efficient IC/BPS therapy.

ASSOCIATION BETWEEN CHRONIC INTERSTITIAL CYSTITIS AND HERPES ZOSTER.

Hsu CY, Lin CL,10, Kao CH. *Int J Environ Res Public Health.* 2020 Mar 26;17(7). pii: E2228. doi: 10.3390/ijerph17072228. PMID: 32224999

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Herpes zoster (HZ) infection has been associated with disease burdens such as infection and depression. However, the relationship between chronic interstitial cystitis (CIC) and HZ is unknown. This study from Taiwan investigated HZ risk in patients with CIC. The Longitudinal Health Insurance Database, which is a subset of the Taiwan National Health Insurance Research Database, was used in the study. The case cohort consisted of patients with newly diagnosed CIC between 2000 and 2012. Each patient with CIC was matched to four controls by age and index year. All participants were traced from the index date to HZ diagnosis, and loss to follow-up or death, or to the end of the study (31 December 2013). A total of 1096 patients with CIC and 4384 controls were enrolled. The incidence rate of HZ in patients with CIC was 10.8 per 1000 person-years, whereas that for controls was 7.25 per 1000 person-years. HZ risk for the case cohort was 1.48 times that for the control cohort. Among participants aged ≤ 49 years, patients with CIC had a 1.91-fold-increased HZ risk compared to those without CIC. It was concluded that patients with CIC had a higher risk of HZ than those without CIC. CIC should not be ignored, particularly in young adults.

THERAPEUTIC EFFECT OF BOTULINUM TOXIN A ON SENSORY BLADDER DISORDERS-FROM BENCH TO BEDSIDE.

Jiang YH, Yu WR, Kuo HC. *Toxins (Basel).* 2020 Mar 9;12(3). pii: E166. doi: 10.3390/toxins12030166. PMID: 32182780

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Bladder oversensitivity arises from several different conditions involving the bladder, bladder outlet, systemic or central nervous system diseases. Increase of the bladder sensation results from activation of the sensory receptors in the urothelial cells or suburothelial tissues. Medical treatment targeting the overactive bladder (OAB) or interstitial cystitis (IC) might relieve oversensitive bladder symptoms (frequency, urgency and pain) in a portion of patients, but a certain percentage of patients still need active management. Botulinum toxin A (BoNT-A) has been demonstrated to have anti-inflammatory and antinociceptive effects in bladder sensory disorders and has been shown effective in the reduction of bladder oversensitivity and the increase of functional bladder capacity. For patients with OAB, urgency and urinary incontinence improved, while in patients with IC, bladder pain could be relieved in association with reduction of bladder oversensitivity after BoNT-A intravesical injection. Histological evidence has confirmed the therapeutic mechanism and clinical efficacy of intravesical BoNT-A injection on patients with OAB or IC. Bladder oversensitivity can also be relieved with the instillation of liposome encapsulated BoNT-A or low energy shock waves (LESWs), which enable the BoNT-A molecule to penetrate into the urothelium and suburothelial space without affecting the detrusor contractility. Liposome encapsulated BoNT-A or combined LESWs and BoNT-A instillation might be future treatment alternatives for bladder oversensitivity in sensory bladder disorders.

CLINICAL APPLICATION OF INTRAVESICAL BOTULINUM TOXIN TYPE A FOR OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS.

Chen JL, Kuo HC. *Investig Clin Urol.* 2020 Feb;61(Suppl 1):S33-S42. doi: 10.4111/icu.2020.61.S1.S33. Epub 2019 Nov 13. PMID: 32055752

After decades of clinical and basic science research, the clinical application of botulinum toxin A (Botox) in urology has been extended to neurogenic detrusor overactivity (NDO), idiopathic detrusor overactivity, refractory overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS), lower urinary tract symptoms, benign prostatic hyperplasia, and neurogenic or non-neurogenic lower urinary tract dysfunction in children. Botox selectively disrupts and modulates neurotransmission, suppresses detrusor overactivity, and modulates sensory function, inflammation, and glandular function. In addition to motor effects, Botox has been found to have sensory inhibitory effects and anti-inflammatory effects; therefore, it has been used to treat IC/BPS and OAB. Currently, Botox has been approved for the treatment of NDO and OAB. Recent clinical trials on Botox for the treatment of IC/BPS have reported promising therapeutic effects, including reduced bladder pain. Additionally, the therapeutic duration was found to be longer with repeated Botox injections than with a single injection. However, the use of Botox for IC/BPS has not been approved. This paper reviews the recent advances in intravesical Botox treatment for OAB and IC/BPS.

EFFECT OF BOTULINUM TOXIN A ON BLADDER PAIN-MOLECULAR EVIDENCE AND ANIMAL STUDIES.

Yeh TC, Chen PC, Su YR, Kuo HC. *Toxins (Basel).* 2020 Feb 3;12(2). pii: E98. doi: 10.3390/toxins12020098. PMID: 32028597

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Botulinum toxin A (BTX-A) is a powerful neurotoxin with long-lasting activity that blocks muscle contractions. In addition to effects on neuromuscular junctions, BTX-A also plays a role in sensory feedback loops, suggesting the potentiality for pain relief. Although the only approved indications for BTX-A in the bladder are neurogenic detrusor overactivity and refractory overactive bladder, BTX-A injections to treat bladder pain refractory to conventional therapies are also recommended. The mechanism of BTX-A activity in bladder pain is complex, with several hypotheses proposed in recent studies. Here, Yeh and colleagues from Taiwan comprehensively reviewed properties of BTX-A in peripheral afferent and efferent nerves, the inhibition of nociceptive neurotransmitter release, the reduction of stretch-related visceral pain, and its anti-inflammatory effects on the bladder urothelium. Studies have also revealed possible effects of BTX-A in the human brain. However, further basic and clinical studies are warranted to provide solid evidence-based support in using BTX-A to treat bladder pain.

MECHANISM OF ACTION OF BOTULINUM TOXIN A IN TREATMENT OF FUNCTIONAL UROLOGICAL DISORDERS.

Lin YH, Chiang BJ, Liao CH. *Toxins (Basel).* 2020 Feb 18;12(2). pii: E129. doi: 10.3390/toxins12020129. PMID: 32085522

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Intravesical botulinum toxin (BoNT) injection is effective in reducing urgency and urinary incontinence. It temporarily inhibits the detrusor muscle contraction by blocking the release of acetylcholine (ACh) from the preganglionic and postganglionic nerves in the efferent nerves. BoNT-A also blocks ATP release from purinergic efferent nerves in the detrusor muscle. In afferent nerves, BoNT-A injection markedly reduces the urothelial ATP release and increases nitric oxide (NO) release from the urothelium. BoNT-A injection in the urethra or bladder has been developed in the past few decades as the treatment method for detrusor sphincter dyssynergia, incontinence due to neurogenic or idiopathic detrusor overactivity, sensory disorders, including bladder hypersensitivity, overactive bladder, and interstitial cystitis/chronic pelvic pain syndrome. Although the FDA only approved BoNT-A injection treatment for neurogenic detrusor overactivity and for refractory overactive bladder, emerging clinical trials have demonstrated the benefits of BoNT-A treatment in functional urological disorders. Cautious selection of patients and urodynamic evaluation for confirmation of diagnosis are crucial to maximize the successful outcomes of BoNT-A treatment.

CAN BOTULINUM TOXIN A PLAY A ROLE IN TREATMENT OF CHRONIC PELVIC PAIN SYNDROME IN FEMALE PATIENTS?-CLINICAL AND ANIMAL EVIDENCE.

Chen CL, Meng E. *Toxins (Basel).* 2020 Feb 10;12(2). pii: E110. doi: 10.3390/toxins12020110. PMID: 32050685

Chronic pelvic pain (CPP) is defined as chronic pain and inflammation in the pelvic organs for more than six months. There are wide ranges of clinical presentations, including pelvic pain, painful intercourse, irritable bowel syndrome, and pain during urinating. Chronic pelvic pain syndrome (CPPS) is a subdivision of CPP, and the pain syndrome may be focused within a single organ or more than one pelvic organ. As there is uncertain pathogenesis, no standard treatment is currently available for CPPS. Botulinum toxin A (BoNT-A) is a potent neurotoxin that blocks acetylcholine release to paralyze muscles. Intravesical BoNT-A injection can reduce

bladder pain in patients with interstitial cystitis/bladder pain syndrome. BoNT-A injected into the pelvic floor muscles of women has also been reported to improve chronic pain syndrome. Due to the reversible effect of BoNT-A, repeated injection appears to be necessary and effective in reducing symptoms. Adverse effects of BoNT-A may worsen the preexisting conditions, including constipation, stress urinary incontinence, and fecal incontinence. This review from Taiwan summarizes the evidence of BoNT-A treatment for CPPS in animal studies and clinical studies regarding the therapeutic effects of BoNT-A for CPPS in female patients.

[INJECTION LOCATION DOES NOT IMPACT BOTULINUM TOXIN A EFFICACY IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS.](#)

Evans RJ, Overholt T, Colaco M, Walker SJ. Can J Urol. 2020 Feb;27(1):10125-10129. PMID: 32065870

Botulinum toxin A (BTX-A) is currently used as a fourth-line therapeutic option for interstitial cystitis/bladder pain syndrome (IC/BPS) management. The purpose of this study was to determine if BTX-A injection can mitigate pain and if injection location (i.e. trigone-including versus trigone-sparing injection template) impacts treatment efficacy and/or treatment complications profile. Female IC/BPS patients refractory to conservative management strategies were prospectively enrolled and asked to complete a baseline history and physical exam, post-void residual (PVR) urine volume determination, O'Leary Sant (OLS) questionnaire, and Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) questionnaire. Participants were randomly assigned to one of two treatment groups and received either: 1) a trigone-including BTX-A injection template or 2) a trigone-sparing injection template. Following therapy, patients were examined in clinic at 30 and 90 day post-treatment with symptom re-assessment via repeat questionnaires and for evidence of post-procedural complications. Compared to baseline, patients in both treatment groups experienced significant improvement in OLS and PUF scores at both 30 and 90 days post-treatment with BTX-A, regardless of which injection template was used. Complications resulting from BTX-A were minimal (most commonly urinary tract infection (UTI) and urinary retention) and not significantly different between the treatment groups. No distant spread of BTX-A was observed in any patient in either treatment group. BTX-A treatment using either a trigone-sparing or trigone-including injection template resulted in significant, but not location-dependent, improvement in IC/BPS symptom scores at 30 and 90 day points post-procedure with no significant difference in post-treatment complication profiles.

[WOMEN'S PERCEPTIONS OF PUBLIC RESTROOMS AND THE RELATIONSHIPS WITH TOILETING BEHAVIORS AND BLADDER SYMPTOMS: A CROSS-SECTIONAL STUDY.](#)

Reynolds WS, Kowalik C, Kaufman MR, Dmochowski RR, Fowke JH. J Urol. 2020 Feb 25:101097JU0000000000000812. doi: 10.1097/JU.0000000000000812. [Epub ahead of print] PMID: 32096679

Because current knowledge about public restroom use and bladder health is limited, Reynolds and colleagues sought to identify why women avoid public restrooms and the associations of lower urinary tract symptoms and toileting behaviors. Between October and December 2017, they recruited a convenience sample of U.S. women to complete a cross-sectional, anonymous questionnaire about public restroom use, lower urinary tract symptoms (ICIQ-FLUTS), and toileting behavior (TB-WEB). They compared women who reported limiting the public restroom use all or most of the time to those who did not limit or did so occasionally or sometimes. Of the 6,004 women in the study, 26% limited public restroom use most or all of the time and were more concerned with cleanliness than those who did not limit public restroom use. They also reported more often using non-sitting positions when away from home and holding urine to avoid public restrooms, higher ICIQ-FLUTS scores, and more frequent overactive bladder and <7 voids a day. It was concluded that a large number of women reported avoiding public restrooms, often over concerns of cleanliness, availabilities of amenities, and privacy. Women who habitually limit public restroom use more frequently reported unhealthy toilet behaviors and LUT conditions. These findings will help guide future research and inform public policy and bladder health awareness.

[URINARY BLADDER SIGMA-1 RECEPTORS: A NEW TARGET FOR CYSTITIS TREATMENT.](#)

González-Cano R, Artacho-Cordón A, Romero L, Tejada MA, Nieto FR, Merlos M, Cañizares FJ, Cendán CM, Fernández-Segura E, Baeyens JM. Pharmacol Res. 2020 Feb 24:104724. doi: 10.1016/j.phrs.2020.104724. [Epub ahead of print] PMID: 32105755

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No adequate treatment is available for painful urinary bladder disorders such as interstitial cystitis/bladder pain syndrome, and the identification of new urological therapeutic targets is an unmet need. The sigma-1 receptor (σ_1 -R) modulates somatic pain, but its role in painful urological disorders is unexplored. The urothelium expresses many receptors typical of primary sensory neurons (e.g. TRPV1, TRPA1 and P2 × 3) and high levels of σ_1 -R have been found in these neurons; the authors from Spain therefore hypothesized that σ_1 -R may also be

expressed in the urothelium and may have functional relevance in this tissue. With western blotting and immunohistochemical methods, they detected σ 1-R in the urinary bladder in wild-type (WT) but not in σ 1-R-knockout (σ 1-KO) mice. Interestingly, σ 1-R was located in the bladder urothelium not only in mouse, but also in human bladder sections. The severity of histopathological (edema, hemorrhage and urothelial desquamation) and biochemical alterations (enhanced myeloperoxidase activity and phosphorylation of extracellular regulated kinases 1/2 [pERK1/2]) that characterize cyclophosphamide-induced cystitis was lower in σ 1-KO than in WT mice. Moreover, cyclophosphamide-induced pain behaviors and referred mechanical hyperalgesia were dose-dependently reduced by σ 1-R antagonists (BD-1063, NE-100 and S1RA) in WT but not in σ 1-KO mice. In contrast, the analgesic effect of morphine was greater in σ 1-KO than in WT mice. Together these findings suggest that σ 1-R plays a functional role in the mechanisms underlying cyclophosphamide-induced cystitis and modulates morphine analgesia against urological pain. Therefore, σ 1-R may represent a new drug target for urinary bladder disorders.

[A SYSTEMATIC REVIEW OF SURGICAL INTERVENTIONS FOR THE TREATMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.](#)

Osman NI, Bratt DG, Downey AP, Esperto F, Inman RD, Chapple CR. *Eur Urol Focus.* 2020 Feb 29. pii: S2405-4569(20)30071-7. doi: 10.1016/j.euf.2020.02.014. [Epub ahead of print] PMID: 32127327

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a poorly understood chronic debilitating condition. Surgery is reserved for severe refractory cases; however, there is no consensus on patient selection or optimal approach. The purpose of this study was to evaluate the evidence relating to the safety and efficacy of surgical interventions for treating BPS/IC. PubMed and Scopus databases were searched for original studies, using keywords "cystectomy", "interstitial cystitis", and "bladder pain syndrome". Articles were reviewed and screened by three independent reviewers. A total of 450 patients were identified from 20 eligible studies: mean age was 54.5 yr and 90.2% were female. The median duration of symptoms preoperatively was 60 mo (range 9-84), with a mean follow-up of 45.5 mo. A total of 448 patients underwent surgery: subtotal cystectomy with cystoplasty (48.6%), cystectomy and orthotopic neobladder (21.9%), cystectomy and ileal conduit (11.2%), and urinary diversion only (18.3%). Symptomatic improvement occurred in 77.2%, with higher rates in the total cystectomy and orthotopic neobladder group. Thirty-one patients (6.9%) required secondary total cystectomy and/or ileal conduit diversion; 48.4% subsequently improved. Seventeen studies reported 102 complications overall (26.5%). Overall mortality was 1.3%. Overall surgical intervention is associated with a 23% risk of failure to improve symptoms. Higher rates of improvement were reported in patients with total cystectomy. Interpretation should be guarded given the small patient number, multiple centres, and variable outcome measurements. There is a need for prospective randomised studies to answer questions regarding patient selection and optimal surgical approach.

PATIENT SUMMARY: In this review, the authors looked at the outcomes of surgery for treatment-refractory bladder pain syndrome/interstitial cystitis. They found overall symptom improvement in 77.2% of patients with a complication rate of 26.5%. However, there remains a need for further studies of higher quality to identify patients who will have symptom improvement and the best surgical option.

[UNDERSTANDING BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.](#)

Tailor V, Torella M, Manriquez V, Digesu GA. *Int Urogynecol J.* 2020 Feb 24. doi: 10.1007/s00192-020-04232-5. [Epub ahead of print]. PMID: 32095957. Editorial

[Free full text, click on title](#)

There is still much to understand on the topic of BPS/IC. In response to Hunner, the scientific community has "awakened to its existence" and made encouraging steps towards identifying the aetiology and optimizing treatment of this "...condition which is not so rare".

[NOTCH CONTROLS UROTHELIAL INTEGRITY IN THE MOUSE BLADDER.](#)

Paraskevopoulou V, Bonis V, Dionellis VS, Paschalidis N, Melissa P, Chavdoula E, Vasilaki E, Pateras IS, Klinakis A. *JCI Insight.* 2020 Feb 13;5(3). pii: 133232. doi: 10.1172/jci.insight.133232. *Toxins (Basel).* 2020 Feb 10;12(2). pii: E110. doi: 10.3390/toxins12020110. PMID: 32051338

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The Notch signalling pathway mediates cell-cell communication regulating cell differentiation and proliferation and cell fate decisions in various tissues. In the urinary bladder, Notch acts as a tumor suppressor in mice, while mutations in Notch pathway components have been identified in human bladder cancer as well. Here Paraskevopoulou and colleagues from Greece and Switzerland report that the genetic inactivation of Notch in mice leads to downregulation of cell-cell and cell-ECM interaction components, including proteins previously

implicated in interstitial cystitis/bladder pain syndrome (IC/BPS), structural defects and mucosal sloughing, inflammation, and leaky urine-blood barrier. Molecular profiling of ailing mouse bladders showed similarities with IC/BPS patient tissue, which also presented low Notch pathway activity as indicated by reduced expression of canonical Notch targets. Urothelial integrity was reconstituted upon exogenous reactivation of the Notch pathway, implying a direct involvement of Notch. Despite damage and inflammation, urothelial cells failed to proliferate, uncovering a possible role for $\alpha 4$ integrin in urothelial homeostasis. They report that their data uncover a broad role for Notch in bladder homeostasis involving urothelial cell crosstalk with the microenvironment.

DOES OBTAINING A DIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IMPROVE SYMPTOMS OR QUALITY OF LIFE? A CROSS-SECTIONAL QUESTIONNAIRE-BASED STUDY.

Volpe KA1, Mandelbaum R, Rodriguez LV, Özel BZ, Rolston R, Dancz CE. Female Pelvic Med Reconstr Surg. 2020 Apr 15. doi: 10.1097/SPV.0000000000000840. [Epub ahead of print] PMID: 32304396

The aim of this study from the US was to investigate whether receiving a clinical diagnosis of interstitial cystitis (IC) or bladder pain syndrome (BPS) improves patients' symptoms, health-related quality of life (HRQOL), or ability to cope with their symptoms. In this cross-sectional study, participants with self-reported IC/BPS completed an online questionnaire recalling their perceived change in symptoms after diagnosis and treatment. The questionnaire included demographic information, overall HRQOL measured on a visual analog scale (VAS), O'Leary-Sant Interstitial Cystitis Problem Index, the Urinary Impact Questionnaire, and questions regarding patient beliefs about diagnosis. HRQOL and symptom impact scales were compared before and after diagnosis and treatment. Demographic data, symptom data, and beliefs were examined for correlation with improvement in quality of life after diagnosis. A total of 1052 participants initiated the survey and were included in the analysis; most of them identified as female, non-Hispanic, and white (90%). Before symptom onset, median VAS HRQOL score was 87. Median scores nadired at 34 after symptom onset before diagnosis but improved to 61 after diagnosis and treatment. Scores remained stable after diagnosis and initiation of treatment with a median score of 65 at the time of survey. Age, insurance type, and improvement in scores on the symptom impact scale predicted improvement in HRQOL after diagnosis and treatment in the multivariable model. Participants reported improvements on global and symptom-specific quality of life measures after diagnosis and treatment for IC/BPS.

CHLOROGENIC ACID ATTENUATES CYCLOPHOSPHAMIDE-INDUCED RAT INTERSTITIAL CYSTITIS.

Luo J, Yang C, Luo X, Yang Y, Li J, Song B, Zhao J, Li L. Life Sci. 2020 Mar 24:117590. doi: 10.1016/j.lfs.2020.117590. [Epub ahead of print] PMID: 32220624

This study from China aimed to investigate the therapeutic effect and molecular mechanism of chlorogenic acid (CGA) on cyclophosphamide (CYP)-induced rat interstitial cystitis (IC). An animal model of IC was established by intraperitoneal injection of CYP in female Sprague-Dawley rats. Eighty rats were randomly assigned to four groups: negative control (NC), NC treated with CGA (NC + CGA), IC, and IC treated with CGA (IC + CGA). Bladder urination function was assessed by analyzing urodynamic parameters. The expression of apoptosis-related proteins and inflammatory biomarkers in bladder specimens was detected using western blot and immunohistochemistry analysis. Compared with the IC group, bladder urinary function was significantly improved in the IC + CGA group. CGA treatment reduced inflammatory damage in the bladder tissue of IC rats. Caspase3 and Bax expression was higher while Bcl-2 expression was lower in the IC group compared to the IC + CGA group. In addition, there were significant differences between the groups in the expression levels of inflammatory biomarkers in the bladder tissue. Furthermore, CGA could inhibit CYP-induced MAPK/NF- κ B phosphorylation in the rat bladder tissue. In a CYP-induced rat model of IC, CGA could reduce inflammation and apoptosis, thus partially restoring bladder function, and the MAPK/NF- κ B pathway was probably involved in it.

EFFICACY OF FRANKINCENSE AND MYRRH IN TREATMENT OF ACUTE INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.

Chen YH, Chen WC, Tsai KS, Liu PL, Tsai MY, Lin TC, Yu SC, Chen HY. Chin J Integr Med. 2020 Apr 4. doi: 10.1007/s11655-020-3216-2. [Epub ahead of print] PMID: 32279153

The purpose of this study from Taiwan was to investigate the efficacy of frankincense and myrrh in the treatment of acute interstitial cystitis/painful bladder syndrome (IC/PBS). The effects of frankincense and myrrh on the proliferation and migration of primary human urothelial cells (HUCs) were assessed in vitro. In the animal study, 48 virgin female rats were randomized into 4 groups (12 in each group): (1) control group (saline-injected control); (2) cyclophosphamide (CYP) group (intraperitoneal injected 150 mg/kg CYP); (3) CYP + pentosan polysulfate sodium group (orally received 50 mg/kg pentosan polysulfate sodium); and (4) CYP + frankincense

and myrrh group [orally received frankincense (200 mg/kg) and myrrh (200 mg/kg)]. Rats orally received pentosan polysulfate sodium or frankincense and myrrh on day 1, 2, and 3. The experiments were performed on day 4. Pain and cystometry assessment behavior test were performed. Voiding interval values were assessed in rats under anesthesia. Finally, immunohistochemistry and Western blot were used to confirm the location and level, respectively, of cell junction-associated protein zonula occludens-2 (ZO-2) expression. Low dose frankincense and myrrh increased cell proliferation and migration in HUCs compared with control. Rats with acute IC/PBS rats exhibited lower voiding interval values, pain tolerance, and ZO-2 expression. Voiding interval values and pain tolerance were higher in the frankincense and myrrh group than CYP group. ZO-2 expression in the bladder was increased in the CYP + pentosan polysulfate and frankincense + myrrh groups compared with the CYP-induced acute IC/PBS group. It was concluded that frankincense and myrrh modulate urothelial wound healing, which ameliorates typical features of acute IC/PBS in rats.

URINE CYTOKINES AS BIOMARKERS FOR DIAGNOSING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND MAPPING ITS CLINICAL CHARACTERISTICS.

Jiang YH, Jhang JF, Hsu YH, Ho HC, Wu YH, Kuo HC. *Am J Physiol Renal Physiol.* 2020 Apr 13. doi: 10.1152/ajprenal.00051.2020. [Epub ahead of print] PMID: 32281420

The objective of this study from Taiwan was to investigate the diagnostic values of urine cytokines in interstitial cystitis/bladder pain syndrome (IC/BPS) patients and to identify their correlations with clinical characteristics. Urine samples were collected from 127 IC/BPS (ESSIC types 1 and 2) patients and 28 controls. Commercially available multiplex immunoassays (MILLIPLEX® map kits) were used to analyze 31 targeted cytokines. Cytokine levels between IC/BPS patients and controls were analyzed using ANOVA. Receiver operating characteristics (ROC) curves of each cytokine to distinguish IC/BPS from controls were generated for calculation of the area under the curve (AUC). IC/BPS Patients had urine cytokine profiles that differed from those of controls. Between ESSIC types 1 and 2 IC/BPS patients, urine cytokine profiles were also different. Among cytokines with high diagnostic values (i.e., AUC > 0.7) with respect to distinguish ESSIC type 2 IC/BPS patients from controls, RANTES, MIP-1 β , and IL-8 were of higher sensitivity, whereas MCP-1, CXCL10, and eotaxin-1 were of higher specificity. Multivariate logistic regression models for controlling for age, gender, body mass index, and diabetes mellitus, the urine cytokines with high diagnostic values (MCP-1, RANTES, CXCL10, IL-12p40, IL-7, and eotaxin-1) remained statistically significant in differentiating IC/BPS and controls. MCP-1, CXCL10, eotaxin-1, and RANTES were positively correlated with glomerulation grade and negatively correlated with maximal bladder capacity. The authors concluded that IC/BPS patients had urine cytokine profiles that clearly differed from those of controls. Urine cytokines might be useful as biomarkers for diagnosing IC/BPS and mapping its clinical characteristics.

ROLE OF DIFFUSION WEIGHTED-MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Daniele P, Cesare R, Bright OH, Nicolo F, Barbara G, Federica M, Catherine K, Gabriella SM, Alfredo F, Daniela B5, Lorenzo P, Claudio S, Arsenio S, Hussein J. *Urology.* 2020 Apr 8. pii: S0090-4295(20)30327-7. doi: 10.1016/j.urology.2020.03.019. [Epub ahead of print] PMID: 32277992

Some recent studies evaluated the introduction of Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) in the diagnosis of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC). The purpose of this study from Italy was to evaluate whether DW-MRI can contribute to non-invasive diagnosis of BPS/IC. The agreement between two raters (two radiologists involved in the study) was also evaluated, the relevance of the "operator-dependent" factor defined. Twenty-two female patients with a diagnosis of BPS-IC were recruited and performed DW-MRI. The same investigation was also performed in 20 patients with pelvic gynecological diseases and no BPS-IC. A significant difference was found between BPS-IC and no-BPS-IC since 17 out of 22 subjects of the first group were positive, compared to 3 out of 20 no-IC subjects, with a P value of 0.001 to highlight the statistical significance. The sensitivity of the exam was 77%, while the specificity was 85%. There was good agreement between the 2 raters in the evaluation of MRI results. DW-MRI helps to obtain a non-invasive diagnosis of BPS/IC, by providing useful information on the choice of which patients may be more appropriately submitted to cystoscopy and bladder biopsy.

MEDICATIONS USED TO TREAT BLADDER DISORDERS MAY ALTER EFFECTS OF NEUROMODULATION.

Ness TJ, McNaught J, Clodfelder-Miller B, Su X. *Neurol Urodyn.* 2020 Apr 24. doi: 10.1002/nau.24373. [Epub ahead of print] PMID: 32330365

Neuromodulation (nerve stimulation) can produce analgesia. One form, bilateral pudendal nerve stimulation (bPNS), suppresses responses to urinary bladder distension (UBD) in hypersensitive rats. Drugs can modify this effect (eg, benzodiazepines, but not opioids, suppress bPNS effects). Prior to a clinical trial of bPNS effects on

bladder pain, Ness and colleagues felt it was prudent to survey the effects of medications commonly used in patients with bladder disorders. Bladder hypersensitivity was produced by neonatal bladder inflammation in rat pups coupled with a second inflammatory insult as an adult. Antimuscarinic (oxybutynin), β_3 -adrenoceptor agonist (mirabegron, CL316243), α_1 -adrenoceptor antagonist (tamsulosin), antidepressant (amitriptyline), muscle relaxing (baclofen), and sedative (propofol) agents were administered and effects of bPNS on responses to UBD assessed. bPNS consisted of bilateral biphasic electrical stimulation of the mixed motor/sensory component of the pudendal nerves. Visceromotor responses (VMRs; abdominal muscle contractile responses) were used as nociceptive endpoints. Many of these drugs directly inhibited the VMRs to UBD, but only mirabegron, at the doses employed, significantly reduced inhibitory effects of bPNS. In the presence of the other drugs, bPNS continued to produce statistically significant inhibition of VMRs to UBD. This study suggests that concurrent therapy with drugs used to treat bladder disorders could affect assessment of the effects of bPNS on bladder hypersensitivity. This study gives guidance to clinical trials using bPNS for the treatment of painful bladder syndromes and suggests potential clinical use of some of these medications in the treatment of these same disorders.

[NORMALIZATION OF MAGNESIUM DEFICIENCY ATTENUATED MECHANICAL ALLODYNIA, DEPRESSIVE-LIKE BEHAVIORS, AND MEMORY DEFICITS ASSOCIATED WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS BY INHIBITING TNF- \$\alpha\$ /NF- \$\kappa\$ B SIGNALING IN FEMALE RATS.](#)

Chen JL, Zhou X, Liu BL, Wei XH, Ding HL, Lin ZJ, Zhan HL, Yang F, Li WB, Xie JC, Su MZ, Liu XG, Zhou XF. J Neuroinflammation. 2020 Apr 2;17(1):99. doi: 10.1186/s12974-020-01786-5. PMID: 32241292

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Bladder-related pain symptoms in patients with bladder pain syndrome/interstitial cystitis (BPS/IC) are often accompanied by depression and memory deficits. Magnesium deficiency contributes to neuroinflammation and is associated with pain, depression, and memory deficits. Neuroinflammation is involved in the mechanical allodynia of cyclophosphamide (CYP)-induced cystitis. Magnesium-L-Threonate (L-TAMS) supplementation can attenuate neuroinflammation. This study from China aimed to determine whether and how L-TAMS influences mechanical allodynia and accompanying depressive symptoms and memory deficits in CYP-induced cystitis. The authors concluded that normalization of magnesium deficiency by L-TAMS attenuated mechanical allodynia, depressive-like behaviors, and STMD in the CYP-induced cystitis model via inhibition of TNF- α /NF- κ B signaling and normalization of NR2B expression and that their study provides evidence that L-TAMS may have therapeutic value for treating pain and comorbid depression or memory deficits in BPS/IC patients.

[\[EXPERIMENTAL EVALUATION OF INTERACTION OF THE NERVE GROWTH FACTOR AND MAST CELLS IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME\].](#) [Article in Russian]

Sholan RF. Urologiia. 2020 Apr;(2):31-34. PMID: 32351060

The purpose of this study from Azerbaijan was to evaluate the level of nerve growth factor (NGF) in the blood and urine and mast cell infiltration of the bladder wall in a model of interstitial cystitis/bladder pain syndrome (IC/BPS) and to analyse their relationships. IC/BPS modelling was performed on 38 female rabbits, divided into 4 groups. In group 1, IC/BPS was simulated by an instillation of 70% alcohol into the bladder, while in group 2 and 3 animals' own urine and normal saline were injected into the bladder wall. Group 4 consisted of intact animals. The NGF level was determined by ELISA. To determine the concentration of mast cell in tissues, each cross-section was divided into 10 sections. The severity of mast cell infiltration was evaluated in each area using the following scale: 0 - no mast cells; 1 - less than 20 cells; 2 - 20-45 cells; 3 - more than 45 cells. The points of all 10 areas were added up, divided by 30 (the maximum possible score) and multiplied by 100. An increase in the NGF level in the blood and urine was seen in different models of IC/BPS, but it was significantly more pronounced in group 2 (toxic model). Mast cells were determined only in group 1. In animals with the urinary toxicity model, mast cell activity was significantly higher in comparison with those in the model with an instillation of 70% alcohol. The level of NGF in blood and urine correlated in different directions. Mast cell proliferation and activation was determined in case of impairment of the bladder wall integrity by the injection of urine. The author concluded that their animal model of IC/BPS, which was created by instillation of 70% alcohol into the bladder and the injection of urine into the bladder wall, showed an increase in the level of NGF in urine and blood and the concentration of mast cells. These findings, as well as relationship between these values indicate the development of neuroimmune inflammation in this pathological condition. Considering the involvement of many factors in the pathogenesis of this syndrome, further research is required.

EFFICACY OF COMBINATION THERAPY WITH PENTOSAN POLYSULFATE SODIUM AND ADIPOSE TISSUE-DERIVED STEM CELLS FOR THE MANAGEMENT OF INTERSTITIAL CYSTITIS IN A RAT MODEL.

Kim BS, Chun SY, Lee EH, Chung JW, Lee JN, Ha YS, Choi JY, Song PH, Kwon TG, Han MH, Kim DH, Yoo ES. *Stem Cell Res.* 2020 Apr 21;45:101801. doi: 10.1016/j.scr.2020.101801. [Epub ahead of print] PMID: 32334368

Kim and colleagues from South Korea evaluated the synergistic effects of pentosan polysulfate sodium (PPS) and mesenchymal stem cells (MSCs) in an interstitial cystitis (IC) rat model. After generation of the IC rat model, the rats were divided into 4 groups according to the treatment they received: phosphate-buffered saline injection into bladder submucosa, daily oral PPS feeding, MSC injection into bladder submucosa, or MSC injection into bladder submucosa with daily oral PPS feeding. After treatment, conscious cystometry and pain scale measurement were performed and their bladders were obtained for histological and proinflammatory-related gene expression analysis. On cystometric analysis, all treatment groups showed significantly increased intercontraction intervals and lower pain scores compared to those of the control group. Histological analysis revealed regenerated urothelium, less fibrosis, and decreased mast cell infiltration in all treatment groups compared to the control group. Significantly lower expression of TNF- α , IFN- γ , MCP, IL-6, TLR2, and TLR11 was observed in the PPS with MSC group compared to the other groups. Combination therapy with PPS and MSCs showed histological and functional effects in an IC rat model, including synergistic effects leading to increased intercontraction interval and decreased inflammatory reactions.

IN-DEPTH STRUCTURAL CHARACTERIZATION OF PENTOSAN POLYSULFATE SODIUM COMPLEX DRUG USING ORTHOGONAL ANALYTICAL TOOLS.

Alekseeva A, Raman R, Eisele G, Clark T, Fisher A, Lee SL, Jiang X, Torri G, Sasisekharan R, Bertini S. *Carbohydr Polym.* 2020 Apr 15;234:115913. doi: 10.1016/j.carbpol.2020.115913. Epub 2020 Jan 27. PMID: 32070534

Rapid advances have been made in developing analytical technologies for characterization of highly heterogeneous active ingredients of complex drugs, such as pentosan polysulfate (PPS), active ingredient of the drug Elmiron[®], approved by the Food and Drug Administration and marketed in the United States to treat interstitial cystitis. PPS sulfated polysaccharides comprise of a repeat unit of β (1-4)-D-xylopyranoses randomly substituted by 4-O-methyl-gluco-pyranosyluronic acid. To define the critical quality attributes (CQAs) of such a complex drug, it is critical to develop an approach that integrates data from orthogonal analytical methodologies. Here, the authors from Italy developed an approach integrating diverse analytical tools including gel permeation chromatography, LC/ESI-MS and NMR to measure CQAs of PPS. The proposed mathematical framework integrates the data from these diverse analytical methods as function of PPS chain length and building blocks. Their approach would facilitate in establishing a scientific foundation for comparative characterization of drug products with complex active ingredients.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE

RETINAL TOXICITY IN A PATIENT ON PENTOSAN POLYSULFATE SODIUM.

Wingelaar MJ, Raevis JJ, Conlin KA, Stepien KE. *Urology.* 2020 Apr 16. pii: S0090-4295(20)30384-8. doi: 10.1016/j.urology.2020.04.006. [Epub ahead of print] PMID: 32305545

Pentosan Polysulfate Sodium (PPS) is commonly used in the treatment of interstitial cystitis/bladder pain syndrome. Recently there has been reported cases of retinal toxicity associated with long-term PPS use. Wingelaar and colleagues from the Department of Ophthalmology at the University of Wisconsin-Madison present a case of a 42 year-old female who had been taking PPS for 10 years who was found to have signs of retinal toxicity but was completely asymptomatic. PPS was discontinued after these retinal findings were discovered.

PENTOSAN POLYSULFATE-ASSOCIATED MACULAR DISEASE IN PATIENTS WITH INTERSTITIAL CYSTITIS.

Lyons RJ, Ahmad S, Ansari S, Foote JE, Jain N. *Obstet Gynecol.* 2020 Apr 9. doi: 10.1097/AOG.0000000000003794. [Epub ahead of print] PMID: 32282604

Recent studies have implicated long-term pentosan polysulfate use with vision loss from a newly described macular condition. Affected patients report difficulty with reading and adjusting to dim lighting, and they occasionally develop severe visual disability. Macular changes resemble those seen in age-related macular degeneration, potentially leading to misdiagnosis. The objectives of this Current Commentary are to summarize studies evaluating the association between pentosan polysulfate use and macular disease, to educate pentosan polysulfate prescribers about the clinical manifestations of this condition, and to provide recommendations for screening at-risk patients.

PENTOSAN-ASSOCIATED MACULOPATHY: PREVALENCE, SCREENING GUIDELINES, AND SPECTRUM OF FINDINGS BASED ON PROSPECTIVE MULTIMODAL ANALYSIS.

Wang D, Au A, Gunnemann F, Hilely A, Scharf J, Tran K, Sun M, Kim JH, Sarraf D. *Can J Ophthalmol.* 2020 Jan 20. pii: S0008-4182(19)31272-4. doi: 10.1016/j.jcjo.2019.12.001. [Epub ahead of print] PMID: 31973791

The purpose of this cross-sectional study was to describe the prevalence and spectrum of multimodal imaging findings of pentosan polysulfate sodium (PPS)-associated maculopathy and to recommend dosage-related screening guidelines. Patients previously or currently treated with PPS at University of California, Los Angeles, were randomly ascertained and prospectively screened for PPS-associated maculopathy with multimodal retinal imaging. Daily and cumulative dosages of PPS exposure were calculated for each patient. Images were studied to identify the characteristic findings of toxicity. The prevalence of PPS-associated maculopathy and screening guidelines were determined. The prevalence of PPS-associated maculopathy in this cohort was 20% (10/50 patients). Both average duration of PPS therapy and average cumulative dosage were significantly lower in the unaffected (6.3 ± 6.6 years, 691.7 ± 706.6 g) versus the affected groups (20.3 ± 6.6 years, 3375.4 ± 1650.0 g, $p < 0.001$). Near-infrared reflectance (NIR) illustrated characteristic punctate retinal pigment epithelium (RPE) macular lesions early. Fundus autofluorescence (FAF) showed speckled autofluorescence in the posterior pole with peripapillary extension. Co-localization with optical coherence tomography (OCT) displayed focal RPE thickening and, in more severe cases, RPE atrophy in the macula and even the periphery. It was concluded that a prevalence of 20% in this study cohort suggests a significant risk of macular toxicity for PPS-treated patients. Characteristic alterations are best detected with FAF and NIR. More significant PPS exposure was associated with more severe atrophy. We recommend an initial baseline eye examination to include OCT and, most importantly, NIR and FAF with annual retinal imaging thereafter especially with cumulative dosages approaching 500 g. Patients exposed to greater than 1500 g of PPS are at significant risk of retinal toxicity.

A CASE OF PENTOSAN POLYSULFATE MACULOPATHY ORIGINALLY DIAGNOSED AS STARGARDT DISEASE.

Vora RA, Patel AP, Yang SS, Melles R. *Am J Ophthalmol Case Rep.* 2020 Jan 25;17:100604. doi: 10.1016/j.ajoc.2020.100604. eCollection 2020 Mar. PMID: 32043016

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The purpose of this case study was to describe a patient with a past diagnosis of Stargardt disease that was later determined to be pentosan polysulfate (PPS) maculopathy. The patient had clinical and imaging findings uncharacteristic of Stargardt disease. Rather, her fundus resembled the recently described maculopathy ascribed to PPS. After genetic testing was found to be negative for pathologic variants, the patient was asked to cease usage of PPS. This case emphasizes the importance of reviewing patient medication profiles prior to rendering a diagnosis of a retinal dystrophy. It is essential that ophthalmologists catch drug toxicities as early as possible, to minimize risk of further irreversible vision loss due to continued medication exposure.

POSSIBLE DRUG-INDUCED, VISION-THREATENING MACULOPATHY SECONDARY TO CHRONIC PENTOSAN POLYSULFATE SODIUM (ELMIRON®) EXPOSURE.

Doiron RC, Bona M, Nickel JC. *Can Urol Assoc J.* 2020 Feb;14(2):10-11. doi: 10.5489/cuaj.6401. Epub 2020 Jan 7. PMID: 31999543

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PREVALENCE OF MACULOPATHY ASSOCIATED WITH LONG-TERM PENTOSAN POLYSULFATE THERAPY.

Vora RA, Patel AP, Melles R. *Ophthalmology.* 2020 Jan 17. pii: S0161-6420(20)30040-3. doi: 10.1016/j.ophtha.2020.01.017. [Epub ahead of print] PMID: 32085877

Pentosan polysulfate sodium (PPS) (Elmiron; Janssen Pharmaceuticals, Titusville, NJ) is the only Food and Drug Administration–approved oral medicine for the treatment of interstitial cystitis (IC).¹ A recent original report studying 6 patients from a single academic practice linked chronic exposure to PPS with the development of a unique pigmentary maculopathy.² Further phenotypic details were defined in a larger follow-up retrospective multicenter study involving 35 patients.³ Since those reports, presumed PPS-related maculopathy has been noted to progress despite drug cessation⁴ and associated with the development of choroidal neovascularization.

GUIDELINES

CLINICAL GUIDELINES FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Homma Y, Akiyama Y, Tomoe H, Furuta A, Ueda T, Maeda D, Lin AT, Kuo HC, Lee MH, Oh SJ, Kim JC, Lee KS. *Int J Urol.* 2020 Apr 14. doi: 10.1111/iju.14234. [Epub ahead of print] *Int J Urol.* 2020 Apr 14. doi: 10.1111/iju.14234. [Epub ahead of print] PMID: 32291805

The clinical guidelines for interstitial cystitis and related symptomatic conditions were revised by Homma and colleagues from Japan and other East Asian countries by updating their previous guidelines. The current guidelines define interstitial cystitis/bladder pain syndrome as a condition with chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by other urinary symptoms, such as persistent urge to void or urinary frequency in the absence of confusable diseases. The characteristic symptom complex is collectively referred as hypersensitive bladder symptoms. Interstitial cystitis/bladder pain syndrome is divided into Hunner-type interstitial cystitis and bladder pain syndrome; Hunner-type interstitial cystitis and bladder pain syndrome represent interstitial cystitis/bladder pain syndrome with Hunner lesions and interstitial cystitis/bladder pain syndrome without Hunner lesions, respectively. So-called non-Hunner-type interstitial cystitis featured by glomerulations or bladder bleeding after distension is included in bladder pain syndrome. The symptoms are virtually indistinguishable between Hunner-type interstitial cystitis and bladder pain syndrome; however, Hunner-type interstitial cystitis and bladder pain syndrome should be considered as a separate entity of disorder. Histopathology totally differs between Hunner-type interstitial cystitis and bladder pain syndrome; Hunner-type interstitial cystitis is associated with severe inflammation of the urinary bladder accompanied by lymphoplasmacytic infiltration and urothelial denudation, whereas bladder pain syndrome shows little pathological changes in the bladder. Pathophysiology would also differ between Hunner-type interstitial cystitis and bladder pain syndrome, involving interaction of multiple factors, such as inflammation, autoimmunity, infection, exogenous substances, urothelial dysfunction, neural hyperactivity and extrabladder disorders. The patients should be treated differently based on the diagnosis of Hunner-type interstitial cystitis or bladder pain syndrome, which requires cystoscopy to determine the presence or absence Hunner lesions. Clinical studies are to be designed to analyze outcomes separately for Hunner-type interstitial cystitis and bladder pain syndrome.

TAXONOMIES FOR CHRONIC VISCERAL PAIN.

Häuser W, Baranowski A, Messelink B, Wesselmann U. *Pain*. 2020 Feb 5. doi: 10.1097/j.pain.0000000000001825. [Epub ahead of print] PMID: 32032194

According to the authors, in the past, pain associated with viscera has typically been considered as a symptom of visceral disease. It was only more recently that the medical specialties of gynecology, gastroenterology, and urology have recognized that visceral pain can be a pain syndrome in its own right. As visceral pain has been recognized as a chronic pain syndrome, which often occurs as a comorbid condition together with other chronic pain syndromes, several medical and scientific associations have developed taxonomies for specific visceral pain conditions.

PLACEBO EFFECT

CAN WE HARNESS THE PLACEBO EFFECT TO IMPROVE CARE IN LOWER URINARY TRACT DYSFUNCTION? ICI-RS 2019.

Khullar V, Rahnama'i MS, Veit-Rubin N, Cardozo L, Wein AJ. *Neurourol Urodyn*. 2020 Apr 20. doi: 10.1002/nau.24351. [Epub ahead of print] PMID: 32311166

The proposal "Can we harness the placebo effect to improve care in lower urinary tract dysfunction?" was discussed at the International Consultation on Incontinence-Research Society (ICI-RS) 2019 meeting. The placebo effect can change the treatment outcome whether the treatment is an active treatment or placebo. The total active treatment outcome is a combination of the placebo and the active treatment effect which is seen in placebo-controlled trials. The placebo effect plays an important role in the treatment of lower urinary tract dysfunction in overactive bladder, bladder pain syndrome, and stress urinary incontinence. In clinical practice, a number of factors can be employed to use the placebo effect to maximize its effect on patients receiving an active treatment, such as having the same environment for review such as the same appointment time, same room, and same clinician. Clinicians should also be aware of the nocebo effect which is increased with an overemphasis on side effects or negative outcomes.

KETAMINE-INDUCED UROPATHY

WHAT UROLOGISTS NEED TO KNOW ABOUT KETAMINE-INDUCED UROPATHY: A SYSTEMATIC REVIEW.

Castellani D, Pirola GM, Gubbiotti M, Rubilotta E, Gudaru K, Gregori A, Dellabella M. *Neurourol Urodyn*. 2020 Apr;39(4):1049-1062. doi: 10.1002/nau.24341. Epub 2020 Mar 25. PMID: 32212278

Ketamine is a general anesthetic. Dissociative effects and low cost led ketamine becoming an illegal recreational drug in young adults. Ketamine-induced uropathy (KIU) is one of the complications observed in abusers. This

study from Italy and the UK aimed to provide a systematic literature review on KIU clinical presentation, pathophysiology, and treatments. Castellani and colleagues performed the literature search in PubMed, Web of Science, Scopus, and Embase using the terms ketamine and bladder. English papers on human and animal studies were accepted. A total of 75 papers were selected. Regular ketamine users complain about severe storage symptoms and pelvic pain. Hydronephrosis may develop in long-term abusers and is correlated to the contracted bladder, ureteral stenosis, or vesicoureteral reflux due to ureteral involvement and/or bladder fibrosis. Cystoscopy shows ulcerative cystitis. Ketamine in urine might exert direct toxicity to the urothelium, disrupting its barrier function and enhancing cell apoptosis. The presence of ketamine/ions in the bladder wall result in neurogenic/IgE-mediated inflammation, stimulation of the inducible nitric oxide synthase-cytokines-cyclooxygenase pathway with persistent inflammation and fibrosis. Abstinence is the first therapeutic step. Anti-inflammatory drugs, analgesics and anticholinergics, intravesical instillation of hyaluronic acid, hydrodistension and intravesical injection of botulin toxin-A were helpful in patients with early-stage KIU. In patients with end-stage disease, the control of intractable symptoms and the increase of bladder capacity were the main recommendations to perform augmentation enterocystoplasty. It was concluded that KIU is becoming a worldwide health concern, which should be taken into account in the differential diagnosis of ulcerative cystitis.

PUDENDAL NEURALGIA

[BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS DUE TO PUDENDAL NERVE COMPRESSION: DESCRIBED IN 1915-A REMINDER FOR TREATING PELVIC PAIN A CENTURY LATER.](#)

Gohritz A, Dellon AL. *J Brachial Plex Peripher Nerve Inj.* 2020 Mar 6;15(1):e5-e8. doi: 10.1055/s-0039-1700538. eCollection 2020 Jan. PMID: 32153650

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Interstitial cystitis (IC) or bladder pain syndrome (BPS) is highly painful and disabling and probably the most misdiagnosed urologic condition. Its classic symptoms of perineal pain, urinary urgency, and frequency despite sterile urine cultures were already described more than a century ago in a report on soldiers during World War (WW) I due to chronic pudendal nerve compression. This article translates a report from 1915 on pudendal neuropathy and discusses its author Georg Zülzer (1870-1949). An English translation of the German original is provided with the biography and work of Zülzer, his clinical observations are discussed regarding modern diagnosis and therapy of pudendal nerve compression. In his article entitled "Irritation of the Pudendal Nerve (Neuralgia). A Frequent Clinical Picture during War Feigning Bladder Catarrh," Zülzer describes his observation of soldiers during WW I, presenting with a triad of perineal pain, urinary urgency, and frequency despite sterile urine cultures excluding urinary infections. He also documented a characteristic skin hypersensitivity of the perineum in a rhomboid shape which corresponds to the innervation area of the pudendal nerve with its two branches deriving from the "pudendal plexus." He regards this symptomology as rare during peace, but as disease of trench warfare which can be easily diagnosed regarding clear urine and a painful skin island overlying the area of the pudendal nerve as tested by simple needle examination. Zülzer, born in Germany, was forced to emigrate to the United States in 1934, was also an important pioneer of diabetes research using pancreas extracts from dogs as early as 1907. Conclusion In this historical description, dating from about a century ago, Georg Zülzer probably gave the first exact clinical description of symptoms due to pudendal nerve compression. Pudendal nerve compression should always be taken into account when examining and treating patients with symptoms of IC/BPS.

[ESTIMATE OF THE PROPORTION OF UNCERTAIN DIAGNOSES OF PUDENDAL NEURALGIA IN WOMEN WITH CHRONIC PELVIC-PERINEAL PAIN: A SYSTEMATIC REVIEW WITH A DESCRIPTIVE DATA SYNTHESIS.](#)

Indraccolo U, Nardulli R, Indraccolo SR. *Neurourol Urodyn.* 2020 Feb 5. doi: 10.1002/nau.24303. [Epub ahead of print] PMID: 32022321

There is a gap between pudendal neuralgia (PN) due to pudendal entrapment syndrome and PN without pudendal entrapment syndrome. The latter could have atypical symptoms. The objective was to define a rate of atypical PN from a clinical series of female patients with chronic pelvic-perineal pain. The atypical PN was defined as a pain not meeting clinical criteria for pudendal entrapment syndrome. The effect size was the rate of atypical PN. Such a rate was expected to be found among patients screened for enrollment in clinical series on pudendal neuropathic pain. A systematic search was performed looking for clinical series on PN. Studies must report information on female patients, pelvic-perineal pain, at least a clinical criterion for diagnosing the pudendal neurogenic origin of pain, the proportion of patients with pain not meeting the clinical criterion/a for diagnosing the pudendal entrapment pain. From 2637 references, nine studies were included for qualitative analysis. Three of them were not suitable for data synthesis: one assessed the rate of PN after hip arthroscopy; second enrolled

miscellaneous patients, a third investigated patients with gynecological diseases. Six studies involved patients with suspicion of pudendal entrapment symptoms (205 patients observed), allowing data synthesis. One of these series was judged as being of good quality. The overall rate of atypical PN is 0.013 (95% confidence interval, 0.008-0.021), 1.2%. Further analysis suggests the risk of bias for all studies. It was concluded that atypical PN in females is low when clinical criteria for pudendal entrapment syndrome are applied.

FIBROMYALGIA

THE FIBROMYALGIA BLADDER INDEX IN 100 CONSECUTIVE WOMEN WITH FIBROMYALGIA.

Hamed N, Rida MA, Uthman I, El Taha L, Assad M, Mikhael E, Bazi T. *Int Urogynecol J.* 2020 Jan 9. doi: 10.1007/s00192-019-04199-y. [Epub ahead of print] PMID: 31919557

The Fibromyalgia Bladder Index (FBI) is a validated instrument to quantify bothersome bladder symptoms specifically in women with fibromyalgia syndrome (FMS). The FBI includes two sub-scales: one addressing urinary urgency and bladder pain (UP), the other addressing urinary frequency and nocturia (FN). The objectives of this study were to evaluate the FBI in a cohort of patients with FMS, to correlate it with certain characteristics in this cohort, and to compare it with controls. Hamed and colleagues performed a case-control study of 100 women with FMS and 155 controls. Demographic data, comorbidities, and other characteristics were registered. Comparison between FBI scores of participants with and without FMS, as well as correlation of FBI scores with the characteristics of FMS patients, were undertaken using independent two-sample t test for continuous outcomes and Pearson's Chi-squared test for categorical outcomes. The mean UP subscale score of the FBI was significantly higher in the FMS group compared with the controls. The mean FN subscale score was significantly higher in the FMS group compared with the controls. FMS patients diagnosed >3 years ago had a higher UP subscale score and a higher FN subscale score compared with FMS patients diagnosed <3 years ago. Menopause and parity significantly increased the FBI scores. Smoking and a history of depression did not significantly affect any of the FBI subscale scores in the FMS group. It was concluded that women with FMS suffer from bothersome bladder symptoms that can be readily identified and quantified.

VULVODYNIA

THE INTERNATIONAL CLASSIFICATION OF DISEASES, 11TH REVISION: A STEP-BACK FOR WOMEN WITH VULVODYNIA?

Radici G, Preti M, Vieira-Baptista P, Stockdale CK, Bornstein J. *J Low Genit Tract Dis.* 2020 Feb 14. doi: 10.1097/LGT.0000000000000513. [Epub ahead of print] PMID: 32068619

The aim of the study was to compare the International Classification of Diseases, 11th revision, (ICD-11) with current terminology of vulvodynia, approved by a broad-based consensus of the International Society for the Study of Vulvovaginal Disease (ISSVD), the International Society for the Study of Women Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS). The diagnostic criteria and descriptions of vulvodynia as well as the definition and classification of chronic pain in ICD-11 were reviewed and compared with the Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia, endorsed in 2015 by the ISSVD, ISSWSH, and IPPS. Diagnostic criteria and descriptors of vulvodynia in the ICD-11 are outdated. Moreover, vulvodynia is not identified among chronic pain diagnoses, despite fulfilling the diagnostic criteria of chronic primary pain. Specifically, vulvodynia is a vulvar pain of at least 3-month duration, which is associated with significant emotional distress and functional disability and is not better accounted for by another specific condition. It was concluded that the ICD-11 is not aligned with current vulvodynia diagnostic criteria and terminology, approved by the ISSVD, ISSWSH, and IPPS. Collaboration among the International Association for the Study of Pain Task Force on Classification of Chronic Pain, ICD team, ISSVD, ISSWSH, and IPPS is needed to harmonize terminologies, codes, and clinical approach regarding vulvar pain and vulvodynia classification.

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