

International Painful Bladder Foundation

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

IPBF e-Newsletter and Research Update

Issue 42, May 2016

An IPBF update 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:

- IC/BPS in India: 2016 a year of activity
- Meeting Reviews
 - IAPO 7th Global Patients Congress held 9-11 April 2016
 - PAE General Assembly 23 February 2016
- Global Pain Management Survey
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IC/BPS IN INDIA: 2016 A YEAR OF ACTIVITY

IC/BPS LOCAL FOCUS MEETING IN MUMBAI: 27-28 AUGUST 2016

A meeting of clinicians across various specialties including Urologists, Gynecologists, Internists and pain experts will be held 27-28 August 2016 at Hotel Orchid in Mumbai, India as a first of its kind. Around one hundred delegates are expected, mostly by invitation, and will include interested medical professionals from India and neighbouring countries. This focus meeting is hoped to raise awareness of IC/BPS together with its diagnosis and treatment among local clinicians, and also to pave the way for the upcoming ESSIC (www.essic.eu) Annual Meeting and Conference on IC/BPS to be held in New Delhi, India 17-19 November 2016. The Mumbai IC/BPS event is being sponsored by Swati Spentose Pvt Limited, manufacturers of Pentosan Polysulfate (PPS), also a main sponsor of ESSIC 2016 in New Delhi.

ESSIC ANNUAL MEETING: NEW DELHI, 17-19 NOVEMBER 2016. PRELIMINARY INFORMATION

The International Society for the Study of BPS (ESSIC) will be holding its annual meeting this year in New Delhi 17-19 November. This should give a further boost to awareness and expertise throughout India with its huge population of 1.3 billion. Further information about this meeting will be made available on the ESSIC website: www.essic.eu.

PATIENT SUPPORT NEWS FROM INDIA

We have encouraging news from India where Balaka Basu from Mumbai is working hard on setting up a patient support group with welcome help and support from urologist Dr Nagendra Mishra who has been active in the

field of IC for many years, Dr Vishal Jajodia from Comfora, and urologist Dr Attar Mohammad Ismail. “In India awareness about IC is still poor and my mission is to spread awareness regarding IC among common people, IC patients and doctors especially gynecologists and general physicians to whom IC patients go first”, she says. As awareness among these doctors is still inadequate, most IC cases remain either undiagnosed or misdiagnosed. Her first step in creating IC awareness was to set up a blog <http://interstitialcystitis-india.blogspot.in/> dealing with the different aspects of IC, including symptoms, diagnosis, treatment, ways to deal with IC including diet specifically geared to Indian patients and will also include sexual aspects. Balaka is also using the blog to interview doctors, not only urologists but also pain management specialists, sexologists, dietitians etc. An interview with Dr Nagendra Mishra can be found at <http://interstitialcystitis-india.blogspot.in/2016/03/Interstitial-Cystitis-Specialist-India.html>. Work is currently in progress with the help of sponsors on a website for patients and short videos to raise awareness. Balaka is in the process of creating a database of IC patients in India. Email: icindiaorg@gmail.com.

MEETING REVIEWS

INTERNATIONAL ALLIANCE OF PATIENTS ORGANIZATIONS (IAPO) 7th GLOBAL PATIENTS CONGRESS HELD 9-11 APRIL 2016

IAPO is an umbrella organization, based on London, with some 250 members from 67 countries representing 47 diseases areas. www.iapo.org.uk

The IAPO 7th Global Patients Congress was held 9-11 April 2016 at the historic Selsdon Park Hotel, Croydon, UK and brought together patient advocates from 48 countries worldwide, representing a wide variety of patients, and varying from the most developed to the most underdeveloped countries and regions. This of course leads to a wide variation in priorities: while developed countries are concerned that their patients may not be able to obtain reimbursement for the most expensive drugs, the underdeveloped countries are concerned that patients cannot obtain medicine at all, may have no access to a doctor and may be relying on traditional practices and magic!

The many topics included universal health coverage from the WHO, patient empowerment and patient centricity, improving health literacy, sharing decision-making between the patient/consumer and health professionals, collaboration between all stakeholders including the patients.

We heard that the European Medicines Agency (EMA) - the EU regulatory body responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union – is steadily increasing concrete involvement by patients/consumers and their organizations in its activities and projects. While the World Health Organization (WHO) is now also promoting patient participation, congress delegates felt that this was still at a theoretical level rather than effective, meaningful participation. Delegates would like far more patient involvement in the International Classification of Diseases (ICD-11). IPBF chair Jane Meijlink also spoke on the need for patient representatives to be involved in development of clinical guidelines and standardisation of terminology and definitions in order to ensure that these are a true reflection of all the key components of a disease or complaint and cannot cause the patient any harm at any point along the healthcare chain.

Everyone agreed that patient representatives ideally need some kind of training or guidelines to help them participate in a meaningful way and to understand what the patient specifically needs to be on the alert for. The EMA is already doing this and provides an excellent example.

The congress also provided practical information and case studies given by patient representatives, often very moving and reminding us why we were all there.

- Data protection, electronic medical records, “apps” and online healthcare – patients and their organisations must be on their guard

One of the issues repeatedly raised throughout the congress by attendees was that of data protection, in relation not only to electronic medical records but also the huge surge in “apps” for patient use and the new concept of online healthcare. Is there any control over who sees and uses this medical/health information, we asked? And who actually owns the information? The answer seemed to be that legislation is lagging behind the rapid developments in this field. Delegates asked IAPO to look into this on their behalf. However, national support groups would do well to check this out in their own countries. Forewarned is forearmed. And when

patient organisations are offered “apps” for their members, they should make a point of asking who could have access to any personal data entered and checking this out very carefully indeed.

Some slide presentations by patients, academics and health experts are now available on the IAPO website: <https://www.iapo.org.uk/gpc-presentations>. Click here if you would like to take a look at the [Congress Handbook](#).

PAIN ALLIANCE EUROPE www.pae-eu.eu

GENERAL ASSEMBLY MEETING HELD ON 23 FEBRUARY 2016

Member Organisations of Pain Alliance Europe (PAE), including the IPBF, were represented at ITS General Assembly on 23 February 2016 at the Thon EU Hotel in Brussels. The member representatives and board members were also joined by a number of stakeholders and sponsors from industry and elsewhere.

Classification of chronic pain for ICD-11: Rolf-Detlef Treede, MD, president of the International Association for the Study of Pain (IASP), gave a presentation on classification of chronic pain for ICD-11. His aim is for the IASP to increase collaboration with patients’ associations in the field of pain. This was certainly welcome news and we look forward to this taking concrete shape.

There was also a presentation about the Societal Impact of Pain (SIP) Platform and the upcoming SIP Symposium 23-24 May 2016 in Brussels which members were encouraged to attend. The SIP is a European platform which provides opportunities for discussion and exchange of information for healthcare professionals, pain and advocacy groups, politicians, insurance companies, health authority representatives, regulators and budget holders. Anyone wishing to attend should contact info@pae-eu.eu or www.sip-platform.eu.

PATIENT SURVEY – GLOBAL PAIN MANAGEMENT SURVEY

INTERNATIONAL PAIN MANAGEMENT NETWORK (IPMN) PATIENT SURVEY

A reminder about the pain survey developed by the International Pain Management Network (IPMN) to gain a better understanding how pain is assessed, treated and viewed by others. The survey will take about ten minutes to complete. Thank you for your help. Please click here to begin the survey: https://www.surveymonkey.com/r/IPM_Network_Survey

FOCUSING ON FIBROMYALGIA

NIH NEWS IN HEALTH: FOCUSING ON FIBROMYALGIA - A PUZZLING AND PAINFUL CONDITION

The February 2016 issue of NIH News in Health focused on fibromyalgia with a useful fact sheet of basic information, with a list of “Wise Choices” or tips for living with fibromyalgia.

“Fibromyalgia can take a powerful toll on health, well-being, and quality of life. “People with fibromyalgia suffer from severe, daily pain that is widespread throughout the body,” says Dr. Leslie J. Crofford, an NIH-supported researcher at Vanderbilt University. “Their pain is typically accompanied by debilitating fatigue, sleep that does not refresh them, and problems with thinking and memory.”“

Read more: <https://newsinhealth.nih.gov/issue/Feb2016/feature2>

HEALTH LITERACY

UROLOGY TIMES: LOW HEALTH LITERACY IS COMMON, BUT CAN BE ADDRESSED

In Urology Times 24/3/2016, Lisa Kerr, PA-C addressed the issue of health literacy and how common this is, even in the developed world. This article can be read at: <http://urologytimes.modernmedicine.com/urology-times/news/low-health-literacy-common-can-be-addressed>

While this article is aimed at health professionals, it also raises the question: are we taking low health literacy, low literacy in general and illiteracy sufficiently into account in the field of IC/BPS when it comes to providing information for patients? How many patient organizations have information available (cartoons, videos) for illiterate/low literacy populations?

BOOKS

CONSUMER'S HANDBOOK OF UROLOGICAL HEALTH, A GUIDEBOOK FOR PATIENTS AND THEIR FAMILIES.

Published by the Canadian Urological Association, www.cua.org

A handbook full of useful information for every patient with urological problems. IC/BPS is not forgotten either. Pages 83-91 are devoted to a chapter on "What to do if your doctor says you have interstitial cystitis" by urologist Dr R.B. Egerdie with a down-to-earth look at symptoms, diagnosis and treatment. Perfect for the patient.

Email: corporate.office@cua.org

PRACTICAL FUNCTIONAL UROLOGY - GUIDE TO THE DIAGNOSIS AND TREATMENT OF FUNCTIONAL DISORDERS FOR UROLOGISTS, UROGYNECOLOGISTS, AND OTHERS

Editors: Heesakkers J, Chapple C, De Ridder D, Farag F.

ISBN 978-3-319-25428-9

Published by: Springer International Publishing Switzerland 2016

Diagnosis and treatment are presented for a variety of conditions, including overactive bladder, detrusor underactivity, painful bladder syndrome/interstitial cystitis, prostatitis, stress urinary incontinence, pelvic organ prolapse, urinary tract infections, and urethral disorders. Chapter 4 (Pages 69-87) deals with "Bladder Pain Syndrome/Interstitial Cystitis: A Large but Heterogeneous Field in Functional Urology", written by David Castro-Diaz and Magnus Fall. This provides a clear overview of diagnosis and treatment with a detailed section on cystoscopy and the Hunner lesion. [Click here](#) for more information.

JOURNAL PUBLICATIONS

FREE OPEN ACCESS JOURNAL SUPPLEMENT REMINDERS

Open access articles and supplements are an ideal way for patients and their organizations to stay up to date with scientific developments in the field of IC/BPS and associated conditions.

- TRANSLATIONAL ANDROLOGY AND UROLOGY (TAU)

SUPPLEMENTS FOCUSED ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: PART I AND PART II

PART I: TRANSLATIONAL ANDROLOGY AND UROLOGY VOL 4, NO 5 (OCTOBER 2015),

<http://www.amepc.org/tau/issue/view/362>. This link takes you to an overview of the articles with open access to HTML or pdf.

PART II: TRANSLATIONAL ANDROLOGY AND UROLOGY VOL 4, NO 6 (DECEMBER 2015)

<http://tau.amegroups.com/issue/view/374> This link takes you to an overview of the articles with open access to HTML or pdf.

- INTERNATIONAL JOURNAL OF UROLOGY

**Special Issue: 3rd International Consultation on Interstitial Cystitis Japan (ICICJ) and International Society for the Study of Bladder Pain Syndrome (ESSIC) Joint Meeting, 21–23 March 2013, Kyoto, Japan
April 2014**

Volume 21, Issue Supplement S1 Pages 1–88, i–vi, A1–A25

Direct link: <http://onlinelibrary.wiley.com/doi/10.1111/iju.2014.21.issue-s1/issuetoc>

- PELVIPERINEOLOGY OPEN ACCESS JOURNAL: SPECIAL ISSUE PLANNED ON CHRONIC PELVIC AND PERINEAL PAIN. CALL FOR PAPERS FROM BOTH MEDICAL PROFESSIONALS AND PATIENT ADVOCATES

Pelviperineology Journal is an open access multidisciplinary pelvic floor journal for a wider approach to chronic pelvic pain.

Pelvipерineology Journal (<http://www.pelvipерineology.org/>) will be publishing a special scientific issue devoted to chronic pelvic and perineal pain including IC/BPS and vulvodynia. The aim of this issue is to bring together all point of views on pelvic and perineal pain, in the same forum, to motivate open-minded debate and unbiased research on the subject. The editors encourage the submission of both original research and review papers on etiology, pathophysiology, diagnostic methods and treatment from medical professionals and patient advocates. All papers will be peer reviewed. Deadline estimated around beginning 2017.

Editorial committee: Prof. Marc Possover, Prof. Paulo Palma, Prof. Mauro Cervigni, Dr Nucelio Lemos, Prof. Michael Hibner, Prof. Juan Diego Villegas, Prof. Jacob Bornstein, Prof. Peter Petros, Dr Darren Gold.

Expressions of interest should be addressed to Prof. Peter Petros pp@kvinno.com

CALENDAR OF UPCOMING EVENTS

SOCIETAL IMPACT OF PAIN (SIP) SYMPOSIUM 2016 “Time for Action”

The SIP Symposium 2016 will be held 23-24 May 2016 in Brussels, Belgium.

On 23 May, this will take place in the European Parliament, Brussels, and on 24 May at Concert Noble, Rue d’Arlon 82-84, Brussels. This symposium is ideal for anyone involved in pain policy e.g. healthcare professionals, politicians, representatives of pain advocacy groups, insurances, health authorities, regulators and budget holders. Topics discussed will include:

1. pain as a quality indicator for healthcare
2. chronic pain: a disease or multi-morbidity?
3. the relevance of pain in cancer care and rehabilitation
4. pain, rehabilitation and reintegration of workers in the workforce.

Further information: www.sip-platform.eu

IC/BPS LOCAL FOCUS MEETING IN MUMBAI: 27-28 AUGUST 2016

A meeting of clinicians across various specialties including Urologists, Gynecologists, Internists and pain experts will be held 27-28 August 2016 at Hotel Orchid in Mumbai, India.

INTERNATIONAL CONTINENCE SOCIETY (ICS) ANNUAL SCIENTIFIC MEETING + 6TH INTERNATIONAL CONSULTATION ON INCONTINENCE (ICI)

13-16 September 2016, in Tokyo, Japan.

The ICS annual scientific forum is increasingly becoming an important platform for chronic pelvic pain and IC/BPS and its 2016 meeting will include a number of sessions on IC/BPS. The 2016 meeting will be combined with the 6th International Consultation on Incontinence with sessions on many different conditions, including a session on IC/BPS chaired by Philip Hanno, MD. <http://www.ics.org/2016>.

CONVERGENCES PP 2016 – CONVERGENCES IN PELVIPERENEAL PAIN

International meeting on chronic pelvic and abdominal pain, 15/16/17 September 2016, Palais des Congres, Aix en Provence, France. Simultaneous translation French/English/Spanish. Includes a 2 hour session on IC/BPS.

www.convergencespp.com

3RD GLOBAL CONGRESS ON LUTD

22 - 23 September 2016 - Vienna, Austria, <http://lutd.org/>

16TH WORLD CONGRESS ON PAIN

The IASP World Congress on Pain, 26–30 September, 2016, Yokohama, Japan

<http://www.iasp-pain.org/Yokohama?navItemNumber=593>

ESSIC ANNUAL MEETING 2016

Preliminary information: ESSIC (International Society for the Study of IC/BPS) will hold its 2016 Annual Meeting in New Delhi, India, 17-19 Nov 2016. www.essic.eu.

1ST MEETING OF THE SOCIETY FOR PELVIC RESEARCH

Preliminary information: December 2-3, 2016. Tentative location is Charleston, SC. Save the date!
website <https://www.pelvicresearch.com/>

3RD WORLD CONGRESS ON ABDOMINAL AND PELVIC PAIN (WCAPP)

Preliminary information: 12-15 October 2017, Washington DC, USA

RESEARCH HIGHLIGHTS

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND RELATED DISORDERS

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

***Terminology:** different published articles use different terminology, for example: interstitial cystitis, painful bladder syndrome, bladder pain syndrome, hypersensitive bladder, chronic pelvic pain (syndrome) or combinations of these. Hunner's ulcer, Hunner lesion and Hunner Disease 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

[INFLAMMATION AND SYMPTOM CHANGE IN INTERSTITIAL CYSTITIS OR BLADDER PAIN SYNDROME: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN RESEARCH NETWORK STUDY.](#)

Schrepf A, O'Donnell MA, Luo Y, Bradley CS, Kreder KJ, Lutgendorf SK. Urology. 2016 Apr;90:56-61. doi: 10.1016/j.urology.2015.12.040. Epub 2016 Jan 6. PMID: 26768711

The purpose of this study from the MAPP Network was to explore inflammatory factors that influence symptom changes in interstitial cystitis or bladder pain syndrome (IC or BPS). This longitudinal, prospective study examined the association of inflammation elicited by Toll-like receptor (TLR) stimulation in peripheral blood mononuclear cells (PBMCs) and diurnal cortisol rhythms with changes in painful and urinary symptoms of IC or BPS and symptom flares over a 48-week period. Participants were 24 women meeting criteria for IC or BPS who supplied blood for isolation of PBMCs and 3 days of salivary cortisol samples prior to a baseline visit. Participants completed the Genitourinary Pain Index (pain and urinary subscales) and reported symptom flares every 2 weeks for 48 weeks. Mixed effects longitudinal and regression models were used to determine if inflammatory variables were associated with the changes in IC or BPS symptoms (time × variable interactions), and the probability of a symptom flare. The authors found that elevated TLR-4 inflammation and elevated TLR-2 inflammation from PBMCs, and flattened diurnal cortisol slope were each associated with less improvement in genitourinary pain over time. Additionally, elevated TLR-4 inflammation was associated with less improvement in urinary symptoms, whereas TLR-2 inflammation and cortisol slopes were not. In contrast, no inflammatory measure was associated with an increased likelihood of reporting a symptom flare. It was concluded that TLR-mediated inflammation and diurnal cortisol slope may be useful as markers of symptom changes in IC or BPS.

[ALTERATIONS IN CONNECTIVITY ON FUNCTIONAL MAGNETIC RESONANCE IMAGING WITH PROVOCATION OF LOWER URINARY TRACT SYMPTOMS: A MAPP RESEARCH NETWORK FEASIBILITY STUDY OF UROLOGICAL CHRONIC PELVIC PAIN SYNDROMES.](#)

Kleinhans NM, NM, Yang CC, Strachan ED, Buchwald DS, Maravilla KR. J Urol. 2016 Mar;195(3):639-45. doi: 10.1016/j.juro.2015.09.092. Epub 2015 Oct 22. PMID: 26497778

Urological chronic pelvic pain syndromes have refractory bladder or pelvic pain as the dominant symptom. This has been attributed to changes in the central nervous system caused by a chronic barrage of noxious stimuli. Kleinhans and colleagues developed what is to our knowledge a novel challenge protocol that induced bladder distention in study participants to reproduce pain and urinary symptoms. They tested to see whether it could discriminate between persons with urological chronic pelvic pain syndrome-like symptoms and asymptomatic controls. They recruited 10 female twin pairs who were discordant for urological chronic pelvic pain syndrome-like symptoms. Before scanning each twin urinated to completion and then consumed 500 cc water. Each twin was scanned with their resting state functional magnetic resonance imaging protocol immediately and approximately 50 minutes after consumption. Time series were extracted from the right and left periaqueductal gray, and the right and left amygdala subregions. They performed the repeated measures 2-sample t-test to assess differences in connectivity between symptomatic and asymptomatic twins before and after bladder distention. Group by condition interaction effects were found from the periaqueductal gray to the right cerebellum VIIIa, the amygdala, the right premotor cortex/supplementary motor area and the insular cortex, and between the amygdala and the frontal pole/medial orbital frontal cortex, the hypothalamus, the insular cortex, the thalamus and the anterior cingulate cortex. These findings demonstrate that the authors' noninvasive bladder distention protocol can detect differences in the processing of urinary sensation between twins discordant for lower urinary tract pain.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

MINDFULNESS-BASED STRESS REDUCTION AS A NOVEL TREATMENT FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A RANDOMIZED CONTROLLED TRIAL.

Kanter G, Komesu YM, Qaedan F, Jeppson PC, Dunivan GC, Cichowski SB, Rogers RG. Int Urogynecol J. 2016 Apr 26. [Epub ahead of print] PMID: 27116196

Mindfulness-based stress reduction (MBSR) is a standardized meditation program that may be an effective therapy for interstitial cystitis/bladder pain syndrome (IC/BPS), a condition exacerbated by stress. The aims of this study from New Mexico USA were to explore whether MBSR improved IC/BPS symptoms and the feasibility/acceptability of MBSR among women with IC/BPS. This randomized controlled trial included women with IC/BPS undergoing first- or second-line therapies. Women were randomized to continuation of usual care (UC) or an 8-week MBSR class + usual care (MBSR). Participants completed baseline and 8-week post-treatment questionnaires, including the O'Leary-Sant Symptom Problem Index (OSPI), the visual analog pain scale (VAS), the Short Form Health Survey (SF-12), the Female Sexual Function Index (FSFI), and the Pain Self-Efficacy Questionnaire (PSEQ). The Global Response Assessment (GRA) was completed post-treatment. Analyses were performed using Student's t test, Chi-squared, and MANOVA where appropriate. Eleven women were randomized to UC and 9 to MBSR, without differences in group characteristics. More MBSR participants' symptoms were improved on the GRA (7 out of 8 [87.5 %] vs 4 out of 11 [36.4 %], $p = 0.03$). The MBSR group showed greater improvement in the OSPI total ($p = 0.0498$) and problem scores ($p = 0.036$); the OSPI symptom score change did not differ. PSEQ scores improved in MBSR compared with UC ($p = 0.035$). VAS, SF-12, and FSFI change did not differ between groups. Eighty-six percent of MBSR participants felt more empowered to control symptoms, and all participants planned to continue MBSR. It was concluded that this trial provides initial evidence that MBSR is a promising adjunctive therapy for IC/BPS. Its benefit may arise from patients' empowerment and ability to cope with symptoms.

CLINICAL PHENOTYPING DOES NOT DIFFERENTIATE HUNNER'S LESION SUBTYPE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS): A RELOOK AT THE ROLE OF CYSTOSCOPY.

Doiron RC, Tolls V, Irvine-Bird K, Kelly KL, Nickel JC. J Urol. 2016 Apr 23. pii: S0022-5347(16)30286-5. doi: 10.1016/j.juro.2016.04.067. [Epub ahead of print] PMID: 27117441

Identification of Hunner's lesions in IC/BPS patients presents an opportunity for objective classification into those with Hunner's lesion IC/BPS (classic IC) and those with non-Hunner's lesion BPS. While currently a diagnosis of Hunner's lesion IC/BPS requires cystoscopy, limited data exists suggesting that these subtypes can be distinguished without endoscopic examination based on the degree of bladder-focused centricity and infrequent association with generalized pain conditions. In this study by Doiron and colleagues from Queens University, Kingston, Canada, patients from a prospective single-center database of IC/BPS patients who had

documented cystoscopic findings were categorized as those with Hunner's lesion IC/BPS and non-Hunner's lesion BPS. Their demographics, pain and symptom scores, voiding symptoms, presence of IBS, and clinical UPOINT scoring were comparatively analyzed. A total of 469 patients were reviewed. Of those, 359 had documented local anesthetic cystoscopic findings; 44 (12.3%) with Hunner's lesion IC/BPS and 315 (87.7%) with non-Hunner's BPS. Patients with Hunner's lesions were older ($p=0.004$), had greater urinary frequency ($p=0.013$), more nocturia ($p=0.0004$) and higher ICSI scores ($p=0.017$). Prevalence of Hunner's lesions was significantly higher in those <50 years old (7.8%) compared to those aged 50 and older (14.9%; $p=0.0095$). There was no difference in number of UPOINT phenotype domains reported, overall UPOINT scores or prevalence of IBS between the groups. A subtype of IC with Hunner's lesions has worse bladder-centric symptoms, but did not have a distinct bladder-centric phenotype. Given the management implications of distinguishing classic IC from non-Hunner's lesion BPS, the authors recommend cystoscopy with local anesthesia for patients diagnosed with IC/BPS.

INVESTIGATIONAL DRUGS FOR BLADDER PAIN SYNDROME (BPS) / INTERSTITIAL CYSTITIS (IC).

Chuang YC, Chermansky C, Kashyap M, Tyagi P. Expert Opin Investig Drugs. 2016 May;25(5):521-9. doi: 10.1517/13543784.2016.1162290. Epub 2016 Mar 22. PMID: 26940379

Bladder pain syndrome (BPS)/interstitial cystitis (IC) is associated with sensory lower urinary tract symptoms. Unfortunately, many of the existing oral treatments are ineffective in most patients of BPS/IC, which is the motivation for developing new drugs and therapeutic approaches. This review from a team from Taiwan and Pittsburgh covers the latest drugs that have been investigated in BPS/IC patients. Intravesical treatments offer the opportunity to directly target the painful bladder with less systemic side effects. In this review, the authors analyze the existing literature supporting the treatment of BPS/IC with conventional drugs including heparin, hyaluronic acid, chondroitin sulfate, and dimethylsulfoxide (DMSO). Furthermore, investigational drugs such as tanezumab and adalimumab, capable of sequestering nerve growth factor (NGF), and Tumor necrosis factor- α (TNF- α) are discussed. Investigational treatments such as liposomes, botulinum toxin (BTX), liposomal BTX, PD-0299685 (a Ca(2+) channel $\alpha 2\delta$ ligand), continuous intravesical lidocaine, and AQX-1125 (a novel SHIP1 activating compound) are also covered. New investigational drugs offer promising improvements in clinical outcomes for BPS/IC patients; however, BPS/IC is a chronic pain disorder that is very vulnerable to a strong placebo effect. In addition, BPS/IC is a heterogeneous disorder that can be classified into several phenotypes. Since different phenotypes of BPS/IC respond differently to systemic and intravesical treatments, the authors believe that new drugs developed for BPS/IC are more likely to meet their predetermined clinical endpoints if the inclusion/exclusion criterion is tailored to specific phenotype of BPS/IC patients.

URINE TROUBLE: ALTERATIONS IN BRAIN FUNCTION ASSOCIATED WITH BLADDER PAIN.

Sadler KE, Kolber BJ. J Urol. 2016 Feb 22. pii: S0022-5347(16)00365-7. doi: 10.1016/j.juro.2015.10.198. [Epub ahead of print] PMID: 26905019

Chronic bladder pain is a debilitating condition often accompanied by alterations in affective and autonomic function. Many symptoms associated with chronic bladder pain are mediated by the central nervous system. In this review data from preclinical animal models and human neuroimaging studies were analyzed and a theoretical supraspinal bladder pain network was generated. The two authors comprehensively reviewed the literature using PubMed® and Google Scholar™. Relevant reviews and original research articles, and the cited references were summarized and then organized on a neuroanatomical basis. The brain loci the most predominant in the bladder pain literature are the thalamus, parabrachial nucleus, cerebral cortex, amygdala, hypothalamus, periaqueductal gray and rostral ventromedial medulla. This review highlights each of these regions, discussing the molecular and physiological changes that occur in each in the context of bladder pain. They concluded that a complex network of brain loci is involved in bladder pain modulation. Studying these brain regions and the changes that they undergo during the transition from acute to chronic bladder pain will provide novel therapeutic strategies for patients with chronic bladder pain diseases such as interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome.

THE LOCATION OF PAIN AND URGENCY SENSATIONS DURING CYSTOMETRY.

Veit-Rubin N, Cartwright R, Esmail A, Digesu GA, Fernando R, Khullar V. NeuroUrol Urodyn. 2016 Feb 16. doi: 10.1002/nau.22975. [Epub ahead of print] PMID: 26879227

The relationship between bladder pain and urinary urgency sensations is poorly understood. Veit-Rubin and colleagues from Imperial College London analyzed the relationship between locations and intensities of urgency and pain sensations felt during filling cystometry. Participants completed the King's Health Questionnaire (KHQ) to indicate presence of bladder pain or urgency. During cystometry, participants scored the intensity of urgency and pain, both in the suprapubic and the urethral region, on a VAS scale of 0-10 at a baseline, at first desire, normal desire, strong desire to void, and at maximum cystometric capacity during filling. The participants were allocated to six groups; those reporting urgency or not, pain or not, both symptoms and neither. Friedman's Test was used to ascertain if all scores increased significantly, the Wilcoxon Signed Rank Test was used to demonstrate the difference between scores, and agreement for findings during cystometry was tested with Mann-Whitney U. A total of 68 women participated; 38 participants reported pain, 57 reported urgency, and 33 reported both symptoms. Pain and urgency scores significantly increased during cystometry. For participants reporting pain, suprapubic pain was rated significantly higher than urethral pain. Participants reporting both symptoms, felt more urgency than pain, and again pain more suprapubically than urethrally. Participants reporting only urgency scored suprapubic and urethral urgency similarly at all desires. The authors concluded that pain and urgency are well differentiated sensations and are felt at different locations although pain is seemingly easier localized.

HYDRODISTENSION OF THE BLADDER FOR THE TREATMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS (BPS/IC).

Hoke TP, Goldstein H, Saks EK, Vakili B. *Neurourol Urodyn.* 2016 Apr 19. doi: 10.1002/nau.23024. [Epub ahead of print] PMID: 27092957

The purpose of this study from Newark USA was to determine whether a transvaginal trigonal block immediately preceding cystoscopy with hydrodistention yields an additional therapeutic benefit compared to cystoscopy with hydrodistention alone for the treatment of bladder pain syndrome/interstitial cystitis(BPS/IC). A retrospective chart review was performed at a single-centre. Performance of a trigonal block prior to hydrodistention was at the discretion of the surgeon. A trigonal block consists of injecting 0.25% bupivacaine with 1.0% Xylocaine into the anterior vagina under the trigone under cystoscopic guidance. Procedures between January 1, 2008 and December 31, 2013 were included. The primary outcome compared change in pain score from the baseline to 1-month post-operative. 183 patients underwent hydrodistention of the bladder. 77 were excluded and of the 106 patients remaining, 48 received a trigonal block and 58 did not. Both groups had a significant improvement in pain scores. There was no difference in change in pain score from baseline between both groups. Distention time was dichotomized into 2 and >5 min based on surgeon preference. There was no difference in change in pain score from baseline between both groups. Hoke and colleagues concluded that hydrodistention of the bladder decreased pain postoperatively regardless of trigonal block or time of distention. A randomized-controlled trial is necessary to determine the benefits of duration of hydrodistention or performance of a block.

BLADDER DISTENSION INCREASES BLOOD FLOW IN PAIN-RELATED BRAIN STRUCTURES IN SUBJECTS WITH INTERSTITIAL CYSTITIS.

Deutsch G, Deshpande H, Frölich MA, Lai HH, Ness TJ. *J Urol.* 2016 Mar 23. pii: S0022-5347(16)03685-5. doi: 10.1016/j.juro.2016.03.135. [Epub ahead of print] PMID: 27018508

In Healthy Control subjects (HCs) certain brain regions of interest (ROIs) demonstrate increased regional cerebral blood flow (rCBF) in response to painful stimuli. The effect of bladder distension on arterial spin label-functional MRI (ASL-fMRI) measures of rCBF within ROIs was examined in subjects with Interstitial Cystitis (ICs). Female ICs (n= 11) and HCs (n=11) underwent three brain perfusion scan studies using ASL-fMRI: with a full bladder; with an empty bladder; and while experiencing heat pain. rCBF was calculated using custom software and individual scans were spatially normalized to the MNI template. An analysis was performed of ROI-based absolute rCBF in each condition and of the within group/within subject rCBF distribution changes induced by each condition. It was concluded that compared to HCs, ICs have limited differences in rCBF in baseline (empty bladder) conditions as well as during heat pain, but robust rCBF increases in the full bladder state in ROIs typically associated with pain, emotion and/or motor control indicating altered processing of bladder-related sensations.

REVISITING THE ROLE OF POTASSIUM SENSITIVITY TESTING AND CYSTOSCOPIC HYDRODISTENTION FOR THE DIAGNOSIS OF INTERSTITIAL CYSTITIS.

Jiang YH, Jhang JF, Kuo HC. *PLoS One.* 2016 Mar 21;11(3):e0151692. doi: 10.1371/journal.pone.0151692. eCollection 2016. PMID: 26999787

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

The purpose of this study from Hualien, Taiwan was to revisit the diagnostic roles of cystoscopic hydrodistention and the potassium sensitivity test (PST) for the diagnosis of interstitial cystitis (IC). Jiang and colleagues prospectively enrolled 214 patients clinically diagnosed with IC, 125 non-IC patients who underwent video urodynamic studies and PST, and another 144 non-IC patients who underwent cystoscopic hydrodistention before transurethral surgery. The sensitivity, specificity, and positive and negative predictive values were calculated for the PST and glomerulations after cystoscopic hydrodistention. After cystoscopic hydrodistention, glomerulations developed in 211/214 (98.6%) IC patients and 61/144 (42.4%) of the non-IC patients including patients with stones (45/67, 67%), hematuria (2/5, 40%), and stress urinary incontinence (SUI) (6/17, 35%). When positive glomerulation was defined as grade 2 or more, the sensitivity was 61.7%. The PST was positive in 183/214 (85.5%) IC patients and 7/17 (41%) with hypersensitive bladder, 7/32 (22%) with detrusor overactivity, 5/27 (18%) with SUI, 2/21 (10%) with lower urinary tract symptoms, and 2/25 (8%) with bladder outlet obstruction. The PST had a sensitivity of 85.5% and a specificity of 81.6% for diagnosis of IC. IC patients with a positive PST had a significantly smaller urgency sensation capacity, smaller voided volume, and greater bladder pain score. Both the PST and glomerulations after hydrodistention are sensitive indicators of IC, but the specificity of glomerulations in the diagnosis of IC is lower than that of the PST. A positive PST is associated with a more hypersensitive bladder and bladder pain, but not the grade of glomerulations in IC patients. Neither test provided 100% diagnostic accuracy for IC. They concluded that they might select patients into different subgroups based on different PST and hydrodistention results, not for making a diagnosis of IC but for guidance of different treatments.

AUTONOMIC RESPONSE DURING BLADDER HYDRODISTENTION REFLECTS THE SEVERITY OF SYMPTOMS IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Kim SW, Son HS, Troya IS, Kim JY, Kim MJ, Fraser MO, Kim JH. *Neurourol Urodyn.* 2016 Mar 29. doi: 10.1002/nau.22994. [Epub ahead of print] PMID: 27028369

The aim of this study from South Korea and USA was to evaluate the correlation between symptom severity of bladder pain syndrome/interstitial cystitis (BPS/IC) and autonomic nervous system activity, examining autonomic responses during bladder hydrodistention. Medical records were collected from a prospective database for patients who underwent bladder hydrodistention with a fixed protocol from March 2012 to December 2013. A total of 40 patients (16 males, 24 females) were included for the analysis. Hydrodistention was performed under general anesthesia (31 patients), spinal anesthesia (six patients), and both types of anesthesia (three patients) at different times. Twenty-five patients who underwent holmium laser enucleation of the prostate served as controls. Pulse rate (PR), systolic (SBP), and diastolic blood pressure (BP) were measured pre-hydrodistention, during hydrodistention, and after drainage. The spinal anesthesia and control groups exhibited little change in BP and PR during hydrodistention, while a significant increase was demonstrated in the general anesthesia group. Under general anesthesia, autonomic response during hydrodistention was more prominent in patients with preoperative visual analogue scale (VAS) pain score ≥ 7 , Hunner's lesion, and glomerulation grade 4. Preoperative maximal cystometric capacity negatively correlated with changes in SBP during hydrodistention, while VAS score and interstitial cystitis problem index demonstrated a positive correlation with the changes. The authors found that under general anesthesia, exaggerated autonomic responses to bladder hydrodistention were demonstrated in BPS/IC patients, which reflected the severity of symptoms. These results support the hypothesis of altered activity of autonomic system in BPS/IC.

DIFFERENCES IN URODYNAMIC PARAMETERS BETWEEN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND SEVERE OVERACTIVE BLADDER.

Shim JS, Kang SG, Park JY, Bae JH, Kang SH, Park HS, Moon DG, Cheon J, Lee JG, Kim JJ¹, Oh MM. *Urology.* 2016 Apr 26. pii: S0090-4295(16)30113-3. doi: 10.1016/j.urology.2016.04.018. [Epub ahead of print] PMID: 27130264

The purpose of this study from Seoul, Republic of Korea was to identify differences in urodynamic parameters between female outpatients with interstitial cystitis (IC)/bladder pain syndrome (BPS) and severe overactive bladder (OAB). This cross-sectional study included 24 and 28 consecutive IC/BPS and severe OAB female patients, respectively. IC/BPS was defined based on the American Urological Association guideline, and severe OAB was defined based on baseline symptoms recorded in a voiding diary. Before treatment, symptom assessment using questionnaires and a 3-day voiding diary, as well as laboratory tests, were performed at the initial visit. The patients' baseline characteristics and urodynamic parameters were compared between the IC/BPS and severe OAB groups. The IC/BPS group showed fewer episodes of urge incontinence and shorter duration of symptoms than the severe OAB group. Volumes at first sense, normal desire, strong desire, and maximal capacity during filling cystometry (MBC) were significantly higher in the severe OAB group than in the IC/BPS group. The IC/BPS and severe OAB groups showed significant differences in urodynamic parameters in terms of MBC and the volume discrepancy between MBC and maximal voided volume. The ROC curve also showed an area under the curve of 0.760 and 0.783 for MBC and volume discrepancy, respectively. The authors concluded that data from their study suggest that combined with other clinical findings, urodynamic studies could provide useful information to differentiate between a diagnosis of IC/BPS or severe OAB.

INCREASED TOXIC URINARY CATIONS IN MALES WITH INTERSTITIAL CYSTITIS: A POSSIBLE CAUSE OF BLADDER SYMPTOMS.

Argade S, Berecz Z, Su Y, Parsons CL. World J Urol. 2016 Mar 30. [Epub ahead of print] PMID: 27027645

The purpose of this study from San Diego USA was to identify and quantify toxic urinary cations in male patients with bladder pain syndrome/interstitial cystitis versus male controls, to compare them in symptomatic patients to those significantly improved, and to evaluate cytotoxicity of these cations to cultured urothelial cells to determine whether Tamm-Horsfall protein (THP) can neutralize the cations. Isolation of cationic fraction (CFs) was achieved by solid phase extraction on urine specimens of 51 male patients with IC and 33 male controls. C₁₈ reverse-phase high-performance liquid chromatography was used to profile and quantify cationic metabolites. Major CF peaks were identified by liquid chromatography-tandem mass spectrometry. HTB-4 urothelial cells were used to determine the cytotoxicity of CFs, individual metabolites, and of metabolite mixture with THP of patient versus THP of control subject. CF content was significantly higher in patients compared to controls ($p < 0.001$). Patients had higher levels of modified nucleosides, amino acids, and their derivatives compared to controls. Cytotoxicity for control versus patient mean (SEM) percent was 1.7 (2.9) % versus 63.0 (3.7) %, respectively. Cytotoxicity of metabolites was reduced in the presence of THP of control compared to THP of patient. The authors concluded that patients with IC had significantly higher levels of cationic metabolites with higher cytotoxicity compared to controls. THP of these patients had reduced ability to sequester cytotoxicity of cationic metabolites. Patients who significantly improved on therapy had the same levels and toxicity of cationic metabolites as symptomatic males, suggesting that these cations may be the cause of epithelial dysfunction in IC.

NOCICEPTIN/ORPHANIN FQ RECEPTOR EXPRESSION IN CLINICAL PAIN DISORDERS AND FUNCTIONAL EFFECTS IN CULTURED NEURONS.

Anand P, Yiangou Y, Anand U, Mukerji G, Sinisi M, Fox M, McQuillan A, Quick T, Korchev YE, Hein P. Pain. 2016 Apr 28. [Epub ahead of print] PMID: 27127846

The Nociceptin/Orphanin FQ peptide receptor (NOP), activated by its endogenous peptide ligand Nociceptin/Orphanin FQ (N/OFQ), exerts several effects including modulation of pain signalling. Anand and colleagues have examined, for the first time, the tissue distribution of the NOP receptor in clinical visceral and somatic pain disorders by immunohistochemistry, and assessed functional effects of NOP and μ opioid receptor activation in cultured human and rat dorsal root ganglion (DRG) neurons. Quantification of NOP-positive nerve fibres within the bladder sub-urothelium revealed a remarkable several-fold increase in Detrusor Overactivity and Painful Bladder Syndrome patient specimens, compared to controls. In post-mortem control human DRGs, 75-80% of small/medium neurons ($\leq 50 \mu\text{m}$ diameter) in the lumbar (somatic) and sacral (visceral) DRG were positive for NOP, and fewer large neurons; avulsion-injured cervical human DRG neurons showed similar numbers. NOP-immunoreactivity was significantly decreased in injured peripheral nerves, and also in painful neuromas. Calcium imaging studies in cultured rat DRG neurons demonstrated dose-dependent inhibition of capsaicin responses in the presence of N/OFQ, with an IC₅₀ of 8.6 pM. In cultured human DRG neurons, 32%

inhibition of capsaicin responses was observed in the presence of 1 pM N/OFQ. The maximum inhibition of capsaicin responses was greater with N/OFQ than μ -opioid receptor agonist DAMGO. Their findings highlight the potential of NOP agonists, particularly in urinary bladder overactivity and pain syndromes. The regulation of NOP expression in visceral and somatic sensory neurons by target-derived neurotrophic factors deserves further study, and the efficacy of NOP selective agonists in clinical trials.

[NURSING CARE OF WOMEN WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.](#)

MacMullen NJ, Dulski LA, Martin PB, Blobaum P. *Nurs Womens Health*. 2016 Apr-May;20(2):168-80. doi: 10.1016/j.nwh.2016.01.006. PMID: 27067933

Interstitial cystitis/painful bladder syndrome is a chronic condition affecting approximately 3.3 million women in the United States. It is defined by the National Institute of Diabetes and Digestive and Kidney Diseases as "urinary pain that cannot be attributed to other causes such as infection or urinary stones." Because of the intimate nature of the symptoms, women are often reluctant to seek treatment. When they do, they require a care provider with specialized nursing skills. Nursing practice based on carefully reviewed literature will result in the provision of comprehensive and compassionate nursing care for women with interstitial cystitis/painful bladder syndrome.

[THERAPEUTIC POTENTIAL OF HUMAN CHORIONIC GONADOTROPIN AGAINST PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS.](#)

Rao CV. *Reprod Sci*. 2016 Mar 22. pii: 1933719116639139. [Epub ahead of print] PMID: 27004802

Painful bladder syndrome/interstitial cystitis is a debilitating chronic bladder disease that primarily affects women. The disease is due to a damage of urothelial cell lining. As a result, potassium particles and other toxic substances in urine can leak into bladder mucosa, causing the symptoms of lower abdominal/pelvic discomfort, pain, increased urination frequency, urgency, nocturia, and so on, all of which can substantially reduce the quality of daily life. There are multiple symptom relieving therapies. Among them, only pentosan polysulfate sodium, sold under the brand name of Elmiron, has been approved for oral use by US Food and Drug Administration. It provides the relief after several months of use. Based on the scientific leads presented in this article, Rao proposes that human chorionic gonadotropin has a therapeutic potential that is worth investigating for the treatment of this disease.

[MANAGING CHRONIC BLADDER DISEASES WITH THE ADMINISTRATION OF EXOGENOUS GLYCOSAMINOGLYCANS: AN UPDATE ON THE EVIDENCE.](#)

Lazzeri M, Hurlle R, Casale P, Buffi N, Lughezzani G, Fiorini G, Peschechera R, Pasini L, Zandegiacomo S, Benetti A, Taverna G, Guazzoni G, Barbagli G. *Ther Adv Urol*. 2016 Apr;8(2):91-9. doi: 10.1177/1756287215621234. Epub 2015 Dec 16. PMID: 27034722

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Lazzeri and colleagues from Italy note that although the pathophysiology of acute chronic cystitis and other 'sensory' disorders, i.e. painful bladder syndrome (PBS) or interstitial cystitis (IC), often remains multifactorial, there is a wide consensus that such clinical conditions may arise from a primary defective urothelium lining or from damaged glycosaminoglycans (GAGs). A 'cascade' of events starting from GAG injury, which fails to heal, may lead to chronic bladder epithelial damage and neurogenic inflammation. To restore the GAG layer is becoming the main aim of new therapies for the treatment of chronic cystitis and PBS/IC. Preliminary experiences with GAG replenishment for different pathological conditions involving the lower urinary tract have been reported. There is a range of commercially available intravesical formulations of these components, alone or in combination. Literature evidence shows that exogenous intravesical hyaluronic acid markedly reduces recurrences of urinary tract infections (UTIs). Patients treated with exogenous GAGs have fewer UTI recurrences, a longer time to recurrence and a greater improvement in quality of life. Exogenous intravesical GAGs have been used for the treatment of PBS/IC. Despite the limitations of most of the studies, findings confirmed the role of combination therapy with hyaluronic acid and chondroitin sulfate as a safe and effective option for the treatment of PBS/IC. To prevent and/or treat radiotherapy and chemotherapy induced cystitis, GAG replenishment therapy has been used showing preliminary encouraging results. The safety profile of exogenous GAGs has been reported to be very favourable, without adverse events of particular significance.

UPDATE ON THE PATHOLOGY AND DIAGNOSIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A REVIEW.

Kim HJ. *Int Neurourol J.* 2016 Mar;20(1):13-7. doi: 10.5213/inj.1632522.261. Epub 2016 Mar 23. PMID: 27032552

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

Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by bladder discomfort, urinary frequency, urgency, and pelvic pain. The etiology and pathogenesis of this condition is still unknown and remains diagnosed by exclusion. The histologic findings are also neither specific for diagnosis nor correlated with symptoms. However, the definition and diagnostic criteria for the condition was established in the last decade. In this paper, Kim and colleagues from Korea review the changes in the definition, terminology, and diagnostic scheme of IC/BPS, and summarize the histologic findings. They also briefly discuss some new pathologic suggestions and new urinary markers, focusing on the most promising ones.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A UROLOGIC MYSTERY

Cho YS. *Int Neurourol J.* 2016 Mar;20(1):3-4. doi: 10.5213/inj.1620edi.002. PMID: 27032550

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The present review addresses history and changes in the definition, terminology, and diagnostic approach of IC/BPS, and summarizes the histologic findings. Some new pathologic suggestions and urinary markers are also briefly mentioned. Without understanding of molecular mechanisms and pathology, we cannot resolve the mystery of diagnosis and treatment of IC/BPS, according to Cho from Korea who expects that comprehensive understanding of many aspects of IC/BPS, including the pathology, will be helpful to patients and physicians dealing with IC/BPS.

POTENTIAL EFFECT OF LIPOSOMES AND LIPOSOME-ENCAPSULATED BOTULINUM TOXIN AND TACROLIMUS IN THE TREATMENT OF BLADDER DYSFUNCTION.

Janicki JJ, Chancellor MB, Kaufman J, Gruber MA, Chancellor DD. *Toxins (Basel).* 2016 Mar 18;8(3). pii: E81. doi: 10.3390/toxins8030081. PMID: 26999210

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Bladder drug delivery via catheter instillation is a widely used treatment for recurrence of superficial bladder cancer. Intravesical instillation of liposomal botulinum toxin has recently shown promise in the treatment of overactive bladder and interstitial cystitis/bladder pain syndrome, and studies of liposomal tacrolimus instillations show promise in the treatment of hemorrhagic cystitis. Liposomes are lipid vesicles composed of phospholipid bilayers surrounding an aqueous core that can encapsulate hydrophilic and hydrophobic drug molecules to be delivered to cells via endocytosis. This review presents new developments on instillations of liposomes and liposome-encapsulated drugs into the urinary bladder for treating lower urinary tract dysfunction.

ADVERSE EVENTS OF INTRAVESICAL ONABOTULINUM TOXIN A INJECTION BETWEEN PATIENTS WITH OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS-DIFFERENT MECHANISMS OF ACTION OF BOTOX ON BLADDER DYSFUNCTION?

Kuo YC, Kuo HC. *Toxins (Basel).* 2016 Mar 16;8(3). pii: E75. doi: 10.3390/toxins8030075. PMID: 26999201

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Intravesical onabotulinumtoxinA (BoNT-A) injections have been proposed to treat both overactive bladder (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS) in patients with refractory conditions. Kuo and Kuo from Taiwan compared adverse events (AEs) after BoNT-A treatment between IC/BPS and OAB in women. IC/BPS patients who failed conventional treatments were enrolled to receive suburothelial injections of BoNT-A (100 U) followed by hydrodistention. Age matched OAB female patients refractory to antimuscarinic agents underwent BoNT-A (100 U) injections. The bladder capacity, maximum flow rate (Qmax), post-void residual (PVR), and voiding efficiency (VE) at baseline, 3 and 6 months, and the post-treatment AEs were analyzed between groups. Finally, 89 IC/BPS and 72 OAB women were included. In the OAB group, the bladder capacity and PVR increased, and VE decreased significantly at three and six months after BoNT-A treatment. In the IC/BPS group, the Qmax increased significantly at six months. There were significant differences in changes of capacity, Qmax, PVR and VE between the two groups. Moreover, OAB patients

suffered more frequently from events of hematuria, UTI, and large PVR (>200 mL), but less frequently from events of straining to void. In conclusion, OAB women had higher PVR volume and lower VE than those in IC/BPS after BoNT-A injections. These results imply that the bladder contractility of OAB patients are more susceptible to BoNT-A, which might reflect the different mechanisms of action of Botox on bladder dysfunction. Further investigations to confirm this hypothesis are warranted.

USE OF BOTULINUM TOXIN A IN THE TREATMENT OF LOWER URINARY TRACT DISORDERS: A REVIEW OF THE LITERATURE.

Moore DC, Cohn JA, Dmochowski RR. *Toxins (Basel)*. 2016 Mar 23;8(4). pii: E88. doi: 10.3390/toxins8040088. PMID: 27023601

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Botulinum neurotoxin (BoNT) is used to treat a variety of ailments, and its therapeutic application in lower urinary tract disorders (LUTDs) is well studied. Robust evidence supporting the efficacy and tolerability of BoNT in the treatment of neurogenic detrusor overactivity (NDO) and non-neurogenic overactive bladder (OAB) has led to regulatory approval for these conditions. Use of BoNT in the treatment of interstitial cystitis/bladderpain syndrome, chronic pelvic pain, and detrusor sphincter dyssynergia has demonstrated some promise, but is still evolving and off-label for these indications. Trials to date do not support the use of BoNT for benign prostatic hyperplasia. This comprehensive review outlines the mechanisms of BoNT in the treatment of LUTDs in adults and presents background and updated data examining the efficacy and adverse events associated with the use of BoNT in common urologic applications.

A PHASE II STUDY OF EFFICACY AND SAFETY OF A NOVEL, ORAL SHIP1 ACTIVATOR, AQX-1125, IN SUBJECTS WITH MODERATE TO SEVERE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS).

Nickel JC, Egerdie B, Davis E, Evans R, Mackenzie L, Shrewsbury SB. *J Urol*. 2016 Mar 8. pii: S0022-5347(16)03368-1. doi: 10.1016/j.juro.2016.03.003. [Epub ahead of print] PMID: 26968644

This 6-week, randomized, double-blind, placebo-controlled, multi-center trial assessed a novel SH2-containing inositol-5'-phosphatase 1 (SHIP1) activator, AQX-1125, on bladder pain and urinary symptoms in IC/BPS. Women with IC/BPS and mean pain of ≥ 5 (11-pt scale) despite treatment were randomized to AQX-1125 or placebo, orally once daily for 6 weeks. Average and maximum pain scores (daily) and urinary frequency (pre-visits) were recorded by e-diary and at clinic visits. O'Leary-Sant Interstitial Cystitis Symptom (ICSI) and Problem Indices (ICPI), Bladder Pain Interstitial Cystitis Symptom Score (BPIC-SS) and Short-Form 12 Health Survey (SF-12v2) questionnaires were administered. Safety was monitored through 6 weeks treatment and 4 weeks follow-up. 37 patients received oral AQX-1125 and 32 received placebo. At 6 weeks, average daily pain (e-diary) decreased by 2.4 points (AQX-1125) versus 1.4 (placebo); average pain (clinic) by 2.6 vs 1.1; maximum daily pain (e-diary) by 2.6 vs 1.4 and maximum pain (clinic) by 2.8 vs 1.1. AQX-1125 reduced ICSI by 3.8 points vs 1.4 (placebo), ICPI by 3.6 vs 1.6 and BPIC-SS by 8.8 points vs 4.0. Urinary frequency decreased on AQX-1125 by 3.6 voids/24 hours vs 0.8 (placebo) ($p=0.040$). Adverse event rates were similar between AQX-1125 (51.4%) and placebo (78.1%). No SAEs reported. It was found that women with moderate to severe IC/BPS, treated with the oral SHIP1 activator, AQX-1125, reported significantly reduced bladder pain and improved urinary symptoms at 6 weeks. AQX-1125 was well tolerated. AQX-1125 may be a potential new treatment for IC/BPS, and warrants further investigation.

A COHORT STUDY OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND HYSTERECTOMY.

Lee MH, Chang KM, Wu SL, Lin HH, Lin HY, Wu HC. *Int Urogynecol J*. 2016 Mar 4. [Epub ahead of print] PMID: 26942595

Symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS) are often confused with uterine conditions. Gynecologists may therefore recommend hysterectomy which was inappropriate for these patients. This study from Taiwan investigated whether IC/BPS increases the risk of hysterectomy in a large nationwide retrospective cohort study. From the Longitudinal Health Insurance Database 2010 (LHID2010) in Taiwan, Lee and colleagues identified women diagnosed with IC/BPS between 2002 and 2013. Those with a history of hysterectomy before IC/BPS diagnosis were excluded. All women were stratified into three subgroups (younger, middle, older age) based on the propensity scores of 15 confounding factors, including age and comorbidities. All were followed until the end of 2013 to detect the event of hysterectomy. The hazard ratio

(HR) of hysterectomy in the IC/BPS cohort was compared with the non-IC/BPS cohort among the three subgroups by Cox regression after adjusting for confounding factors. In addition to the representative middle age, subgroup 2 had similar rates of comorbidities as the general population. The study was both externally and internally valid. The risk of hysterectomy in the IC/BPS cohort was significantly higher than in the non-IC/BPS cohort in subgroup 2. The mean time to hysterectomy after diagnosis of IC/BPS was 2.97 years. In this nationwide study, the authors found that IC/BPS has a causal impact on hysterectomy in the middle-age subgroup in LHID 2010. The possibility of a woman having IC/BPS should be evaluated prior to hysterectomy to avoid inappropriate surgery.

F16357, A NOVEL PAR1 ANTAGONIST IMPROVES URODYNAMIC PARAMETERS IN A RAT MODEL OF INTERSTITIAL CYSTITIS.

Monjotin N, Gillespie J, Farrie M, Le Grand B, Junquero D, Vergnolle N. Br J Pharmacol. 2016 Apr 25. doi: 10.1111/bph.13501. [Epub ahead of print] PMID: 27111354

The aim of the present study from France and the UK was to characterize the role of PAR1 in rat bladder under inflammatory conditions, and determine whether a selective PAR1 antagonist, namely F16357, can prevent the pathophysiological parameters of CYP-induced IC. Immunohistochemistry, contractile activity in isolated bladder and urodynamics were performed before and after CYP treatment. F16357 was administered intravesically during the acute phase of inflammation and effects on PAR1 receptors and PAR1-related bladder contraction were evaluated 24H after CYP injection. For telemetric experiments, urodynamics and associated voided volumes were recorded 7H and 24H after CYP.

THE EXPRESSION OF INFLAMMATORY MEDIATORS IN BLADDER PAIN SYNDROME.

Offiah I, Didangelos A, Dawes J, Cartwright R, Khullar V, Bradbury EJ, O'Sullivan S, Williams D, Chessell IP, Pallas K, Graham G, O'Reilly BA, McMahon SB. Eur Urol. 2016 Mar 7. pii: S0302-2838(16)00248-7. doi: 10.1016/j.eururo.2016.02.058. [Epub ahead of print] PMID: 26965559

Bladder pain syndrome (BPS) pathology is poorly understood. Treatment strategies are empirical, with limited efficacy, and affected patients have diminished quality of life. Offiah and colleagues examined the hypothesis that inflammatory mediators within the bladder contribute to BPS pathology. 15 women with BPS and 15 women with stress urinary incontinence without bladder pain were recruited from Cork University Maternity Hospital from October 2011 to October 2012. During cystoscopy, 5-mm bladder biopsies were taken and processed for gene expression analysis. The effect of the identified genes was tested in laboratory animals. The authors studied the expression of 96 inflammation-related genes in diseased and healthy bladders. They measured the correlation between genes and patient clinical profiles using the Pearson correlation coefficient. Analysis revealed 15 differentially expressed genes, confirmed in a replication study. FGF7 and CCL21 correlated significantly with clinical outcomes. Intravesical CCL21 instillation in rats caused increased bladder excitability and increased c-fos activity in spinal cord neurons. CCL21 atypical receptor knockout mice showed significantly more c-fos upon bladder stimulation with CCL21 than wild-type littermates. There was no change in FGF7-treated animals. The variability in patient samples presented as the main limitation. They used principal component analysis to identify similarities within the patient group. Their study identified two biologically relevant inflammatory mediators in BPS and demonstrated an increase in nociceptive signalling with CCL21. Manipulation of this ligand is a potential new therapeutic strategy for BPS. Patient summary: We compared gene expression in bladder biopsies of patients with bladder pain syndrome (BPS) and controls without pain and identified two genes that were increased in BPS patients and correlated with clinical profiles. We tested the effect of these genes in laboratory animals, confirming their role in bladder pain. Manipulating these genes in BPS is a potential treatment strategy.

PROTEASE-ACTIVATED RECEPTOR 4 INDUCES BLADDER PAIN THROUGH HIGH MOBILITY GROUP BOX-1.

Kouzoukas DE, Ma F, Meyer-Siegler KL, Westlund KN, Hunt DE, Vera PL. PLoS One. 2016 Mar 24;11(3):e0152055. doi: 10.1371/journal.pone.0152055. eCollection 2016. PMID: 27010488

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Pain is the significant presenting symptom in Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS). Activation of urothelial protease activated receptor 4 (PAR4) causes pain through release of urothelial macrophage migration inhibitory factor (MIF). High Mobility Group Box-1 (HMGB1), a chromatin-binding protein,

mediates bladder pain (but not inflammation) in an experimental model (cyclophosphamide) of cystitis. To determine if PAR4-induced bladder hypersensitivity depends on HMGB1 downstream, Kouzoukas and colleagues from the USA tested whether: 1) bladder PAR4 stimulation affected urothelial HMGB1 release; 2) blocking MIF inhibited urothelial HMGB1 release; and 3) blocking HMGB1 prevented PAR4-induced bladder hypersensitivity. HMGB1 release was examined in immortalized human urothelial cultures (UROtsa) exposed to PAR4-activating peptide (PAR4-AP; 100 μ M; 2 hours) or scrambled control peptide. Female C57BL/6 mice, pretreated with a HMGB1 inhibitor (glycyrrhizin: 50 mg/kg; ip) or vehicle, received intravesical PAR4-AP or a control peptide (100 μ M; 1 hour) to determine 1) HMGB1 levels at 1 hour in the intravesical fluid (released HMGB1) and urothelium, and 2) abdominal hypersensitivity to von Frey filament stimulation 24 hours later. They also tested mice pretreated with a MIF blocker (ISO-1: 20 mg/kg; ip) to determine whether MIF mediated PAR4-induced urothelial HMGB1 release. PAR4-AP triggered HMGB1 release from human (in vitro) and mice (in vivo) urothelial cells. Intravesical PAR4 activation elicited abdominal hypersensitivity in mice that was prevented by blocking HMGB1. MIF inhibition prevented PAR4-mediated HMGB1 release from mouse urothelium. Urothelial MIF and HMGB1 represent novel targets for therapeutic intervention in bladder pain conditions.

BLADDER HYPERSENSITIVITY

A NOVEL ROLE FOR FOLLISTATIN IN HYPERSENSITIVITY FOLLOWING CYSTITIS.

Shaffer AD, Feng B, La JH, Joyce SC, Gebhart GF. NeuroUrol Urodyn. 2015 Dec 29. doi: 10.1002/nau.22941. [Epub ahead of print] PMID: 26713850

Previous studies have shown that the activin-binding protein follistatin reduces inflammation in several mouse models of colitis. To determine whether follistatin also has a beneficial effect following bladder inflammation, Shaffer and colleagues induced cystitis in mice using cyclophosphamide (CYP) and examined the relationship between bladder hypersensitivity and bladder follistatin expression. Adult female C57BL/6 mice were treated with CYP (100 mg/kg) or vehicle (saline) three times over 5 days. Bladder hypersensitivity was assessed by recording the visceromotor response (VMR) to urinary bladder distension and in vitro single-fiber bladder afferent recording. Follistatin gene expression was measured using qRT-PCR. Immunohistochemistry was employed for further characterization. Bladder hypersensitivity was established by day 6 and persisted to day 14 in CYP-treated mice. On day 14, hypersensitivity was accompanied by increases in follistatin gene expression in the bladder. Follistatin-like immunoreactivity colocalized with laminin, and the percentage of structures in the lamina propria that were follistatin-positive was increased in CYP-treated mice. Exogenous follistatin increased VMR and afferent responses to bladder distension in CYP- but not vehicle-treated mice. Chronic bladder pain following CYP treatment is associated with increased follistatin expression in the bladder. These results suggest a novel, pro-nociceptive role for follistatin in cystitis, in contrast with its proposed therapeutic role in colitis. This protein has exciting potential as a biomarker and therapeutic target for bladder hypersensitivity.

LIPOSOME BASED INTRAVESICAL THERAPY TARGETING NERVE GROWTH FACTOR AMELIORATES BLADDER HYPERSENSITIVITY IN RATS WITH EXPERIMENTAL COLITIS.

Kawamorita N, Yoshikawa S, Kashyap M, Tyagi P, Arai Y, Chancellor MB, Yoshimura N. J Urol. 2016 Jan 11. pii: S0022-5347(16)00009-4. doi: 10.1016/j.juro.2015.12.090. [Epub ahead of print] PMID: 26780168

Pelvic organ cross sensitization is considered to contribute to overlapping symptoms in chronic pelvic pain syndrome. Nerve growth factor over expression in the bladder is reportedly involved in the symptom development of bladder pain syndrome/interstitial cystitis. Kawamorita and colleagues from Japan and Pittsburgh USA examined whether a reduction of over expressed nerve growth factor in the bladder by intravesical treatment with liposome and oligonucleotide conjugates would ameliorate bladder hypersensitivity in a rat colitis model. Adult female rats were divided into 1) a control group, 2) a colitis-oligonucleotide group with intracolonic TNBS (2,4,6-trinitrobenzen sulfonic acid) enema and intravesical liposome-oligonucleotide treatments, 2) a colitis-saline group with intracolonic TNBS and intravesical saline treatments, 4) a sham oligonucleotide group with intravesical liposome-oligonucleotide treatment without colitis and 5) a sham-saline group with intravesical saline treatment without colitis. Liposomes conjugated with nerve growth factor antisense oligonucleotide or saline solution were instilled in the bladder and 24 hours later

colitis was induced by TNBS enema. Effects of nerve growth factor antisense treatment were evaluated by pain behavior, cystometry, molecular analyses and immunohistochemistry 10 days after TNBS treatment. In colitis-oligonucleotide rats nerve growth factor antisense treatment ameliorated pain behavior and decreased a reduction in the intercontraction interval in response to acetic acid stimulation as well as nerve growth factor expression in the bladder mucosa. All were enhanced in colitis-saline rats compared to sham rats. Nerve growth factor over expression in the bladder mucosa and bladder hypersensitivity induced after colitis were decreased by intravesical application of liposome-oligonucleotide targeting nerve growth factor. This suggests that local antinerve growth factor therapy could be effective treatment of bladder symptoms in chronic pelvic pain syndrome.

KETAMINE CYSTITIS

[PATIENT CHARACTERISTICS FOR DIFFERENT THERAPEUTIC STRATEGIES IN THE MANAGEMENT KETAMINE CYSTITIS.](#)

Jhang JF, Birder LA, Chancellor MB, Kuo HC. Neurorol Urodyn. 2016 Mar 21. doi: 10.1002/nau.22996. [Epub ahead of print] PMID: 26998599

Ketamine cystitis (KC) is receiving continuing attention in different parts of the world. This joint USA/Taiwan study reports that long-term ketamine abuse results in severely inflamed bladder and intractable bladder pain. Currently there is no guideline for clinicians to follow on how to manage patients with ketamine cystitis (KC). This study analysed the KC patient characteristics between those who received conservative management and those who underwent augmentation enterocystoplasty (AE). A total of 53 patients with chronic ketamine abuse and lower urinary tract symptoms were included in this study. All the patients were initially treated conservatively but failed. They were admitted for detailed urological examinations. Patients were classified according to their maximal bladder capacity (MBC). The patients with extremely small MBC with or without upper urinary tract damage and very small MBC with upper urinary tract damage were recommended to receive AE. The patient characteristics and treatment outcome are compared between patients with AE and conservative treatment. Among them, 28 patients underwent AE and 25 were managed with conservative treatment. The only significant difference between groups was that more patients with urgency urinary incontinence underwent AE. Patients who underwent AE had significantly smaller MBC, thicker bladder wall, and higher incidence of vesicoureteral reflux. Patients who underwent AE reported a good outcome. Most patients who received conservative treatment had a fair result. In KC patients who already developed a contracted bladder with extremely small bladder capacity with irreversible urinary tract change, partial cystectomy, and AE seems necessary for early restoration of a normal lower urinary tract function. The treatment outcome of AE is better than patients with conservative treatment.

[KETAMINE-INDUCED APOPTOSIS IN NORMAL HUMAN UROTHELIAL CELLS: A DIRECT, N-METHYL-D-ASPARTATE RECEPTOR-INDEPENDENT PATHWAY CHARACTERIZED BY MITOCHONDRIAL STRESS.](#)

Baker SC, Shabir S, Georgopoulos NT, Southgate J. Am J Pathol. 2016 May;186(5):1267-77. doi: 10.1016/j.ajpath.2015.12.014. Epub 2016 Mar 18. PMID: 27001627

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

Recreational abuse of ketamine has been associated with the emergence of a new bladder pain syndrome, ketamine-induced cystitis, characterized by chronic inflammation and urothelial ulceration. The authors investigated the direct effects of ketamine on normal human urothelium maintained in organ culture or as finite cell lines in vitro. Exposure of urothelium to ketamine resulted in apoptosis, with cytochrome c release from mitochondria and significant subsequent caspase 9 and 3/7 activation. The anesthetic mode-of-action for ketamine is mediated primarily through N-methyl d-aspartate receptor (NMDAR) antagonism; however, normal (nonimmortalized) human urothelial cells were unresponsive to NMDAR agonists or antagonists, and no expression of NMDAR transcript was detected. Exposure to noncytotoxic concentrations of ketamine (≤ 1 mmol/L) induced rapid release of ATP, which activated purinergic P2Y receptors and stimulated the inositol trisphosphate receptor to provoke transient release of calcium from the endoplasmic reticulum into the cytosol. Ketamine concentrations >1 mmol/L were cytotoxic and provoked a larger-amplitude increase in cytosolic Ca(2+) concentration that was unresolved. The sustained elevation in cytosolic Ca(2+) concentration was associated with pathological mitochondrial oxygen consumption and ATP deficiency. Damage to

the urinary barrier initiates bladder pain and, in ketamine-induced cystitis, loss of urothelium from large areas of the bladder wall is a reported feature. This study offers first evidence for a mechanism of direct toxicity of ketamine to urothelial cells by activating the intrinsic apoptotic pathway.

CHRONIC PELVIC PAIN

CHRONIC PELVIC PAIN IN WOMEN.

Speer LM, Mushkbar S, Erbele T. Am Fam Physician. 2016 Mar 1;93(5):380-7. PMID: 26926975

In this review of chronic pelvic pain, Speer and colleagues from Toledo USA note that chronic pelvic pain in women is defined as persistent, noncyclic pain perceived to be in structures related to the pelvis and lasting more than six months. Often no specific etiology can be identified, and it can be conceptualized as a chronic regional pain syndrome or functional somatic pain syndrome. It is typically associated with other functional somatic pain syndromes (e.g., irritable bowel syndrome, nonspecific chronic fatigue syndrome) and mental health disorders (e.g. posttraumatic stress disorder, depression). Diagnosis is based on findings from the history and physical examination. Pelvic ultrasonography is indicated to rule out anatomic abnormalities. Referral for diagnostic evaluation of endometriosis by laparoscopy is usually indicated in severe cases. Curative treatment is elusive, and evidence-based therapies are limited. Patient engagement in a biopsychosocial approach is recommended, with treatment of any identifiable disease process such as endometriosis, interstitial cystitis/painful bladder syndrome, and comorbid depression. Potentially beneficial medications suggested by the authors include depot medroxyprogesterone, gabapentin, nonsteroidal anti-inflammatory drugs, and gonadotropin-releasing hormone agonists with add-back hormone therapy. Pelvic floor physical therapy may be helpful. Behavioral therapy is an integral part of treatment. In select cases, neuromodulation of sacral nerves may be appropriate. Hysterectomy may be considered as a last resort if pain seems to be of uterine origin, although significant improvement occurs in only about one-half of cases. Chronic pelvic pain should be managed with a collaborative, patient-centred approach.

PELVIC FLOOR DYSFUNCTION AND SENSORY IMPAIRMENT: CURRENT EVIDENCE.

Mahoney C, Smith A, Marshall A, Reid F. NeuroUrol Urodyn. 2016 Mar 31. doi: 10.1002/nau.23004. [Epub ahead of print] PMID: 27037643

The purpose of this study from the United Kingdom was to explore the role of sensory nerve impairment in women with pelvic organ prolapse, painful bladder syndrome, urinary and fecal incontinence, and sexual dysfunction. Research to date has included small numbers of participants, used poorly matched controls, lacked a systemic sensory examination and applied non-standardized sensory testing techniques. However, the evidence suggests women with pelvic organ prolapse demonstrate sensory dysfunction. The role of sensory impairment in stress urinary incontinence is inconclusive. In women with urge urinary incontinence there is some evidence to suggest it may be urethrally mediated. Women with painful bladder syndrome may have more sensitive nerve endings which are unable to ignore repeated stimuli. Sensory impairment is common in women with sexual dysfunction, typically involving larger nerve fibres. There were no studies evaluating sensory function in women with fecal incontinence. Current evidence suggests women with pelvic floor dysfunction demonstrate sensory impairment though the causes remain unclear. Further studies are needed to investigate the different conditions of pelvic floor dysfunction using standardized sensory testing techniques, as well as evaluate the timing and mechanism by which any sensory impairment develops.

PAIN AND THE BRAIN

WHY SICKNESS HURTS: A CENTRAL MECHANISM FOR PAIN INDUCED BY PERIPHERAL INFLAMMATION.

Karshikoff B, Jensen KB, Kosek E, Kalpouzos G, Soop A, Ingvar M, Olgart Höglund C, Lekander M, Axelsson J. Brain Behav Immun. 2016 Apr 4. pii: S0889-1591(16)30073-3. doi: 10.1016/j.bbi.2016.04.001. [Epub ahead of print] PMID: 27058164

Low-grade systemic inflammation has been implicated in chronic pain, as well as in comorbid diseases like depression and fatigue. Karshikoff and colleagues from Sweden have previously shown that women's pain perception and regulation is more affected by systemic inflammation than that of men. Here they investigated the neural substrates underlying these effects using an fMRI paradigm previously employed in a clinical

population. 51 participants (29 women) were injected with 0.6ng/kg lipopolysaccharide (LPS) or saline to induce a peripheral inflammatory response. The subjects were then tested with a pressure pain fMRI paradigm designed to capture descending pain inhibitory activity 2h after injection, and blood was sampled for cytokine analysis. The subjects injected with LPS became more pain sensitive compared to the placebo group, and the heightened pain sensitivity was paralleled by decreased activity in the ventrolateral prefrontal cortex and the rostral anterior cingulate cortex (rACC) compared to placebo; areas involved in descending pain regulation. The LPS group also had higher activity in the anterior insular cortex, an area underpinning affective and interoceptive pain processing. Women displayed overall less pain-evoked rACC activity compared to men, which may have rendered women less resilient to immune provocation, possibly explaining sex differences in LPS-induced pain sensitivity. Their findings elucidate the pain-related brain circuits affected by experimental peripheral inflammation, strengthening the theoretical link between systemic inflammation and weakened pain regulation in chronic pain disorders. The results further suggest a possible mechanism underlying the female predominance in many chronic pain disorders.

FIBROMYALGIA

[FIBROMYALGIA AND CHRONIC PAIN SYNDROMES: A WHITE PAPER DETAILING CURRENT CHALLENGES IN THE FIELD.](#)

Arnold LM, Choy E, Clauw DJ, Goldenberg DL, Harris RE, Helfenstein M Jr, Jensen TS, Noguchi K, Silverman SL, Ushida T, Wang G. Clin J Pain. 2016 Mar 28. [Epub ahead of print] PMID: 27022674

This paper by a group of leading chronic pain researchers and clinicians from around the world addresses the state of knowledge about fibromyalgia and identify ongoing challenges in the field of fibromyalgia and other chronic pain syndromes that may be characterized by pain centralization/amplification/hypersensitivity. There have been many exciting developments in research studies of the pathophysiology and treatment of fibromyalgia and related syndromes that have the potential to improve the recognition and management of patients with fibromyalgia and other conditions with fibromyalgia-like pain. However, as patients are only too aware, much of the new information has not reached all clinicians, especially primary care clinicians, who have the greatest potential to use this new knowledge to positively impact their patients' lives. Furthermore, misconceptions about fibromyalgia persist and there is a lack of consensus regarding its diagnosis and treatment. This White Paper presents a framework for future global efforts to improve the understanding and treatment of fibromyalgia and other associated chronic pain syndromes, disseminate research findings, identify ways to enhance advocacy for these patients, and improve global efforts to collaborate and reach consensus about key issues related to fibromyalgia and chronic pain in general.

[FIBROMYALGIA SYNDROME PATHOLOGY AND ENVIRONMENTAL INFLUENCES ON AFFLICTIONS WITH MEDICALLY UNEXPLAINED SYMPTOMS.](#)

Albrecht PJ, Rice FL. Rev Environ Health. 2016 Apr 22. pii: /j/reveh.ahead-of-print/reveh-2015-0040/reveh-2015-0040.xml. doi: 10.1515/reveh-2015-0040. [Epub ahead of print] PMID: 27105483

Fibromyalgia syndrome (FMS) is a clinical disorder predominant in females with unknown etiology and medically unexplained symptoms (MUS), similar to other afflictions, including irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), post-traumatic stress disorder (PTSD), Gulf War illness (GFI), and others. External environmental stimuli drive behavior and impact physiologic homeostasis (internal environment) via autonomic functioning. These environments directly impact the individual affective state (mind), which feeds back to regulate physiology (body). FMS has emerged as a complex disorder with pathologies identified among neurotransmitter and enzyme levels, immune/cytokine functionality, cortical volumes, cutaneous innervation, as well as an increased frequency among people with a history of traumatic and/or emotionally negative events, and specific personality trait profiles. Yet, quantitative physical evidence of pathology or disease etiology among FMS has been limited (as with other afflictions with MUS). Previously, this group published findings of increased peptidergic sensory innervation associated with the arterio-venous shunts (AVS) in the glabrous hand skin of FMS patients, which provides a plausible mechanism for the wide-spread FMS symptomology. This review focuses on FMS as a model affliction with MUS to discuss the implications of the recently discovered peripheral innervation alterations, explore the role of peripheral innervation to central

sensitization syndromes (CSS), and examine possible estrogen-related mechanisms through which external and internal environmental factors may contribute to FMS etiology and possibly other afflictions with MUS.

VULVODYNIA/VULVAL PAIN SYNDROME

2015 ISSVD, ISSWSH, AND IPPS CONSENSUS TERMINOLOGY AND CLASSIFICATION OF PERSISTENT VULVAR PAIN AND VULVODYNIA.

Bornstein J, Goldstein AT, Stockdale CK, Bergeron S, Pukall C, Zolnoun D, Coady D; consensus vulvar pain terminology committee of the International Society for the Study of Vulvovaginal Disease (ISSVD). Collaborators (28). J Sex Med. 2016 Apr;13(4):607-12. doi: 10.1016/j.jsxm.2016.02.167. Epub 2016 Mar 25. PMID: 27045260

In 2014, the Executive Council of the International Society for the Study of Vulvovaginal Disease (ISSVD), the Boards of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS) acknowledged the need to revise the current terminology of vulvar pain, based on the significant increase in high quality etiologic studies published in the last decade. The new terminology was achieved in four steps. The first involved a terminology consensus conference with representatives of the three societies, held in April 2015. Then, an analysis of the relevant published studies was used to establish a level of evidence for each factor associated with vulvodynia. The terminology was amended based on feedback from members of the societies. Finally, each society's board accepted the new terminology. In 2015, the ISSVD, ISSWSH, and IPPS adopted a new vulvar pain and vulvodynia terminology that acknowledges the complexity of the clinical presentation and pathophysiology involved in vulvar pain and vulvodynia, and incorporates new information derived from evidence-based studies conducted since the last terminology published in 2003.

VULVODYNIA: DEFINITION, PREVALENCE, IMPACT, AND PATHOPHYSIOLOGICAL FACTORS.

Pukall CF, Goldstein AT, Bergeron S, Foster D, Stein A, Kellogg-Spadt S, Bachmann G. J Sex Med. 2016 Mar;13(3):291-304. doi: 10.1016/j.jsxm.2015.12.021. PMID: 26944461

Vulvodynia constitutes a highly prevalent form of chronic genital pain in women, and current information regarding its definition, prevalence, impact, and pathophysiologic factors involved is needed. The aim of this paper was to update the scientific evidence published in 2010 from the Third International Consultation of Sexual Medicine pertaining to the definition, prevalence, impact, and pathophysiologic factors of women's sexual pain. An expert committee, as part of the Fourth International Consultation of Sexual Medicine, comprised of researchers and clinicians from biological and social science disciplines, reviewed the scientific evidence on the definition, prevalence, impact, and pathophysiologic factors related to chronic genital pain. They found that vulvodynia is a prevalent and highly impactful genital pain condition. Numerous factors have been implicated in its development and maintenance. What is becoming increasingly apparent is that it likely represents the end point of different factors that can differ from patient to patient. Longitudinal research is needed to shed light on risk factors involved in the expression of vulvodynia, as well as in potential subgroups of affected patients, in order to develop an empirically supported treatment algorithm.

VULVODYNIA: ASSESSMENT AND TREATMENT.

Goldstein AT, Pukall CF, Brown C, Bergeron S, Stein A, Kellogg-Spadt S. J Sex Med. 2016 Apr;13(4):572-90. doi: 10.1016/j.jsxm.2016.01.020. Epub 2016 Mar 25. PMID: 27045258

Vulvodynia constitutes a highly prevalent form of sexual pain in women, and current information regarding its assessment and treatment is needed. The aim of this paper was to update the scientific evidence published in 2010, from the Third International Consultation on Sexual Medicine, pertaining to the assessment and treatment of women's sexual pain. An expert committee, as part of the Fourth International Consultation on Sexual Medicine, was comprised of researchers and clinicians from biological and social science disciplines for the review of the scientific evidence on the assessment and treatment of women's genital pain. The authors recommend the following treatments for the management of vulvodynia: psychological interventions, pelvic floor physical therapy, and vestibulectomy (for provoked vestibulodynia). They also support the use of multidisciplinary treatment approaches for the management of vulvodynia; however, more studies are needed to determine which components are most important. They recommend waiting for more empirical evidence before recommending alternative treatment options, anti-inflammatory agents, hormonal agents, and

anticonvulsant medications. Although they do not recommend lidocaine, topical corticosteroids, or antidepressant medication for the management of vulvodynia, they suggest that capsaicin, botulinum toxin, and interferon be considered second-line avenues and that their recommendation be revisited once further research is conducted. A comprehensive assessment is needed to understand the pain experience of women presenting with vulvodynia. In addition, treatment typically progresses from less invasive to more invasive, and several treatment options are worth pursuing.

NEUROIMAGING OF CENTRAL SENSITIVITY SYNDROMES: KEY INSIGHTS FROM THE SCIENTIFIC LITERATURE.

Walitt B, Ceko M, Gracely JL, Gracely RH. Curr Rheumatol Rev. 2016;12(1):55-87. PMID: 26717948

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Central sensitivity syndromes are characterized by distressing symptoms, such as pain and fatigue, in the absence of clinically obvious pathology. The scientific underpinnings of these disorders are not currently known. Modern neuroimaging techniques promise new insights into mechanisms mediating these postulated syndromes. Walitt and colleagues review the results of neuroimaging applied to five central sensitivity syndromes: fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular joint disorder, and vulvodynia syndrome. Neuroimaging studies of basal metabolism, anatomic constitution, molecular constituents, evoked neural activity, and treatment effect are compared across all of these syndromes. Evoked sensory paradigms reveal sensory augmentation to both painful and nonpainful stimulation. This is a transformative observation for these syndromes, which were historically considered to be completely of hysterical or feigned in origin. However, whether sensory augmentation represents the cause of these syndromes, a predisposing factor, an endophenotype, or an epiphenomenon cannot be discerned from the current literature. Further, the result from cross-sectional neuroimaging studies of basal activity, anatomy, and molecular constituency are extremely heterogeneous within and between the syndromes. A defining neuroimaging "signature" cannot be discerned for any of the particular syndromes or for an over-arching central sensitization mechanism common to all of the syndromes. Several issues confound initial attempts to meaningfully measure treatment effects in these syndromes. At this time, the existence of "central sensitivity syndromes" is based more soundly on clinical and epidemiological evidence. A coherent picture of a "central sensitization" mechanism that bridges across all of these syndromes does not emerge from the existing scientific evidence.

SJÖGREN'S SYNDROME

ONE YEAR IN REVIEW 2016: SJÖGREN'S SYNDROME.

Ferro F, Vagelli R, Bruni C, Cafaro G, Marcucci E, Bartoloni E, Baldini C. Clin Exp Rheumatol. 2016 Mar-Apr;34(2):161-71. Epub 2016 Apr 13. PMID: 27095672

In this useful review from Italy, Ferro and colleagues report that Sjögren's syndrome (SS) is a complex heterogeneous disease characterised by a broad spectrum of clinical and serological manifestations, including non-Hodgkin's lymphoma (NHL). Last year, 2015, was an exciting year for research into SS with novel insights into disease pathogenesis, clinical aspects and long-term outcomes. In addition, the use of biologic therapy in SS is rapidly expanding, with new evidence emerging regarding potential therapeutic targets. In this article, the authors provide an overview of the recent literature on the pathogenesis, clinical features and novel treatments of SS.

PELVIC FLOOR DYSFUNCTION IN FEMALE SJÖGREN'S SYNDROME: AN 8-YEAR AUDIT.

Budden AK, Te West NI, Sturgess AD, Moore KH. Int Urogynecol J. 2016 Mar 10. [Epub ahead of print] PMID: 26965411

Budden and colleagues from Australia note that the classic triad of dry eyes, mouth and vagina is known to most gynaecologists as pathognomonic of Sjögren's syndrome, but rheumatologists seldom consider vaginal symptoms. The authors' hypothesis was that women with Sjögren's syndrome would have an increased likelihood of postoperative voiding dysfunction, severe vaginal stenosis or poor response to anticholinergics compared with the general urogynaecology patient. All patients with Sjögren's syndrome were prospectively recorded from July 2007 to June 2015. Presenting complaint, pelvic examination findings, previous/subsequent pelvic surgery, voiding dysfunction and response to anticholinergics were noted. The denominator, all new

urogynaecology patients, was prospectively recorded. Fifteen patients were identified over 8 years (0.5 % of 2794 new presentations). Of the seven patients who had previously undergone surgery elsewhere, all had demonstrable pelvic tissue fibrosis; five had such severe fibrosis that no speculum could be passed. Anticholinergic medications were completely intolerable in 10/11 (91 %) women, and severe postoperative voiding dysfunction occurred in 6/9 (67 %) women. Only 2/15 (13 %) women were unaffected by fibrosis, postoperative voiding dysfunction or intolerance to anticholinergics. This audit demonstrates a substantial risk of vaginal stenosis, postoperative voiding dysfunction or severe intolerance to anticholinergics in women with Sjögren's syndrome.

IRRITABLE BOWEL SYNDROME

IRRITABLE BOWEL SYNDROME AND VISCERAL HYPERSENSITIVITY: RISK FACTORS AND PATHOPHYSIOLOGICAL MECHANISMS.

Deiteren A, de Wit A, van der Linden L, De Man JG, Pelckmans PA, De Winter BY. Acta Gastroenterol Belg. 2016 Jan-Mar;79(1):29-38. PMID: 26852761

Irritable bowel syndrome (IBS) is a common functional gastro-intestinal disorder, characterized by abdominal pain and altered intestinal motility. Visceral hypersensitivity is an important hallmark feature of IBS and is believed to underlie abdominal pain in patients with IBS. The two main risk factors associated with the development of IBS are gastrointestinal inflammation and psychological distress. On a peripheral level, visceral sensitivity seems to be modulated by several mechanisms. Immune cells in the mucosal wall, such as mast cells, and enterochromaffin cells may sensitize afferent nerves by release of their mediators. Furthermore, increased mucosal permeability, altered intestinal microflora and dietary habits may contribute to this feature. On a central level, an increased prevalence of psychiatric comorbidities is demonstrated in IBS patients, alongside alterations in the hormonal brain-gut axis, increased vigilance towards intestinal stimuli and functional and structural changes in the brain. The pathogenesis of IBS is complicated and multifactorial and the treatment remains clinically challenging. Dietary measures and symptomatic control are the cornerstones for IBS treatment and may be sufficient for patients experiencing mild symptoms, alongside education, reassurance and an effective therapeutic physician-patient relationship. New pharmacological therapies are aimed at interfering with mediator release and/or blockade of the relevant receptors within the gut wall, while modulation of the intestinal flora and diet may also be of therapeutic benefit. Tricyclic anti-depressants and serotonin reuptake inhibitors act both on a central and peripheral level by modulating pain signalling pathways.

VISCERAL PAIN

THE PHARMACOLOGY OF VISCERAL PAIN.

Johnson AC, Greenwood-Van Meerveld B. Adv Pharmacol. 2016;75:273-301. doi: 10.1016/bs.apha.2015.11.002. Epub 2016 Jan 6. PMID: 26920016

Visceral pain describes pain emanating from the internal thoracic, pelvic, or abdominal organs. Unlike somatic pain, visceral pain is generally vague, poorly localized, and characterized by hypersensitivity to a stimulus such as organ distension. While current therapeutics provides some relief from somatic pain, drugs used for treatment of chronic visceral pain are typically less efficacious and limited by multiple adverse side effects. Thus, the treatment of visceral pain represents a major unmet medical need. Further, more basic research into the physiology and pathophysiology of visceral pain is needed to provide novel targets for future drug development. In concert with chronic visceral pain, there is a high comorbidity with stress-related psychiatric disorders including anxiety and depression. The mechanisms linking visceral pain with these overlapping comorbidities remain to be elucidated. However, persistent stress facilitates pain perception and sensitizes pain pathways, leading to a feed-forward cycle promoting chronic visceral pain disorders. This paper focuses on stress-induced exacerbation of chronic visceral pain and provide supporting evidence that centrally acting drugs targeting the pain and stress-responsive brain regions may represent a valid target for the development of novel and effective therapeutics.

PUDENDAL NEURALGIA

[PUDENDAL NEURALGIA DUE TO PUDENDAL NERVE ENTRAPMENT: WARNING SIGNS OBSERVED IN TWO CASES AND REVIEW OF THE LITERATURE.](#)

Ploteau S, Cardaillac C, Perrouin-Verbe MA, Riant T, Labat JJ. Pain Physician. 2016 Mar;19(3):E449-54. PMID: 27008300

Free full text

In this useful open access paper from the well-known Federative Pelvic Pain Centre in Nantes, France, Ploteau and colleagues note that pudendal neuralgia is a chronic neuropathic pelvic pain that is often misdiagnosed and inappropriately treated. The Nantes Criteria provide a basis for the diagnosis of pudendal neuralgia due to pudendal nerve entrapment. The 5 essential diagnostic criteria are: pain situated in the anatomical territory of the pudendal nerve, worsened by sitting, the patient is not woken at night by the pain, and no objective sensory loss is detected on clinical examination. The fifth criterion is a positive pudendal nerve block. The authors report that they have also clarified a number of complementary diagnostic criteria and several exclusion criteria that make the diagnosis unlikely. When pudendal neuralgia due to pudendal nerve entrapment is diagnosed according to the Nantes criteria, no further investigation is required and medical or surgical treatment can be proposed. Nevertheless, a number of warning signs suggesting other possible causes of pudendal neuralgia must not be overlooked. These warning signs (red flags) are: waking up at night, excessively neuropathic nature of the pain (for example, associated with hypoesthesia), specifically pinpointed pain, which can suggest neuroma and pain associated with neurological deficit. In these atypical presentations, the diagnosis of pain due to pudendal nerve entrapment should be reconsidered and a radiological examination should be performed. The 2 cases described in this report (tumour compression of the pudendal nerve) illustrate the need to recognize atypical pudendal neuralgia and clarify the role of pelvic magnetic resonance imaging (MRI), as MRI provides very valuable information for the evaluation of diseases involving the ischiorectal fossa. The presence of red flags must be investigated in all cases of pudendal neuralgia to avoid missing pudendal neuralgia secondary to a mechanism other than nerve entrapment.

[SELECTION CRITERIA FOR SURGICAL TREATMENT OF PUDENDAL NEURALGIA.](#)

Charlotte W, Sebastian D, Viviane T, Luc B. Neurourol Urodyn. 2016 Mar 21. doi: 10.1002/nau.22988. [Epub ahead of print] PMID: 26999519

The authors from Brussels, Belgium report that pudendal neuralgia is the clinical expression of a chronic compression of the pudendal nerve. The diagnosis is based on a set of five criteria, called Nantes Criteria. Four of the criteria are clinical and the last requires evaluation of the anesthetic response to CT-guided infiltration of the pudendal nerve. The aim of this study was to evaluate the relevance of anesthetic test response to select patients for surgery, and whether this criterion can be used to predict its success. Retrospective analysis of a cohort of 34 patients undergoing surgical treatment. In their cohort, the authors included six patients with negative CT-guided pudendal nerve infiltration test. Of the 28 patients that met all five Nantes criteria, 64% (18 patients) responded well to surgery. In contrast, 100% of the six patients with a negative anesthetic test failed to show an amelioration of symptoms after surgical treatment. In their analysis, there was no significant difference in surgery response when men were compared to women, when procedure was unilateral or bilateral, or when duration of symptoms was long. They observed a difference in terms of age between the group of responders and non-responders, although this difference did not reach the threshold of significance. The authors conclude that the selection of candidates for surgery should always include a single diagnostic anesthetic injection of the pudendal nerve, as the fifth of the Nantes criteria is an effective predictor of the success of surgery.

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