

# International Painful Bladder Foundation

*The IPBF is a voluntary non-profit organization for interstitial cystitis/bladder pain syndrome/hypersensitive bladder*  
[www.painful-bladder.org](http://www.painful-bladder.org)

## IPBF e-Newsletter and Research Update

Issue 37, September 2014

*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, chronic pelvic pain and associated disorders.*

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

- **Meeting Reviews**
- **Upcoming Events**
- **Patient Organization News (congratulations to COB Foundation on LUTS awards)**
- **Books**
- **Websites**
- **Research Highlights**
- **Donations & Sponsoring**

### MEETING REVIEWS

#### REVIEW OF THE ESSIC ANNUAL MEETING 2014 13-15 JUNE, PHILADELPHIA, USA

The 2014 ESSIC annual meeting was a unique occasion because it was the first ESSIC (International Society for the Study of Bladder Pain Syndrome) annual meeting to be held in the United States.

#### **New ESSIC President Professor Jean-Jacques Wyndaele**

It was announced at this meeting that Professor Jørgen Nordling from Denmark, who took the initiative to set up ESSIC a decade ago, would be retiring as President of ESSIC and that Professor Jean-Jacques Wyndaele from Antwerp, Belgium would be taking over the reins as the new President. We wish him every success.

Meeting hosts Philip Hanno, MD, Kristene Whitmore, MD, and Jørgen Nordling, MD emphasised that the focus of the meeting would be on the differences between patients with and without Hunner lesion, with the aim of making it an interactive meeting with maximum discussion. Attendees from around the world included patient advocates Lee Claassen (ICA Executive Director, USA), Rhonda Garrett (ICA, USA), Vicki Ratner, MD (Founder and President Emeritus ICA, USA), Loredana Nasta (President AICI, Italy) and Jane Meijlink (Chair IPBF, Netherlands), all of whom played an active role in this meeting.

There was a detailed update on the NIH/NIDDK MAPP project (Multidisciplinary Approach to the study of chronic Pelvic Pain) presented by Chris Mullins, PhD, from the NIDDK, followed by J. Quentin Clemens, MD (from University of Michigan Medical Center) who is chair of the MAPP Network.

The working groups on the second day, focusing on different themes related to Hunner lesion, also included a patient advocates working group. It is hoped that all working group findings will be included in an article for publication.

At the end of the meeting, Professor Jørgen Nordling announced that the 2015 annual meeting of ESSIC would be held in Rome in September.

**For a detailed review of the meeting, [click here](#) or go to the IPBF home page at [www.painful-bladder.org](http://www.painful-bladder.org).**

## UPCOMING EVENTS

### 15<sup>TH</sup> WORLD CONGRESS ON PAIN, 6-11 OCTOBER 2014, BUENOS AIRES

The 15th World Congress on Pain, organised by the International Association for the Study of Pain (IASP) takes place 6-11 October 2014, in Buenos Aires, Argentina and will be attended by over 6,000 pain specialists from all over the world to learn about new developments and advances in the field of pain, from laboratory science to clinical diagnosis, management, and prevention. The programme includes plenary sessions, topical workshops, refresher courses, and poster sessions covering every aspect of acute and chronic pain from basic science to clinical practice. [Click here](#) for further information.

### INTERNATIONAL CONTINENCE SOCIETY (ICS) ANNUAL SCIENTIFIC MEETING RIO DE JANEIRO, 20 - 24 OCTOBER 2014

The ICS Annual Scientific Meeting is to be held in Rio de Janeiro, Brazil this year. The scientific programme will include posters and abstract presentation on IC/BPS and related topics as well as a number of workshops:

#### New Continenence Awareness Forum in Rio

The Continenence Promotion Committee (CPC) is pleased to announce this year's public forum will have a facelift as well as a name change. This year in Rio, it will be presenting the "**Continenence Awareness Forum**".

This event will take place on Wednesday 22nd October 2014 from 17.00-20.00 hrs. As well as the general public, health care providers from all fields as well as patient advocacy groups are invited. The ICS plans on having various national patient advocacy groups exchange and share their knowledge and expertise, as well as ICS opinion leaders on important news and changes. It is hoped that this will be an exchange of information on incontinence and its treatment among countries including patients, healthcare professionals and industry representatives.

As reimbursement issues are becoming a hot topic, the CPC looks forward to discussing and hearing about these issues and policies at its forum. This will enable countries with treatment insurance problems to learn from each other. The event will be filmed and will be available via ICS TV, news pages and social media.

[Click here](#) for a programme overview of the ICS annual scientific meeting.

### PAIN ALLIANCE EUROPE AND SOCIETAL IMPACT OF PAIN (SIP) 2014, 17-18 NOVEMBER, 2014, BRUSSELS

The Pain Alliance Europe (PAE) members General Assembly will take place in Brussels on Monday, November 17. A press conference disseminating the results of the Pain Patient Pathway Recommendations is scheduled for the afternoon. The following day, the SIP (Societal Impact of Pain) Symposium will be held in the European Parliament. This meeting gives everyone a chance to share thoughts, opinions, plan effective actions and meet key people. The timing of this year's SIP symposium is scheduled to coincide with the Italian Presidency of the EU council as during this period for this first TIME ever all EU Health Ministers will be discussing the societal burden of Chronic Pain and Palliative Care and will be actively debating how to address this health policy priority in the years to come. It was decided to celebrate the 5th SIP symposium by inviting Nick Ross, one of Europe's most well-known journalists and scientific moderators to lead four interactive panel discussions. Once a year politicians, key stakeholders representing all the interest groups such as budget holders, decision makers, HTA bodies, health care professionals and pain advocacy groups gather for the annual SIP symposium in Brussels to create awareness about the societal impact of pain in Europe and to develop and foster European-wide policy strategies & activities for improved pain care in Europe. The SIP symposium also provides the opportunity to exchange information on best practices and to network with stakeholders from all over Europe. Further information: [www.sip-platform.eu](http://www.sip-platform.eu)

### **MEDITERRANEAN INCONTINENCE AND PELVIC FLOOR SOCIETY (MIPS) 2<sup>nd</sup> ANNUAL MEETING, 26-29 NOVEMBER, 2014**

The second annual meeting of MIPS will be held in Nimes, France at the Novotel Atria Hotel. The theme will be: Pelvic Floor Dysfunctions in the Mediterranean: climbing a long hill? There will be simultaneous translation English/French. <http://www.mipsnet.org>

### **ABDOMINOPELVIC PAIN SYMPOSIUM 2014**

18 December 2014, National Hospital for Neurology and Neurosurgery, Queen Square, London. The symposium will include lectures and interactive workshops on key topics in abdominal and pelvic pain management. For registration and further information: [www.pelvicpainsymposium.com](http://www.pelvicpainsymposium.com)

### **13TH INTERNATIONAL SYMPOSIUM ON SJÖGREN'S SYNDROME**

The 13<sup>th</sup> International Symposium on Sjögren's Syndrome will be held 19-22 May, 2015 in Bergen, Norway. Further information will be available on <http://www.sicca.org/iss2015/>

### **2<sup>nd</sup> WORLD CONGRESS ON ABDOMINAL AND PELVIC PAIN (WCAPP), 11-13 JUNE 2015, NICE, FRANCE**

Following the great success of the 1<sup>st</sup> WCAPP held in Amsterdam, this 2nd WCAPP will be organised 11-13 June 2015 in Nice, France by Convergences PP in collaboration with IPPS and APP-IASP. Further information will be published on [www.pelvicpain-meeting.com](http://www.pelvicpain-meeting.com).

### **2<sup>ND</sup> GLOBAL CONGRESS ON LOWER URINARY TRACT DYSFUNCTION 2015**

The Second Global Congress on LUTD will be held 24-26 June 2015 in Rome, Italy. <http://lutd.org>

### **ESSIC ANNUAL MEETING 2015**

To be held in Rome, Italy in September, 2015. Further details will follow. [www.essic.eu](http://www.essic.eu)

## **PATIENT ORGANIZATION NEWS**

### **CONGRATULATIONS TO COB FOUNDATION ON UK LUTS AWARDS!**

We would like to warmly congratulate the Cystitis and Overactive Bladder (COB) Foundation for patients with IC/BPS, cystitis and overactive bladder for scooping two top awards in the National LUTS Continence Care Awards where COB was voted the best organisation in the United Kingdom for providing clear accurate patient information, while their telephone advice staff also won the award for giving the best quality, empathetic advice to callers. A fantastic achievement and an inspiration to others! The COB Foundation also produces an excellent magazine three times a year which now has a new name: **"Your Bladder Health"**. For further information about the COB Foundation, go to: [www.cobfoundation.org](http://www.cobfoundation.org)

## **BOOKS**

### **Interstitial Cystitis**

By Dr Rajesh Taneja (India)

Published by Kontentworx

ISBN: 978-93-83988-00-6

Email: [contact@kontentworx.com](mailto:contact@kontentworx.com)

A useful reference book for health professionals in India, but also very readable by patients. With chapters contributed by Drs Philip Hanno and Jorgen Nordling.

And a reminder about the comprehensive book:

## **Bladder Pain Syndrome**

### ***A Guide for Clinicians***

Jørgen Nordling, Jean-Jacques Wyndaele, Joop P van de Merwe, Pierre Bouchelouche, Mauro Cervigni, Magnus Fall (Editors.)

Published by Springer 2013, 365 p.

ISBN 978-1-4419-6929-3

[Click here](#) for the Content of the book

<http://www.springer.com/medicine/urology/book/978-1-4419-6928-6>

And in the field of co-morbid pain syndromes, the following from the IASP may be of interest:

***Orofacial Pain: Recent Advances in Assessment, Management, and Understanding of Mechanisms*, Barry J. Sessle** (editor).

Published by IASP Press, July 2014. 496 pages.

ISBN 978-0-931092-17-6.

*Orofacial Pain* provides the most up-to-date, complete, and integrated coverage of advances in research and new evidence. *Orofacial Pain* is published in conjunction with the [Global Year on Orofacial Pain](#). The International Association for the Study of Pain (IASP) sponsors and promotes the Global Year Against Pain, a year-long initiative designed to raise international awareness of a specific type of pain. Further information from the IASP website: <http://www.iasp-pain.org>.

## **WEBSITES**

### **PUDENDAL NEURALGIA ASSOCIATION (PNA)**

The PNA's mission is to provide educational services to medical personnel and those affected by pudendal neuralgia and their families through conferences, meetings, workshops, pamphlets, and online information.

<http://pudendalassociation.org>

### **INTERNATIONAL NEUROMODULATION SOCIETY (INS)**

The International Neuromodulation Society (INS) is a nonprofit group of clinicians, scientists and engineers dedicated to the scientific development and awareness of neuromodulation – the alteration of nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body. While specifically for professionals, it nevertheless is a useful site for patients wishing to know more about neuromodulation.

<http://www.neuromodulation.com>

### **NATIONAL KIDNEY AND UROLOGIC DISEASES INFORMATION CLEARINGHOUSE (NKUDIC) IN THE USA**

A useful A-Z list of health topics in the field of kidney and urologic diseases can be found at: <http://kidney.niddk.nih.gov/KUDiseases/a-z.aspx>. The NIDDK also has downloadable fact sheets, easy-to-read booklets and an awareness and prevention series with links from this A-Z page.

### **NIDDK PATIENT INFORMATION: DIGESTIVE SYSTEM**

Since many IC/BPS patients suffer from irritable bowel syndrome with chronic abdominal pain, cramps, bloating, gas, constipation, and diarrhoea, it is useful to note the following updates:

[The National Institute of Diabetes and Digestive and Kidney Diseases](#) (NIDDK) recently updated its information on The Digestive System and how it works:

<http://www.digestive.niddk.nih.gov/ddiseases/pubs/yrdd/index.aspx>. The NIDDK has free resources about IBS and related digestive disorders available to the public, including:

[Irritable Bowel Syndrome](#) [Irritable Bowel Syndrome in Children](#) [Irritable Bowel Syndrome: What You Need to Know](#) (En Español) [What I need to know about Irritable Bowel Syndrome](#)

### **AUA WEBCASTS 2014**

The American Urological Association has many webcasts of its 2014 meeting available free online. Go to:

<http://www.aa2014.org/webcasts/>

## A NEW SHORT FOOD SENSITIVITY QUESTIONNAIRE FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

A new food sensitivity questionnaire for Interstitial Cystitis/Bladder Pain Syndrome is available to assist with patient care. See: Shorter B, Ackerman M, Varvara M, Moldwin R, Statistical Validation of the Shorter-Moldwin Food Sensitivity Questionnaire for Patients with Interstitial Cystitis/Bladder Pain Syndrome, J of Urol 2014;191:1793.

Virtually all guidelines today suggest dietary changes as first line treatment for IC/BPS. This short form diet history questionnaire based on a previously validated long form\* is a reliable, newly validated instrument that will help identify comestibles associated with IC/BPS pain syndrome symptoms. Its brevity makes it simple to administer and useful for dietary management in IC/BPS patients.

\* Shorter B, Lesser M, Moldwin R, Kushner L, Effect of Comestibles on Symptom of Interstitial Cystitis, J of Urol 2007;178:145.

## 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 are synonymous. When reviewing the article, we generally use the terminology used by the authors.

#### Reminder

#### INTERNATIONAL JOURNAL OF UROLOGY (IJU) SPECIAL ISSUE

The proceedings of the 3rd International Consultation on Interstitial Cystitis, Japan (ICICJ) and the International Society for the Study of Bladder Pain Syndrome (ESSIC) Joint Meeting, held 21–23 March 2013, Kyoto, Japan, have been published in a special issue of the International Journal of Urology, April 2014, Volume 21, Supplement S1. [Click here](#) for the state-of-the-art in the field of IC/BPS and associated disorders or go to <http://onlinelibrary.wiley.com/doi/10.1111/iju.2014.21.issue-s1/issuetoc>.

All articles in this special supplement have free access.

#### THE MAPP RESEARCH NETWORK: DESIGN, PATIENT CHARACTERIZATION AND OPERATIONS.

Landis JR, Williams DA, Lucia MS, Clauw DJ, Naliboff BD, Robinson NA, van Bokhoven A, Sutcliffe S, Schaeffer AJ, Rodriguez LV, Mayer EA, Lai HH, Krieger JN, Kreder KJ, Afari N, Andriole GL, Bradley CS, Griffith JW, Klumpp DJ, Hong BA, Lutgendorf SK, Buchwald D, Yang CC, Mackey S, Pontari MA, Hanno P, Kusek JW, Mullins C, Clemens JQ; MAPP Research Network Study Group. Collaborators (119). BMC Urol. 2014 Aug 1;14:58. doi: 10.1186/1471-2490-14-58.PMID: 25085119

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The "Multidisciplinary Approach to the Study of Chronic Pelvic Pain" (MAPP) Research Network was established by the NIDDK to better understand the pathophysiology of urologic chronic pelvic pain syndromes (UCPPS), to inform future clinical trials and improve clinical care. The evolution, organization, and scientific scope of the MAPP Research Network, and the unique approach of the network's central study and common data elements are described. The primary scientific protocol for the Trans-MAPP Epidemiology/Phenotyping (EP) Study comprises a multi-site, longitudinal observational study, including bi-weekly internet-based symptom assessments, following a comprehensive in-clinic deep-phenotyping array of urological symptoms, non-urological symptoms and psychosocial factors to evaluate men and women with UCPPS. Healthy controls,

matched on sex and age, as well as "positive" controls meeting the non-urolologic associated syndromes (NUAS) criteria for one or more of the target conditions of Fibromyalgia (FM), Chronic Fatigue Syndrome (CFS) or Irritable Bowel Syndrome (IBS), were also evaluated. Additional, complementary studies addressing diverse hypotheses are integrated into the Trans-MAPP EP Study to provide a systemic characterization of study participants, including biomarker discovery studies of infectious agents, quantitative sensory testing, and structural and resting state neuroimaging and functional neurobiology studies. A highly novel effort to develop and assess clinically relevant animal models of UCPPS was also undertaken to allow improved translation between clinical and mechanistic studies. Recruitment into the central study occurred at six Discovery Sites in the United States, resulting in a total of 1,039 enrolled participants, exceeding the original targets. The biospecimen collection rate at baseline visits reached nearly 100%, and 279 participants underwent common neuroimaging through a standardized protocol. An extended follow-up study for 161 of the UCPPS participants is ongoing. The MAPP Research Network represents a novel, comprehensive approach to the study of UCPPS, as well as other concomitant NUAS. Findings are expected to provide significant advances in understanding UCPPS pathophysiology that will ultimately inform future clinical trials and lead to improvements in patient care. Furthermore, the structure and methodologies developed by the MAPP Network provide the foundation upon which future studies of other urologic or non-urolologic disorders can be based.

#### **THE MAPP RESEARCH NETWORK: A NOVEL STUDY OF UROLOGIC CHRONIC PELVIC PAIN SYNDROMES.**

*Clemens JQ, Mullins C, Kusek JW, Kirkali Z, Mayer EA, Rodriguez LV, Klumpp DJ, Schaeffer AJ, Kreder KJ, Buchwald D, Andriole GL, Lucia MS, Landis JR, Clauw DJ; MAPP Research Network Study Group. BMC Urol. 2014 Aug 1;14:57. doi: 10.1186/1471-2490-14-57. PMID: 25085007*

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Urologic chronic pelvic pain syndrome (UCPPS) may be defined to include interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The hallmark symptom of UCPPS is chronic pain in the pelvis, urogenital floor, or external genitalia often accompanied by lower urinary tract symptoms. Despite numerous past basic and clinical research studies there is no broadly identifiable organ-specific pathology or understanding of etiology or risk factors for UCPPS, and diagnosis relies primarily on patient reported symptoms. In addition, there are no generally effective therapies. Recent findings have, however, revealed associations between UCPPS and "centralized" chronic pain disorders, suggesting UCPPS may represent a local manifestation of more widespread pathology in some patients. Here, the authors describe a new and novel effort initiated by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the U.S. National Institutes of Health (NIH) to address the many long standing questions regarding UCPPS, the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. The MAPP Network approaches UCPPS in a systemic manner, in which the interplay between the genitourinary system and other physiological systems is emphasized. The network's study design expands beyond previous research, which has primarily focused on urologic organs and tissues, to utilize integrated approaches to define patient phenotypes, identify clinically-relevant subgroups, and better understand treated natural history and pathophysiology. Thus, the MAPP Network provides an unprecedented, multi-layered characterization of UCPPS. Knowledge gained is expected to provide important insights into underlying pathophysiology, a foundation for better segmenting patients for future clinical trials, and ultimately translation into improved clinical management. In addition, the MAPP Network's integrated multi-disciplinary research approach may serve as a model for studies of urologic and non-urolologic disorders that have proven refractory to past basic and clinical study.

#### **INCREASED BRAIN GRAY MATTER IN THE PRIMARY SOMATOSENSORY CORTEX IS ASSOCIATED WITH INCREASED PAIN AND MOOD DISTURBANCE IN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME PATIENTS.**

*Kairys AE, Schmidt-Wilcke T, Puiu T, Ichesco E, Labus JS, Martucci K, Farmer MA, Ness TJ, Deutsch G, Mayer EA, Mackey S, Apkarian AV, Maravilla K, Clauw DJ, Harris RE. J Urol. 2014 Aug 14. pii: S0022-5347(14)04213-X. doi: 10.1016/j.juro.2014.08.042. [Epub ahead of print] PMID: 25132239*

Emerging data suggests there are central neurobiological components to the etiology of this disease. Here we report the first brain structural imaging findings from the Multidisciplinary Approach to Pelvic Pain (MAPP) network, with data on over 300 participants. Kairys et al used Voxel-Based Morphometry (VBM) to determine

whether human patients with chronic IC display changes in brain morphology as compared to healthy controls (HCs). 33 female IC patients without comorbidities and 33 age- and sex-matched controls, taken from the larger sample, underwent structural magnetic resonance imaging at 5 different MAPP sites across the United States. When compared to controls, females with IC displayed significant increased gray matter (GM) volume in several regions of the brain including the right primary somatosensory cortex (S1), the superior parietal lobule bilaterally, and the right supplementary motor area. GM volume in the right S1 was associated with greater pain, mood (anxiety), and urological symptoms. The authors explored these correlations in a linear regression model and found independent effects of these three measures on S1 GM volume: clinical pain (McGill pain sensory total), a measure of "urgency," and anxiety (HADS). They conclude that these data support the notion that changes in somatosensory GM may play an important role in pain sensitivity as well as affective and sensory aspects of IC. Further studies are needed to confirm the generalizability of these findings to other pain conditions.

#### **INFLAMMATION AND INFLAMMATORY CONTROL IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: ASSOCIATIONS WITH PAINFUL SYMPTOMS.**

*Schrepf A, O'Donnell M, Luo Y, Bradley CS, Kreder K, Lutgendorf S; Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. Pain. 2014 Jun 5. pii: S0304-3959(14)00262-0. doi: 10.1016/j.pain.2014.05.029. [Epub ahead of print] PMID: 24907404*

Toll-like receptors (TLR) are known to play a role in chronic pain, from animal models and limited research in humans, but their role in interstitial cystitis/bladder pain syndrome (IC/BPS) is unknown. Similarly, alterations of the hypothalamic-pituitary-adrenal axis have been reported in some pain conditions. The objectives were to identify inflammatory processes that might distinguish individuals with IC/BPS from healthy controls (HC) and to examine their associations with IC/BPS symptoms. Female participants (58IC/BPS patients and 28HCs) completed pain and urinary symptom questionnaires and collected saliva for cortisol as part of the Multidisciplinary Approach to Pelvic Pain study. Inflammatory cytokines were assayed in plasma, and in TLR-2- and TLR-4-stimulated peripheral blood mononuclear cells. Controlling for BMI and negative effect, between-group differences were analyzed by general linear models, and relationships between symptoms and inflammatory variables were analyzed by regression. Compared to HCs, IC/BPS patients had higher levels of plasma interleukin-6, greater interleukin-1 $\beta$  responsive to TLR-2 stimulation, and flatter diurnal cortisol slopes, indicating inflammatory dysregulation. In IC/BPS patients, inflammation after TLR-4 stimulation was associated with multiple symptoms, including genitourinary pain, sexual pain, and marginally with urinary symptoms. Genitourinary pain severity, frequency, and pain with intercourse were strongly associated with TLR-4 inflammatory response. TLR-4 appears to play a central role in painful symptoms of IC/BPS patients, which may be linked to poor endogenous inflammatory control. These findings may help to identify new mechanisms in IC/BPS and lead to new therapeutic approaches.

#### **POLYOMAVIRUS BK - A POTENTIAL NEW THERAPEUTIC TARGET FOR PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS?**

*Van der Aa F, Beckley I, de Ridder D. Med Hypotheses. 2014 Sep;83(3):317-20. doi: 10.1016/j.mehy.2014.06.004. Epub 2014 Jun 13. PMID: 24973060*

An interesting study from Belgium and the United Kingdom that investigated the role of urinary BK polyoma virus (BKPyV) in the pathophysiology and prognosis of patients with painful bladder syndrome/interstitial cystitis (PBS/IC). Urine samples were collected from 15 patients with PBS/IC and 8 control patients (with urolithiasis, overactive bladder and benign prostatic hyperplasia). BKPyV titres were quantitatively determined using real time PCR. Fisher's exact test was used to compare virus titre levels between the two groups. The PBS/IC patients subsequently underwent cystoscopy, hydrodistension and bladder biopsy. Finally, a chart review was performed in order to correlate PBS/IC subtype and treatment outcomes with BKPyV status. Positive BKPyV titres were found in 11 out of 15 PBS/IC patients but none of the controls. Cystoscopy was performed in 13 of the 15 PBS/IC patients (in 2 BKPyV positive patients, cystoscopy was not performed). Bladder ulceration and glomerulations were observed in all 9 BKPyV positive PBS/IC patients but only 1 out of 4 BKPyV negative patients. None of the non-ulcerative PBS/IC patients had BKPyV positive urine. Viral titres were not predictive of the clinical course however, 3 patients with the highest viral titres eventually underwent cystectomy. The authors report that they identified BKPyV in the urine of virtually all their patients with

ulcerative PBS/IC. This finding suggests there may be a pathophysiological association between the virus and the haemorrhagic manifestations of PBS/IC. Classifying PBS/IC patients into BKPyV positive or negative groups may prove useful in future research on markers of disease prognosis and the subtypes of PBS/IC. They believe that BKPyV may therefore have a role as a potential therapeutic target in PBS/IC.

#### **EVIDENCE FOR BLADDER UROTHELIAL PATHOPHYSIOLOGY IN FUNCTIONAL BLADDER DISORDERS.**

Keay SK, Birder LA, Chai TC. *Biomed Res Int.* 2014;2014:865463. doi: 10.1155/2014/865463. Epub 2014 May 8. PMID:24900993

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Understanding of the role of urothelium in regulating bladder function is continuing to evolve. While the urothelium is thought to function primarily as a barrier for preventing injurious substances and microorganisms from gaining access to bladder stroma and upper urinary tract, studies indicate it may also function in cell signalling events relating to voiding function. This review highlights urothelial abnormalities in bladder pain syndrome/interstitial cystitis (BPS/IC), feline interstitial cystitis (FIC), and nonneurogenic idiopathic overactive bladder (OAB). These bladder conditions are typified by lower urinary tract symptoms including urinary frequency, urgency, urgency incontinence, nocturia, and bladder discomfort or pain. Urothelial tissues and cells from affected clinical subjects and asymptomatic controls have been compared for expression of proteins and mRNA. Animal models have also been used to probe urothelial responses to injuries of the urothelium, urethra, or central nervous system, and transgenic techniques are being used to test specific urothelial abnormalities on bladder function. BPS/IC, FIC, and OAB appear to share some common pathophysiology including increased purinergic, TRPV1, and muscarinic signaling, increased urothelial permeability, and aberrant urothelial differentiation. One challenge is to determine which of several abnormally regulated signalling pathways is most important for mediating bladder dysfunction in these syndromes, with a goal of treating these conditions by targeting specific pathophysiology.

#### **VARIATIONS IN THE REPORTING OF OUTCOMES USED IN SYSTEMATIC REVIEWS OF TREATMENT EFFECTIVENESS RESEARCH IN BLADDER PAIN SYNDROME.**

Tirlapur SA, Riordain RN, Khan KS; EBM-CONNECT Collaboration. *Eur J Obstet Gynecol Reprod Biol.* 2014 Jun 13;180C:61-67. doi: 10.1016/j.ejogrb.2014.06.003. [Epub ahead of print]. PMID: 25020277

This paper from London investigates the quality of outcomes reported in systematic reviews and randomised controlled trials (RCTs) of bladder pain syndrome and its relationship with study quality and journal impact factor. Tirlapur and colleagues searched until August 2013 the Cochrane Library, EMBASE, Medline, CINAHL, LILACS and SIGLE, without language restrictions. Quality of outcome reporting in systematic reviews and constituent RCTs was assessed using a 6-point scale. Overall study quality was assessed using the AMSTAR and Jadad scoring systems, and impact factor in the year of publication was noted. Spearman's rank correlation was calculated. There were 8 systematic reviews, with a total of 28 RCTs (1732 patients), reporting 5 outcomes using 19 different measurement scales. The outcomes reported in individual RCTs were urinary symptoms (100%), pain (64%), quality of life (39%), general wellbeing (36%) and bladder capacity (36%). The mean quality of outcomes reported was 1.63 for systematic reviews and 3.25 for RCTs. The quality of outcomes reported showed correlation with overall study quality but not with journal impact factor. Multivariable linear regression showed a relationship between quality of outcome reporting and study quality, adjusting for effects of study type, impact factor and journal type. There is a need to generate consensus over a set of core outcomes in bladder pain syndrome using standardised reporting tools and to disseminate these through good publication practice.

#### **CORRELATION OF GENE EXPRESSION WITH BLADDER CAPACITY IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.**

Colaco M, Koslov DS, Keys<sup>2</sup>, Evans RJ, Badlani GH, Andersson KE, Walker SJ. *J Urol.* 2014 May 17. pii: S0022-5347(14)03576-9. doi: 10.1016/j.juro.2014.05.047. [Epub ahead of print] PMID: 24840534

Interstitial cystitis and bladder pain syndrome are terms used to describe a heterogeneous chronic pelvic and bladder pain disorder. Despite its significant prevalence, our understanding of disease etiology is poor. Colaco and colleagues molecularly characterized interstitial cystitis/bladder pain syndrome and determined whether there are clinical factors that correlate with gene expression. Bladder biopsies from female subjects with



interstitial cystitis/bladder pain syndrome and female controls without signs of the disease were collected and divided into those with normal and low anesthetized bladder capacity, respectively. Samples then underwent RNA extraction and microarray assay. A total of 16 subjects were included in the study. Principal component analysis and unsupervised hierarchical clustering showed clear separation between gene expression in tissues from subjects with low compared to normal bladder capacity. Gene expression in tissue from patients with interstitial cystitis/bladder pain syndrome who had normal bladder capacity did not significantly differ from that in controls without interstitial cystitis/bladder pain syndrome. Pairwise analysis revealed that pathways related to inflammatory and immune response were most involved. Microarray analysis provides insight into the potential pathological condition underlying interstitial cystitis/bladder pain syndrome. This pilot study shows that patients with this disorder who have low compared to normal bladder capacity have significantly different molecular characteristics, which may reflect a difference in disease pathophysiology.

#### **MELATONIN TREATMENT FURTHER IMPROVES ADIPOSE-DERIVED MESENCHYMAL STEM CELL THERAPY FOR ACUTE INTERSTITIAL CYSTITIS IN RAT.**

*Chen YT, Chiang HJ, Chen CH, Sung PH, Lee FY, Tsai TH, Chang CL, Chen HH, Sun CK, Leu S, Chang HW, Yang CC, Yip HK. J Pineal Res. 2014 Aug 6. doi: 10.1111/jpi.12164. [Epub ahead of print] PMID: 25132326*

This study from Kaohsiung, Taiwan tests the hypothesis that combined melatonin and adipose-derived mesenchymal stem cell (ADMSC,  $1.2 \times 10^6$  given intravenously) treatment offer superior protection against cyclophosphamide (CYP 150 mg/kg)-induced acute interstitial cystitis (AIC) in rats. Male adult Sprague-Dawley rats were treated as follows: sham controls, AIC alone, AIC + melatonin, AIC + ADMSC, and AIC + melatonin + ADMSC. When melatonin was used, it was given as follows: 20 mg/kg at 30 min after CYP and 50 mg/kg at 6 and 18 hr after CYP. Twenty-four-hour urine volume, urine albumin level, and severity of hematuria were highest in AIC rats and lowest in the controls; likewise urine volume was higher in AIC + melatonin rats than in AIC + ADMSC and AIC + melatonin + ADMSC treated rats. The numbers of CD14+, CD74+, CD68+, MIP+, Cox-2+, substance P+, cells and protein expression of IL-6, IL-12, RANTES, TNF- $\alpha$ , NF- $\kappa$ B, MMP-9, iNOS (i.e. inflammatory biomarkers), glycosaminoglycan level, expression of oxidized protein, and protein expression of reactive oxygen species (NOX-1, NOX-2, NOX-4) in the bladder tissue exhibited an identical pattern compared with that of hematuria among the five groups. The integrity of epithelial layer and area of collagen deposition displayed an opposite pattern compared to that of hematuria among all groups ( $P < 0.0001$ ). The cellular expressions of antioxidants showed a significant progressive increase from controls to AIC + melatonin + ADMSC. Combined regimen of melatonin and ADMSC was superior to either alone in protecting against CYP-induced AIC.

#### **URINARY NERVE GROWTH FACTOR COULD BE A BIOMARKER FOR INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: A META-ANALYSIS.**

*Qu HC, Zhang W, Yan S, Liu YL, Wang P. PLoS One. 2014 Sep 2;9(9):e106321. doi: 10.1371/journal.pone.0106321. eCollection 2014. PMID: 25181532*

The purpose of this study from Shenyang, China was to examine whether urinary nerve growth factor (NGF) could serve as a biomarker for interstitial cystitis/painful bladder syndrome (IC/PBS). Qu and colleagues conducted a comprehensive meta-analysis of 9 studies. Among the studies considered, patients with IC/PBS had higher urinary NGF and NGF/Cr levels compared to those of healthy people. In addition, there was a significant difference between patients with IC/PBS and patients with overactive bladder. Furthermore, patients had a significantly lower urinary NGF level after successful treatment. In conclusion, the authors suggest that urinary NGF could be a useful biomarker for the diagnosis of OAB, a urinary biomarker for the differential diagnosis of IC/PBS and OAB (when a critical urinary NGF or NGF/Cr level is needed), and a predictive biomarker to help guide treatment.

#### **CLINICAL AND PSYCHOLOGICAL PARAMETERS ASSOCIATED WITH PAIN PATTERN PHENOTYPES IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS).**

*Nickel JC, Tripp DA, International Interstitial Cystitis Study Group. J Urol. 2014 Aug 1. pii: S0022-5347(14)04148-2. doi: 10.1016/j.juro.2014.07.108. [Epub ahead of print]. PMID: 25092637*

The International Interstitial Cystitis Study Group, led by JC Nickel, note that it has recently been suggested that two distinct clinical phenotypes can be described in patients with UCPPS: Pelvic pain only (PP Only) and pelvic

pain and beyond (PP Beyond). IC/BPS patient data, which included body pain location mapping and associated medical and psychosocial phenotyping, was examined to validate these body pain maps within a cohort of tertiary care female IC/BPS patients. Validated questionnaires from 173 diagnosed outpatient female IC/BPS patients included a body pain area diagram, demographics/history, pain assessment, IC/BPS symptoms, depression, anxiety, stress, fatigue, sexual functioning, catastrophizing, QoL and data on other chronic pain conditions. Two pain phenotypes, created based on counts of body locations, PP Only and PP Beyond, were comprehensively examined. Patients identified with PP Beyond reported more sensory-type pain, poorer physical quality of life, greater somatic depression and sleep disturbance than those categorized as PP Only. Sexual pain scored higher in the PP Only group. Furthermore, patients with PP Beyond phenotype report a higher prevalence of IBS and fibromyalgia as well as more general fatigue symptoms and psychiatric conditions. The study group concluded that two distinct pain location phenotypes of PP Only and PP Beyond have been demonstrated by their independent analysis of IC/BPS patients. Assessment of clinical phenotypes based on pain patterns has significant ramifications in our improved understanding of both the etiology and management of female patients diagnosed with IC/BPS.

#### **EXPLORING ASSOCIATIONS BETWEEN LUTS AND GI PROBLEMS IN WOMEN: A STUDY IN WOMEN WITH UROLOGICAL AND GI PROBLEMS VERSUS A CONTROL POPULATION.**

Wyndaele M, De Winter BY, Pelckmans PA, De Wachter S, Van Outryve M, Wyndaele JJ. *BJU Int.* 2014 Aug 15. doi: 10.1111/bju.12904. [Epub ahead of print]. PMID: 25124824

The purpose of this study from Belgium was firstly to study the prevalence of self-reported LUTS in women consulting a Gastroenterology clinic with complaints of functional constipation (FC), fecal incontinence (FI) or both, compared to a female control population. Secondly, to study the influence of FC, FI, or both on self-reported LUTS in women attending a Urology clinic. This was a retrospective study of data collected through a validated self-administered bladder and bowel symptom questionnaire in a tertiary referral hospital from three different female populations: 104 controls, 159 gastroenterological patients and 410 urological patients. Based on the reported bowel symptoms, patients were classified as having FC, FI, a combination of both, or, no FC or FI. LUTS were compared between the control population and the gastroenterological patients, and between urological patients with and without concomitant gastroenterological complaints. Results were corrected for possible confounders through logistic regression analysis. As LUTS are reported significantly more often by female gastroenterological patients than by a control population, and as there is a difference in self-reported LUTS between female urological patients with different concomitant gastroenterological complaints, the authors suggest that general practitioners, gastroenterologists and urologists should always include the assessment of symptoms of the other pelvic organ system in their patient evaluation. The clinical correlations between bowel and LUT symptoms may be explained by underlying neurological mechanisms.

#### **EXAMINATION OF THE SIGNIFICANT PLACEBO EFFECT IN THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.**

Bosch PC. *Urology.* 2014 Aug;84(2):321-6. doi: 10.1016/j.urology.2014.04.011. Epub 2014 Jun 21. PMID: 24958479

The placebo effect has always been a mystery in IC-BPS patients. This study by Bosch examined the significant "placebo effect" in a randomized, double-blind, placebo-controlled interstitial cystitis/bladder pain syndrome trial. Randomized clinical trials are the reference standard for therapeutic impact assessment. However, proving efficacy of treatments for IC/BPS with rigorous placebo-controlled trials is difficult due to a significant effect of the placebo intervention. IC/BPS patients were randomized to receive subcutaneous adalimumab or subcutaneous placebo every 2 weeks for 12 weeks and outcome measures were assessed. Of the 43 patients, 21 received adalimumab and 22 received placebo. Of the patients who received placebo, there was a statistically significant improvement demonstrated in the O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes of -8.1, Interstitial Cystitis Symptom Index of -3.7, Interstitial Cystitis Problem Index of -4.4, and Pelvic Pain, Urgency, Frequency scale of -6.9 at week 12 compared with baseline. It is interesting that Bosch reports that most of the significantly improved placebo patients felt their improvement was because they were more conscientious about following physician advice and feeling less stress while in the study. Patients with moderate to severe interstitial cystitis/bladder pain syndrome had significant improvement after

receiving only advice and support. This intervention is risk free and inexpensive. Physicians should review standard advice with all interstitial cystitis/bladder pain syndrome patients before starting medical therapy.

**[SYMPTOM PERSISTENCE IN A COMMUNITY COHORT OF WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME \(IC/BPS\): 3-, 6-, 9-, AND 12-MONTH FOLLOW-UP FROM THE RICE COHORT.](#)**

*Suskind AM, Berry SH, Suttorp MJ, Elliott MN, Clemens JQ. Int Urogynecol J. 2014 Jun 11. [Epub ahead of print]. PMID: 24915839*

The persistence of interstitial cystitis/bladder pain syndrome (IC/BPS) symptoms has been described in women seeking medical care. The purpose of this study by Suskind and colleagues from Michigan was to determine whether symptoms persist among a population-based sample of women. A probability sample of US women was identified through a two-stage telephone screening process using the Research and Development (RAND) Interstitial Cystitis Epidemiology (RICE) high-sensitivity case definition. A randomly selected subgroup (n = 508) was enrolled in a longitudinal study and interviewed about their symptoms at baseline, 3, 6, 9, and 12 months. Bivariate and multivariate linear regression analyses determined predictors of persistence of symptoms over the four waves. A total of 436 women with a mean age of 47.5 years responding to all waves were included in the analysis. Forty-one percent met the RICE high-sensitivity case definition at baseline and in all four waves; an additional 21 % met the definition at baseline and in three waves. Women with a college degree and who were younger had higher chances of symptom persistence at each wave. Scoring one standard deviation higher on the continuity of symptoms and the O'Leary-Sant Interstitial Cystitis Symptom index increased the chances of symptom persistence by 4 % and 2 %, respectively. The majority of women demonstrated symptom persistence across at least three of four waves over 12 months. These women tended to be younger, college-educated, and to have reported a history of greater continuity of symptoms and higher severity of symptoms at baseline.

**[THE OVERLAP AND DISTINCTION OF SELF-REPORTED SYMPTOMS BETWEEN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND OVERACTIVE BLADDER: A QUESTIONNAIRE-BASED ANALYSIS.](#)**

*Lai HH, Vetter J, Jain S, Gereau RW 4th, Andriole GL. J Urol. 2014 Jun 4. pii: S0022-5347(14)03716-1. doi: 10.1016/j.juro.2014.05.102. [Epub ahead of print]. PMID: 24907443*

This study compared the self-reported symptoms between IC/BPS and OAB based on patient-reported symptoms on validated questionnaires. 26 patients diagnosed with IC/BPS, 53 diagnosed with OAB and 30 healthy controls were prospectively recruited to participate in a questionnaire-based study that inquired their lower urinary tract symptoms using the following questionnaires: 1) Genitourinary pain index, 2) Interstitial cystitis symptom index and problem index, 3) International consultation on incontinence - overactive bladder, 4) International consultation on incontinence - urinary incontinence short form (ICIQ-UI), 5) Urgency severity scale, 6) numeric rating scales (NRS) of the severity of their bladder "pain, pressure, or discomfort", and 7) NRS of severity of their urgency and 8) frequency symptoms. In univariate analyses, IC/BPS patients reported significantly more severe pain symptoms compared to OAB. OAB patients reported significantly more severe urinary incontinence symptoms compared to IC/BPS. There were no differences in the severity of frequency and urgency between IC/BPS and OAB. Surprisingly, 33% of OAB patients reported pain or discomfort when the bladder filled, while 46% of IC/BPS patients reported urgency incontinence. In multivariate analyses, the total scores on the ICIQ-UI Short Form and the severity (NRS) of bladder pain distinguished OAB from IC/BPS with a sensitivity of 90.6% and a specificity of 96.1% (OAB has higher ICIQ-UI and lower pain scores on NRS). The authors concluded that there is considerable overlap of self-reported symptoms between IC/BPS and OAB. This overlap raises the possibility that IC/BPS and OAB represent a continuum of a bladder hypersensitivity syndrome.

**[LUMINAL DMSO: EFFECTS ON DETRUSOR AND UROTHELIAL/LAMINA PROPRIA FUNCTION.](#)**

*Smith KJ, Chess-Williams R, McDermott C. Biomed Res Int. 2014;2014:347616. doi: 10.1155/2014/347616. Epub 2014 May 18. PMID: 24949435*

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DMSO is used as a treatment for interstitial cystitis and this study from Australia examined the effects of luminal DMSO treatment on bladder function and histology. Porcine bladder was incubated without (controls) or with DMSO (50%) applied to the luminal surface and the release of ATP, acetylcholine, and LDH assessed during incubation and in tissues strips after DMSO incubation. Luminally applied DMSO caused ATP, Ach, and

LDH release from the urothelial surface during treatment, with loss of urothelial layers also evident histologically. In strips of urothelium/lamina propria from DMSO pretreated bladders the release of both ATP and Ach was depressed, while contractile responses to carbachol were enhanced. Detrusor muscle contractile responses to carbachol were not affected by DMSO pretreatment, but neurogenic responses to electrical field stimulation were enhanced. The presence of an intact urothelium/lamina propria inhibited detrusor contraction to carbachol by 53% and this inhibition was significantly reduced in DMSO pretreated tissues. Detection of LDH in the treatment medium suggests that DMSO permeabilised urothelial membranes causing leakage of cytosolic contents including ATP and Ach rather than enhancing release of these mediators. The increase in contractile response and high levels of ATP are consistent with initial flare up in IC/PBS symptoms after DMSO treatment.

#### **INTRAVESICAL TRPV4 BLOCKADE REDUCES REPEATED VARIATE STRESS-INDUCED BLADDER DYSFUNCTION BY INCREASING BLADDER CAPACITY AND DECREASING VOIDING FREQUENCY IN MALE RATS.**

Merrill L, Vizzard MA. *Am J Physiol Regul Integr Comp Physiol.* 2014 Aug 15;307(4):R471-80. doi: 10.1152/ajpregu.00008.2014. Epub 2014 Jun 25. PMID: 24965792

Merrill and Vizzard from Vermont, USA note that individuals with functional lower urinary tract disorders including interstitial cystitis (IC)/bladder pain syndrome (BPS) and overactive bladder (OAB) often report symptom (e.g., urinary frequency) worsening due to stress. One member of the transient receptor potential ion channel vanilloid family, TRPV4, has recently been implicated in urinary bladder dysfunction disorders including OAB and IC/BPS. These studies address the role of TRPV4 in stress-induced bladder dysfunction using an animal model of stress in male rats. To induce stress, rats were exposed to 7 days of repeated variate stress (RVS). Quantitative PCR data demonstrated significant increases in TRPV4 transcript levels in urothelium but not detrusor smooth muscle. Western blot analyses of split urinary bladders (i.e., urothelium and detrusor) showed significant increases in TRPV4 protein expression levels in urothelial tissues but not detrusor smooth muscle. The authors previously showed that RVS produces bladder dysfunction characterized by decreased bladder capacity and increased voiding frequency. The functional role of TRPV4 in RVS-induced bladder dysfunction was evaluated using continuous, open outlet intravesical infusion of saline in conjunction with administration of a TRPV4 agonist, GSK1016790A (3  $\mu$ M), a TRPV4 antagonist, HC067047 (1  $\mu$ M), or vehicle (0.1% DMSO in saline) in control and RVS-treated rats. Bladder capacity, void volume, and intercontraction interval significantly decreased following intravesical instillation of GSK1016790A in control rats and significantly increased following administration of HC067047 in RVS-treated rats. These results demonstrate increased TRPV4 expression in the urothelium following RVS and that TRPV4 blockade ameliorates RVS-induced bladder dysfunction consistent with the role of TRPV4 as a promising target for bladder function disorders.

#### **USE OF VANILLOIDS IN UROLOGIC DISORDERS.**

Foster HE Jr, Lake AG. *Prog Drug Res.* 2014;68:307-17. PMID: 24941675

The bladder is an organ rich in vanilloid targets: dense unmyelinated c-fibers partially responsible for bladder sensation and response to noxious stimuli. Drugs such as capsaicin and resiniferatoxin (RTX) interact with the VR1 vanilloid receptor subtype to initially excite then subsequently desensitize the c-fibers. This chapter examines the literature describing the use of vanilloid receptor agonists in the treatment of the following urological disorders: neurogenic bladder (NGB), overactive bladder (OAB), and interstitial cystitis/painful bladder syndrome (IC/PBS). Review of the literature was performed using Pubmed and the following key words "capsaicin," "resiniferatoxin (RTX)," and "neurogenic bladder," "overactive bladder (OAB)," and "interstitial cystitis," "painful bladder syndrome." Articles focusing on randomized trials comparing intravesical administration of a vanilloid receptor agonist to placebo and those in English were reviewed. The authors conclude that capsaicin and RTX do appear to provide some acceptable treatment results in patients with neurogenic bladder, though larger studies are needed to confirm this. Although efficacy has been shown in some studies, currently the use of vanilloids cannot be recommended for routine use in patients with OAB as the need for catheterization may cause the risk to outweigh the benefit of treatment. Similarly, for the treatment of BPS, vanilloid receptor agonists lack strong evidence for efficacy or tolerability; larger studies are needed to define their role. Understanding how vanilloids are able to impact these disorders, however, may help further elucidate their underlying pathophysiological processes.

**DABIGATRAN INDUCED HEMORRHAGIC CYSTITIS IN A PATIENT WITH PAINFUL BLADDER SYNDROME.**

Otteno H, Smith E, Huffaker RK. *Case Rep Urol.* 2014;2014:871481. doi: 10.1155/2014/871481. Epub 2014 Mar 13. PMID: 24744952

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An 82-year-old female presented with longstanding history of both painful bladder syndrome and atrial fibrillation. She underwent hydrodistension remarkable for hematuria without temporary discontinuation of Dabigatran. Subsequently, patient was admitted to the hospital secondary to anemia and hemorrhagic cystitis. According to the authors, Dabigatran results in an increased risk of bleeding without a method to easily reverse the bleeding [1]. The possibility of increased risk of hemorrhage from the bladder in a patient with painful bladder syndrome should be considered. Dabigatran has not been previously linked with hemorrhagic cystitis.

**INTRAVESICAL APPLICATION OF REBAMIPIDE PROMOTES UROTHELIAL HEALING IN A RAT CYSTITIS MODEL.**

Funahashi Y, Yoshida M, Yamamoto T, Majima T, Takai S, Gotoh M. *J Urol.* 2014 Jun 30. pii: S0022-5347(14)03919-6. doi: 10.1016/j.juro.2014.06.081. [Epub ahead of print] PMID: 24992331

Rebamipide is used as a topical therapeutic agent for various organs. Funahashi and colleagues from Japan examined the healing effects of intravesical rebamipide on damaged urothelium in a rat model of chemically induced cystitis. Intravesically administered rebamipide permeated the bladder, particularly in hydrochloride treated rats, and the pharmacologically effective tissue dose remained for greater than 6 hours. Bladder histological evaluation revealed polymorphological inflammatory cell infiltration and decreased positive staining for uroplakin 3A in hydrochloride treated rats. Scanning electron microscopy showed damaged tight junctions in the hydrochloride group. Evans blue absorption in the bladder wall was increased in hydrochloride treated rats. These findings, which were associated with urothelial injury and increased permeability, were dependently suppressed by the rebamipide treatment dose. Cystometrogram demonstrated that the intercontraction interval was shorter in hydrochloride treated rats but prolonged by rebamipide. The increased nociceptive behaviours observed after intravesical resiniferatoxin administration were also suppressed by rebamipide. It was concluded by the authors that intravesical rebamipide accelerated the repair of damaged urothelium, protected urothelial barrier function and suppressed bladder overactivity and nociception.

**ALTERED DETRUSOR GAP JUNCTION COMMUNICATIONS INDUCE STORAGE SYMPTOMS IN BLADDER INFLAMMATION: A MOUSE CYCLOPHOSPHAMIDE-INDUCED MODEL OF CYSTITIS.**

Okinami T, Imamura M, Nishikawa N, Negoro H, Sugino Y, Yoshimura K, Kanematsu A, Hashitani H, Ogawa O. *PLoS One.* 2014 Aug 6;9(8):e104216. doi: 10.1371/journal.pone.0104216. eCollection 2014. PMID: 25099633

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Lower urinary tract symptoms (LUTS) include storage, voiding and post-micturition symptoms, featuring many urological diseases. Storage symptoms are the most frequent among these and associated with overactive bladder and non-bacterial bladder inflammation such as interstitial cystitis/bladder pain syndrome (IC/BPS). Gap junction, a key regulator of hyperactive conditions in the bladder, has been reported to be involved in pathological bladder inflammation. Here we report involvement of gap junction in the etiology of storage symptoms in bladder inflammation. In this study, cyclophosphamide-induced cystitis was adapted as a model of bladder inflammation. Cyclophosphamide-treated mice showed typical storage symptoms including increased urinary frequency and reduced bladder capacity, with concurrent up-regulation of connexin 43 (GJA1), one of the major gap junction proteins in the bladder. In isometric tension study, bladder smooth muscle strips taken from the treated mice showed more pronounced spontaneous contraction than controls, which was attenuated by carbenoxolone, a gap junction inhibitor. In voiding behavior studies, the storage symptoms in the treated mice characterized by frequent voiding were alleviated by 18 $\alpha$ -glycyrrhetic acid, another gap junction inhibitor. These results demonstrate that cyclophosphamide-induced mouse model of cystitis shows clinical storage symptoms related with bladder inflammation and that gap junction in the bladder may be a key molecule of these storage symptoms. Therefore, gap junction in the bladder might be an alternative therapeutic target for storage symptoms in bladder inflammation.

**INSTILLATION OF HYALURONIC ACID VIA ELECTROMOTIVE DRUG ADMINISTRATION CAN IMPROVE THE EFFICACY OF TREATMENT IN PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: A RANDOMIZED PROSPECTIVE STUDY.**

Gülpinar O, Haliloğlu AH, Gökçe Mİ, Arıkan N. *Korean J Urol.* 2014 May;55(5):354-9. doi: 10.4111/kju.2014.55.5.354. Epub 2014 May 12. PMID: 24868341

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In the treatment of interstitial cystitis, intravesical hyaluronic acid application may be suggested as a treatment option. In this randomized prospective study from Turkey, the authors aimed to identify whether instilling the hyaluronic acid with electromotive drug administration (EMDA) would increase the tissue uptake and improve the efficacy. The data of 31 patients who had been diagnosed with bladder pain syndrome/interstitial cystitis (BPS/IC) between 2004 and 2005 were examined. The patients were randomized to two groups: patients in group A received hyaluronic acid directly with a catheter and patients in group B received hyaluronic acid with EMDA. The patients were followed for 24 months and the two groups were compared at certain time intervals. The primary end points of the study were visual analogue scale (VAS) score, global response assessment, and micturition frequency in 24 hours. There were 6 males and 25 females. The two groups were similar in baseline parameters. The decrease in VAS score and the micturition frequency in 24 hours were significantly lower with EMDA at months 6 and 12. The difference between the two groups was not significant at months 1 and 24. Also, treatment with EMDA, positive KCl test, and pretreatment voiding frequency >17 were associated with higher response rates. The authors concluded that hyaluronic acid installation is an effective glycosaminoglycan substitution therapy in patients with BPS/IC. Instillation of hyaluronic acid via EMDA can improve the efficacy of the treatment; however, lack of long-term efficacy is the major problem with this glycosaminoglycan substitution therapy.

#### [ASSOCIATION OF DYSMENORRHEA WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A CASE-CONTROL STUDY.](#)

Chung SD, Liu SP, Lin HC, Kang JH. *Acta Obstet Gynecol Scand.* 2014 Sep;93(9):921-5. doi: 10.1111/aogs.12437. Epub 2014 Jul 23. PMID: 24903852

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disabling condition of the urological system. Many gynecological conditions are reported to be associated with IC/BPS. This case-control study by Chung and colleagues from Taiwan presents epidemiological evidence of a possible association between dysmenorrhea and IC/BPS, using population-based data. The study sample was retrieved from Taiwan's Longitudinal Health Insurance Database 2000, i.e. 291 women aged 18-45 years with a diagnosis of IC/BPS between January 2000 and December 2010 (cases) and 873 randomly selected controls matched on age and index date of ambulatory care visit. The authors used logistic regression conditioned on age to calculate the odds ratio of cases having a prior diagnosis of dysmenorrhea relative to controls. Prior dysmenorrhea was found in 87 (29.9%) cases and in 163 (18.7%) of the controls. This population-based study found that there is an association between IC/BPS and prior dysmenorrhea.

#### **DIAGNOSIS AND TREATMENT**

#### [TREATING INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AS A CHRONIC DISEASE.](#)

Bosch PC, Bosch DC. *Rev Urol.* 2014;16(2):83-7. PMID: 25009448

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The management of interstitial cystitis/bladder pain syndrome (IC/BPS) is both frustrating and difficult. The etiology is uncertain and there is no definitive treatment. Consequently, both patients and doctors tend to be unhappy and unsatisfied with the quality of care. The American Urological Association (AUA) provides a guideline for the diagnosis and treatment of IC/BPS. Recommended first-line treatments include patient education, self-care practices, behaviour modifications, and stress management. Management of IC/BPS may be also improved if both patients and doctors treat this condition as a chronic disease. This article reviews the AUA first-line treatments for IC/BPS and considers the benefits of treating this condition as a chronic disease.

#### [DIAGNOSIS AND MANAGEMENT OF INTERSTITIAL CYSTITIS.](#)

Barr S. *Obstet Gynecol Clin North Am.* 2014 Sep;41(3):397-407. doi: 10.1016/j.ogc.2014.04.001. Epub 2014 Jul 9. PMID: 25155121

Interstitial cystitis is a diagnosis of exclusion. The definition has expanded over the years to encompass painful bladder syndrome. It is disease state that is often delayed in its diagnosis and difficult to manage. Treatment

options include oral and intravesical therapies as well as both minor and major surgical options. Also, a patient can improve symptoms by following self-management recommendations that focus on both diet and stress management. Treatment options should be periodically evaluated with validated questionnaires to insure they are improving the patient's symptoms, and a multidisciplinary approach is best to manage the patient.

#### **INTERSTITIAL CYSTITIS: EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND CLINICAL PRESENTATION.**

*McLennan MT. Obstet Gynecol Clin North Am. 2014 Sep;41(3):385-395. doi: 10.1016/j.ogc.2014.05.004. Epub 2014 Jul 9. PMID: 25155120*

Interstitial cystitis, or painful bladder syndrome, can present with lower abdominal pain/discomfort and dyspareunia, and pain in any distribution of lower spinal nerves. Patients with this condition experience some additional symptoms referable to the bladder, such as frequency, urgency, or nocturia. It can occur across all age groups, although the specific additional symptoms can vary in prevalence depending on patient age. It should be considered in patients who have other chronic pain conditions such as fibromyalgia, chronic fatigue, irritable bowel, and vulvodynia. The cause is still largely not understood, although there are several postulated mechanisms.

#### **LOWER URINARY TRACT: ICI-RS 2013**

##### **DO WE UNDERSTAND ANY MORE ABOUT BLADDER INTERSTITIAL CELLS? ICI-RS 2013.**

*Kanai A, Fry C, Hanna-Mitchell A, Birder L, Zabbarova I, Bijos D, Ikeda Y. NeuroUrol Urodyn. 2014 Jun;33(5):573-6. doi: 10.1002/nau.22591. Epub 2014 May 16. PMID: 24838179*

Kanai and colleagues present a brief review of discussions from "Do we understand any more about lower urinary tract interstitial cells?" session at the 2013 International Consultation on Incontinence-Research Society (ICI-RS) meeting in Bristol, UK. The discussion focused on bladder interstitial cell (IC) subtypes, their localization and characterization, and communication between themselves, the urothelium, and detrusor smooth muscle. The role of ICs in bladder pathologies and new methods for studying ICs were also addressed. ICs have been studied extensively in the lower urinary tract and have been characterized based on comparisons with ICs of Cajal in the gastro-intestinal tract. In fetal bladders it is believed that ICs drive intrinsic contractions to expel urine through the urachus. These contractions diminish postpartum as bladder innervation develops. Voiding in human neonates occurs when filling triggers a spinal cord reflex that contracts the detrusor; in rodents, maternal stimulation of the perineum triggers voiding. Following spinal cord injury, intrinsic contractions, and spinal micturition reflexes develop, similar to those seen during neonatal development. These enhanced contractions may stimulate nociceptive and mechanosensitive afferents contributing to neurogenic detrusor overactivity and incontinence. The IC-mediated activity is believed to be initiated in the lamina propria by responding to urothelial factors. These IC may act syncytially through gap junction coupling and modulate detrusor activity through unknown mechanisms. There has been a great deal of information discovered regarding bladder ICs, however, many of their (patho)physiological functions and mechanisms are still unclear and necessitates further research.

##### **UROTHELIAL MUCOSAL SIGNALING AND THE OVERACTIVE BLADDER-ICI-RS 2013.**

*Birder LA, Andersson KE, Kanai AJ, Hanna-Mitchell AT, Fry CH. NeuroUrol Urodyn. 2014 Jun;33(5):597-601. doi: 10.1002/nau.22604. Epub 2014 May 16. PMID: 24838393*

There is abundant evidence that the lower urinary tract (LUT) mucosal layer is involved both in mechanosensory functions that regulate bladder contractile activity and in urethral sensation. Changes to the mucosa can be associated with a number of bladder pathologies. For example, alterations of the urothelium and underlying lamina propria at both the molecular and structural levels have been reported in both patients and animals associated with disorders such as bladder pain syndrome and diabetic cystopathy. In contrast to the urinary bladder, much less is known about the urothelium/lamina propria of the bladder neck/proximal urethra. There are important gender differences in the outflow region both anatomically and with respect to innervation, hormonal sensitivity, and location of the external urethral sphincter. There is reasonable evidence to support the view that the mucosal signalling pathway in the proximal urethra is important for normal voiding, but it has also been speculated that the proximal urethra can initiate bladder overactivity. When

dysfunctional, the proximal urethra may be an interesting target, for example, botulinum toxin injections aiming at eliminating both urgency and incontinence due to detrusor overactivity.

## **KETAMINE ABUSE AND THE BLADDER**

### **LONG-TERM KETAMINE ABUSE INDUCES CYSTITIS IN RATS BY IMPAIRING THE BLADDER EPITHELIAL BARRIER.**

*Gu D, Huang J, Yin Y, Shan Z, Zheng S, Wu P. Mol Biol Rep. 2014 Aug 5. [Epub ahead of print] PMID: 25091940.*

Long-term ketamine abuse is known to affect the lower urinary tract and produce symptoms of cystitis. However, the pathophysiology and causative mechanism of the changes in bladder function remain unclear. This study from China investigated the existence of ketamine-induced cystitis in a rat model and characterized the underlying mechanisms. Rats were assigned to blank control, normal saline (NS), low-dose ketamine (LK, 5 mg/kg), and high-dose ketamine (HK, 50 mg/kg) groups. The two experimental groups received ketamine hydrochloride daily for 16 weeks. All rats were housed individually for assessment of urinary frequency and urine volume. Urinary biomarkers were measured at different time points. Rat bladders were excised for histopathology, immunohistochemistry, and western blot analysis. Ketamine-treated rats had increased urinary frequency compared to NS-treated rats at Week 16. Urinary nitric oxide and antiproliferative factor levels were increased in ketamine-treated rats within the first 30 h after administration. After long-term ketamine administration, urinary glycoprotein GP51 and potassium levels were decreased in the HK and LK groups compared to the NS group. Ketamine-treated rats showed thickened bladder epithelial layer, increased expression of inducible nitric oxide synthase and occludin, and decreased expression of zonula occludens-1 in the bladder wall. Ketamine, or its urinary metabolites, disrupted the proliferation of bladder epithelial cells, resulting in defected bladder epithelial barrier. Subsequent leakage of urinary potassium causes a stress response in the bladder and provokes cystitis.

### **ELEVATED SERUM IGE MAY BE ASSOCIATED WITH DEVELOPMENT OF KETAMINE CYSTITIS.**

*Jhang JF, Hsu YH, Jiang YH, Kuo HC. J Urol. 2014 May 22. pii: S0022-5347(14)03616-7. doi: 10.1016/j.juro.2014.05.084. [Epub ahead of print] PMID: 24859443*

Previous studies revealed bladder mast cell and eosinophil cell infiltration in patients with ketamine cystitis. Due to possible hypersensitivity in those with this condition, Jhang and colleagues from Taiwan investigated the association of serum Ig, histology findings and symptoms in patients with ketamine cystitis. They evaluated patients with ketamine cystitis for maximal bladder capacity, serum IgE, IgG and IgM, and pain visual analog scale score. Bladder biopsies were assessed for mast cells and eosinophils. Patients with interstitial cystitis/bladder pain syndrome, acute bacterial cystitis and controls were also studied. Median serum IgE was significantly higher in the 20 patients with ketamine cystitis than in the 10 controls and the 15 with acute bacterial cystitis. It was marginally higher than in the 13 patients with interstitial cystitis/bladder pain syndrome. Of patients with ketamine cystitis the median visual analog scale pain score was significantly higher in those with serum IgE greater than compared to less than 200 IU/ml. Maximal bladder capacity was significantly less in patients with ketamine cystitis who had higher IgE. Patients with severe or moderate bladder eosinophil infiltration had a greater visual analog scale score, higher serum IgE and smaller maximal bladder capacity than patients with no or mild eosinophil infiltration. Serum IgE and the visual analog scale score correlated significantly. Patients with ketamine cystitis had higher serum IgE than patients with interstitial cystitis/bladder pain syndrome or acute bacterial cystitis, or controls. Serum IgE and the severity of eosinophil infiltration were associated with bladder pain severity and small maximal bladder capacity.

### **BILATERAL HYDRONEPHROSIS AND CYSTITIS RESULTING FROM CHRONIC KETAMINE ABUSE.**

*Tran VH, Nelson M, Nogar J, Bramante RM. West J Emerg Med. 2014 Jul;15(4):382-4. doi: 10.5811/westjem.2014.4.205712014.4.20571. PMID: 25035738*

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Ketamine associated urinary dysfunction has become increasingly more common worldwide. Point-of-care ultrasound (POCUS) is an established modality for diagnosing hydronephrosis in the emergency department. The authors describe a case of a young male ketamine abuser with severe urinary urgency and frequency in which POCUS performed by the emergency physician demonstrated bilateral hydronephrosis and a focally



thickened irregular shaped bladder. They advise that emergency physicians should consider using POCUS evaluate for hydronephrosis and bladder changes in ketamine abusers with lower urinary tract symptoms. However, the mainstay of treatment is discontinuing ketamine abuse.

## **METHOXETAMINE ABUSE AND THE BLADDER**

### **THREE MONTHS OF METHOXETAMINE ADMINISTRATION IS ASSOCIATED WITH SIGNIFICANT BLADDER AND RENAL TOXICITY IN MICE.**

*Dargan PI, Tang HC, Liang W, Wood DM, Yew DT. Clin Toxicol (Phila). 2014 Mar;52(3):176-80. doi: 10.3109/15563650.2014.892605. PMID: 24580056*

Methoxetamine is a ketamine analogue that has recently emerged as a novel psychoactive substance. Chronic ketamine use is associated with significant bladder and renal toxicity. Methoxetamine has been marketed as "bladder friendly", but there is no data to be able to substantiate this claim. The purpose of this study from London was to characterise the patterns of bladder and renal toxicity associated with 3 months of methoxetamine administration in an animal model. Two-month-old Institute of Cancer Research mice were administered 30 mg/kg methoxetamine intraperitoneally (n = 5) or saline (n = 3 control) for 3 months. The animals were then sacrificed and histological examination, immuno-cytochemistry using polyclonal anti-CD4 antibodies and sirius-red staining for collagen were performed. This study has shown that 3 months of daily 30 mg/kg intra-peritoneal methoxetamine results in significant bladder and renal toxicity in mice. Changes in the bladder included inflammatory changes with subsequent fibrosis and changes in the kidney were seen at both a tubular and glomerular level. These changes are similar to those seen in comparable animal models of chronic ketamine administration. Further work is required to determine the time course of the onset of these effects and whether the effects are reversible with methoxetamine cessation.

### **METHOXETAMINE - A NOVEL RECREATIONAL DRUG WITH POTENT HALLUCINOGENIC PROPERTIES.**

*Zawilska JB. Toxicol Lett. 2014 Aug 13. pii: S0378-4274(14)01298-3. doi: 10.1016/j.toxlet.2014.08.011. [Epub ahead of print]. PMID: 25128700*

Methoxetamine is one of the constantly growing group of novel psychoactive substances that has emerged in recent years. The compound belongs to the arylcyclohexylamine class, which is used for its recreational and psychedelic effects. Methoxetamine is a structural analogue of ketamine, with a much longer duration of action and intensity of effects, and has been extensively advertised as its 'legal' and 'bladder friendly' alternative. This review surveys the current state of knowledge regarding the metabolism, pharmacology, prevalence and pattern of methoxetamine use, and analytical methods of its detection. Consumption of methoxetamine bears a significant health risk and may even lead to fatal intoxication. A significant amount of research is still needed in order to fully quantify the short- and long-term effects of methoxetamine and its interaction with other drugs of abuse.

## **COMORBIDITIES + IC**

### **NON-BLADDER CONDITIONS IN FEMALE TAIWANESE PATIENTS WITH INTERSTITIAL CYSTITIS/HYPERSENSITIVE BLADDER SYNDROME.**

*Fan YH, Lin AT, Lu SH, Chuang YC, Chen KK. Int J Urol. 2014 Aug;21(8):805-9. doi: 10.1111/iju.12456. Epub 2014 Apr 13. PMID: 24724573*

The purpose of this study by Fan and colleagues from Taiwan was to detect non-bladder conditions in patients with interstitial cystitis/hypersensitive bladder syndrome. A total of 122 female interstitial cystitis/hypersensitive bladder syndrome patients and a control group of 122 age-matched female patients with stress urinary incontinence completed screening questionnaires for irritable bowel syndrome, temporomandibular disorder, multiple chemical sensitivities, tension and migraine headache, localized myofascial pain disorder, and fibromyalgia. Interstitial cystitis/hypersensitive bladder syndrome patients also completed questionnaires on interstitial cystitis/hypersensitive bladder syndrome symptom severity, including the O'Leary-Sant symptom index, and the visual analog scale for pain and urgency. Interstitial

cystitis/hypersensitive bladder syndrome patients were more likely to meet diagnostic criteria for irritable bowel syndrome than controls and tension/migraine headache. The prevalence of temporomandibular disorder, multiple chemical sensitivities, localized myofascial pain disorders and fibromyalgia did not reach a statistical significant difference between the two groups. It was concluded that interstitial cystitis/hypersensitive bladder syndrome patients are more likely to have multiple non-bladder conditions. These conditions correlate with the severity of interstitial cystitis/hypersensitive bladder syndrome symptoms.

## **FIBROMYALGIA**

### **ANALGESIC AND ANTI-HYPERALGESIC EFFECTS OF MUSCLE INJECTIONS WITH LIDOCAINE OR SALINE IN PATIENTS WITH FIBROMYALGIA SYNDROME.**

*Staud R, Weyl EE, Bartley E, Price DD, Robinson ME. Eur J Pain. 2014 Jul;18(6):803-12. doi: 10.1002/j.1532-2149.2013.00422.x. Epub 2013 Nov 5. PMID: 24193993*

Patients with musculoskeletal pain syndrome including fibromyalgia (FM) complain of chronic pain from deep tissues including muscles. Previous research suggests the relevance of impulse input from deep tissues for clinical FM pain. Staud and colleagues from the USA hypothesized that blocking abnormal impulse input with intramuscular lidocaine would decrease primary and secondary hyperalgesia and FM patients' clinical pain.

They enrolled 62 female patients with FM into a double-blind controlled study of three groups who received 100 or 200 mg of lidocaine or saline injections into both trapezius and gluteal muscles. Study variables included pressure and heat hyperalgesia as well as clinical pain. In addition, placebo factors like patients' anxiety and expectation for pain relief were used as predictors of analgesia. Primary mechanical hyperalgesia at the shoulders and buttocks decreased significantly more after lidocaine than saline injections. Similar results were obtained for secondary heat hyperalgesia at the arms. After muscle injections, clinical FM pain significantly declined by 38% but was not statistically different between lidocaine and saline conditions. Placebo-related analgesic factors (e.g., patients' expectations of pain relief) accounted for 19.9% of the variance of clinical pain after the injections. Injection-related anxiety did not significantly contribute to patient analgesia. The authors are of the opinion that their results suggest that muscle injections can reliably reduce clinical FM pain, and that peripheral impulse input is required for the maintenance of mechanical and heat hyperalgesia of patients with FM. Whereas the effects of muscle injections on hyperalgesia were greater for lidocaine than saline, the effects on clinical pain were similar for both injectates.

### **PROBLEM-FOCUSED COPING AND SELF-EFFICACY AS CORRELATES OF QUALITY OF LIFE AND SEVERITY OF FIBROMYALGIA IN PRIMARY FIBROMYALGIA PATIENTS.**

*Alok R, Das SK, Agarwal GG, Tiwari SC, Salwahan L, Srivastava R. J Clin Rheumatol. 2014 Sep;20(6):314-6. doi: 10.1097/RHU.000000000000130. PMID: 25160014*

Patients with fibromyalgia syndrome (FMS) often experience problems such as poor quality of life (QoL), loss of self-efficacy (SE), inappropriate coping behavior, and chronic widespread pain along with other symptoms. Recent studies have indicated that sense of SE and effective coping strategies (CSs) are the crux on which the management of chronic pain and enrichment of QoL of FMS patients depend. Realizing the importance of this subject for the rehabilitation of the people with FMS, this study from India aimed at analyzing the correlation between severity of FMS, and QoL, SE, and CSs among the patients of FMS. One hundred patients with fibromyalgia (FM) and 100 control subjects were studied. Fibromyalgia Impact Questionnaire-Revised, Quality of Life Scale, Arthritis Self-efficacy Scale, and COPE Scales for CSs were administered to both the groups. Significantly lower SE, poor QoL, and less use of CSs were reported by FM patients versus healthy people. Problem-focused coping and SE were found to be significantly and positively associated with QoL. Components of Fibromyalgia Impact Questionnaire-Revised, namely, pain, function, and symptoms, were found to be significantly and negatively associated with problem-focused coping, SE, and QoL. According to the authors, this study confirms that problem-focused CSs and SE are important correlates of QoL and severity of FM in Indian as well as other populations.

### **AN INSIGHT INTO THE GASTROINTESTINAL COMPONENT OF FIBROMYALGIA: CLINICAL MANIFESTATIONS AND POTENTIAL UNDERLYING MECHANISMS.**

*Slim M, Calandre EP, Rico-Villademoros F. Rheumatol Int. 2014 Aug 14. [Epub ahead of print] PMID: 25119830*

Fibromyalgia syndrome is characterized by chronic generalized pain accompanied by a broad symptomatologic spectrum. Besides chronic fatigue, sleep disturbances, headaches and cognitive dysfunction that are extensively described in the literature, a considerable proportion of patients with fibromyalgia experience gastrointestinal symptoms that are commonly overlooked in the studies that are not specifically dedicated to evaluate these manifestations. Nevertheless, various attempts were undertaken to explore the gastrointestinal dimension of fibromyalgia. Several studies have demonstrated an elevated comorbidity of irritable bowel syndrome (IBS) among patients with fibromyalgia. Other studies have investigated the frequency of presentation of gastrointestinal symptoms in fibromyalgia in a nonspecific approach describing several gastrointestinal complaints frequently reported by these patients such as abdominal pain, dyspepsia and bowel changes, among others. Several underlying mechanisms that require further investigation could serve as potential explanatory hypotheses for the appearance of such manifestations. These include sensitivity to dietary constituents such as gluten, lactose or FODMAPs or alterations in the brain-gut axis as a result of small intestinal bacterial overgrowth or subclinical enteric infections such as giardiasis. The gastrointestinal component of fibromyalgia constitutes a relevant element of the multidisciplinary pathophysiologic mechanisms underlying fibromyalgia that need to be unveiled, as this would contribute to the adequate designation of relevant treatment alternatives corresponding to these manifestations.

#### **ABERRANT CEREBRAL BLOOD FLOW RESPONSES DURING COGNITION: IMPLICATIONS FOR THE UNDERSTANDING OF COGNITIVE DEFICITS IN FIBROMYALGIA.**

*Montoro CI, Duschek S, Muñoz Ladrón de Guevara C, Fernández-Serrano MJ, Reyes Del Paso GA. Neuropsychology. 2014 Aug 25. [Epub ahead of print]. PMID: 25151113*

There is ample evidence for cognitive deficits in fibromyalgia syndrome (FMS). The present study investigated cerebral blood flow responses in forty-five FMS patients and 32 matched healthy controls during arithmetic processing in FMS patients and its relationship with performance. The influence of clinical factors on performance and blood flow responses were also analyzed. It was concluded that cognitive impairment in FMS is associated with alterations in cerebral blood flow responses during cognitive processing. These results suggest a potential physiological pathway through which psychosocial and clinical factors may affect cognition.

#### **SJÖGREN'S SYNDROME**

#### **SJÖGREN'S SYNDROME ACCOMPANIED WITH INTERSTITIAL CYSTITIS: A CASE REPORT AND REVIEW OF THE LITERATURE.**

*Liang D, Lu J, Guo A. Clin Rheumatol. 2014 Aug;33(8):1189-93. doi: 10.1007/s10067-013-2480-3013-2480-3. Epub 2014 Jan 7. PMID: 24395198*

Liang and colleagues from China present a case report of a patient with Sjögren's syndrome accompanied with interstitial cystitis. A 64-year-old woman complained of dry mouth for 21 years, recurrent swelling and pain on the right parotid in 2000, and urinary irritation symptoms in the past 2 years. Several courses of different types of antibiotics could not relieve her urinary irritation symptoms. Bladder hydraulic dilatation had only transient effects. Urine sediment contained neither erythrocytes nor leukocytes, and urine cultures yielded no growth. However, increased  $\gamma$ -globulin, positive antinuclear antibodies, and anti-SS-A and anti-SS-B antibodies were detected. Histopathological data of labial salivary glands showed three foci of numerous mononuclear cells. Cystoscopy revealed redness, edema, angiectasis, and extensive ecchymosis of the mucosal surface and several small floating cruor entities in the bladder. Urinary bladder biopsy specimens revealed the absence of urothelium and edematous lamina propria and submucosa, with diffuse or multiple focal chronic inflammatory cell infiltration. Based on these findings, she was diagnosed with Sjögren's syndrome accompanied with interstitial cystitis. Therapy with corticosteroids relieved the symptoms significantly.

#### **RENAL TUBULAR ACIDOSIS IN SJÖGREN'S SYNDROME: A CASE SERIES**

*Ram R, Swarnalatha G, Dakshinamurty KV. Am J Nephrol. 2014 Aug 20;40(2):123-130. [Epub ahead of print]. PMID: 25171149*

The exact frequency of distal and proximal renal tubular acidosis (RTA) in Sjögren's syndrome is unknown. Other features of Sjögren's syndrome like polyuria, glomerular manifestations, familial occurrence and

pregnancy are not widely reported. The aim of this study from India was to prospectively study the clinical features and outcome of distal and proximal RTA in Sjögren's syndrome and also report on other renal manifestations of Sjögren's syndrome. This study is a prospective consecutive case series of patients who presented with a history suggestive of RTA and Sjögren's syndrome. All patients were followed for 1 year. The diagnosis of RTA was by fractional excretion of bicarbonate. The diagnosis of Sjögren's syndrome was according to the American-European classification system. The total number of RTA patients diagnosed during this period was 149. Sjögren's syndrome accounted for 34.8% (52 of 149) of RTA patients. The important symptoms and laboratory parameters were oral and ocular symptoms in 23 (44.2%), dental caries in 12 (23%), body pains in 47 (90.3%), mean serum pH  $7.202 \pm 0.03$ , mean serum bicarbonate,  $14.03 \pm 1.66$  mmol/l, and mean urine pH,  $7.125 \pm 0.54$ . There were 30 (57.6%) patients with distal RTA and 22 (42.3%) patients with proximal RTA. Ram and colleagues concluded that the clinical implication of the present study is that RTA is a common feature of Sjögren's syndrome. It may be missed if the presentation is not due to oral and ocular symptoms. The present study is also the only one with a 1-year follow-up.

*Please note: For more detailed information about Sjögren's syndrome and associated disorders for patients and professionals in English and Dutch languages, [click here](#).*

*Sjögren's India has a website at: <http://www.sjogrensindia.org>*

## **GASTRO-INTESTINAL DISORDERS**

### **IRRITABLE BOWEL SYNDROME: A CONCISE REVIEW OF CURRENT TREATMENT CONCEPTS.**

*Wall GC, Bryant GA, Bottenberg MM, Maki ED, Miesner AR. World J Gastroenterol. 2014 Jul 21;20(27):8796-8806. PMID: 25083054*

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Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders causing patients to seek medical treatment. It is relatively resource intensive and the source of significant morbidity. Recent insights into the pathophysiology and treatment of IBS have given clinicians more options than ever to contend with this disorder. The purpose of this paper is to review older, "classic" treatments for IBS as well as newer agents and "alternative" therapies. Wall and colleagues discuss the evidence base of these drugs and provide context to help develop appropriate treatment plans for IBS patients.

### **IRRITABLE BOWEL SYNDROME: CURRENT AND EMERGING TREATMENT OPTIONS.**

*Peyton L, Greene J. P T. 2014 Aug;39(8):567-78. PMID: 25136255*

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Irritable bowel syndrome, a functional gastrointestinal disorder of uncertain pathophysiology, affects up to 55 million Americans. Medications available or in development include antispasmodics, antidepressants, and antidiarrheals. This is a useful update and overview of treatments.

## **VULVODYNIA**

### **ETIOLOGY, DIAGNOSIS, AND CLINICAL MANAGEMENT OF VULVODYNIA.**

*Sadownik LA. Int J Womens Health. 2014 May 2;6:437-49. doi: 10.2147/IJWH.S37660. eCollection 2014. PMID: 24833921*

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Chronic vulvar pain or discomfort for which no obvious etiology can be found (vulvodynia) can affect up to 16% of women. It may affect girls and women across all age groups and ethnicities. Vulvodynia is a significant burden to society, the health care system, the affected woman, and her intimate partner. The etiology is multifactorial and may involve local injury or inflammation, and peripheral and or central sensitization of the nervous system. An approach to the diagnosis and management of a woman presenting with chronic vulvar pain should address the biological, psychological, and social/interpersonal factors that contribute to her illness. The gynecologist has a key role in excluding other causes for vulvar pain, screening for psychosexual and pelvic floor dysfunction, and collaborating with other health care providers to manage a woman's pain. An important

component of treatment is patient education regarding the pathogenesis of the pain and the negative impact of experiencing pain on a woman's overall quality of life. An individualized, holistic, and often multidisciplinary approach is needed to effectively manage the woman's pain and pain-related distress.

## **PUDENDAL NEURALGIA**

### **MANAGEMENT OF PUDENDAL NEURALGIA.**

*Pérez-López FR, Hita-Contreras F. Climacteric. 2014 Jul 4:1-3. [Epub ahead of print] PMID: 24716710*

Vulvodynia includes different manifestations of chronic vulvar pain with no known cause. Many women do not receive a diagnosis and appropriate treatment. Pudendal neuralgia is a painful condition caused by inflammation, compression or entrapment of the pudendal nerve; it may be related to or be secondary to childbirth, pelvic surgery, intense cycling, sacroiliac skeletal abnormalities or age-related changes. Clinical characteristics include pelvic pain with sitting which increases throughout the day and decreases with standing or lying down, sexual dysfunction and difficult with urination and/or defecation. To confirm pudendal neuralgia, the Nantes criteria are recommended. Treatment includes behavioural modifications, physiotherapy, analgesics and nerve block, surgical pudendal nerve decompression, radiofrequency and spinal cord stimulation.

### **PUDENDAL NEURALGIA.**

*Khoder W, Hale D. Obstet Gynecol Clin North Am. 2014 Sep;41(3):443-452. doi: 10.1016/j.ogc.2014.04.002. Epub 2014 Jul 9. PMID: 25155124*

Pudendal neuralgia is a painful condition affecting the nerve distribution of the pudendal nerve. The Nantes criteria give some structure for making this diagnosis. A step-ladder approach to therapy, as described, is suggested when treating these patients.

## **CHRONIC (PELVIC) PAIN**

### **CURRENT ADVANCEMENTS IN THE DIAGNOSIS AND TREATMENT OF CHRONIC PELVIC PAIN.**

*Morrissey D, Ginzburg N, Whitmore K. Curr Opin Urol. 2014 Jul;24(4):336-44. doi: 10.1097/MOU.000000000000062. PMID: 24837873*

The diagnosis and treatment of chronic pelvic pain (CPP) have moved away from targeting a specific organ to multifactorial and multidisciplinary individualized approach to treatment strategies. The purpose of this article From Drexel University, Philadelphia is to review the current advancements in diagnosis and treatment of CPP. Recognition that response to current treatment approach to CPP syndrome is variable; organizations such as the European Association of Urology, American Urologic Association, International Continence Society, International Association for the Study of Pain, and others have integrated the most current evidence and management strategies from multiple specialties (urology, gynaecology, pain medicine, gastroenterology, colorectal surgery, neurology, physiotherapy, and psychology). The 1st World Congress on Abdominal and Pelvic Pain met in 2013 to further collaborate on diagnosis and management of CPP. A multimodal clinical phenotype system has also been implemented to help understand cause and guide therapy. New classification systems allow for overlap of mechanisms between conditions and a multidisciplinary treatment approach.

### **COMPLEMENTARY TREATMENT IN CHRONIC PELVIC PAIN SYNDROME: A CASE REPORT STUDY.**

*Latifi SA, Minaiee B, Kamalinejad M, Nazem E, Gooran S. Iran Red Crescent Med J. 2014 Apr;16(4):e13681. doi: 10.5812/ircmj.13681. Epub 2014 Apr 5. PMID: 24910801*

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In this interesting article from Iran, Latifi and colleagues note that the use of traditional medicine has been emerged in the treatment of BPS (bladder pain syndrome) due to its high prevalence and expenses and its insufficient treatment by conventional therapies. Iranian traditional medicine has discussed such diseases. Considering the signs and symptoms of BPS and "reeh", the proposed mechanism of flatulency as casualty of recurrent circulating pains seems to be a proper diagnose. So, as a preliminary study the authors administered Horse Mint as one of effective traditional herbs on flatulent pain in a patient with BPS. A 60-year-old female was referred with the diagnosis of BPS. Six clinical visits with 2-week intervals were performed for patient, and

the NIH-ICSI was completed, which was used as a pretreatment symptom quantifier and post-treatment outcome tool. Horse mint (*Mentha longifolia*) was prescribed twice a day for 12 weeks. Clinical visits showed alleviation of signs, symptoms, and changes in the patient's NIH-ICSI score, suggesting further studies on this field.

#### **CHRONIC PELVIC FLOOR DYSFUNCTION.**

*Hartmann D, Sarton J. Best Pract Res Clin Obstet Gynaecol. 2014 Jul 17. pii: S1521-6934(14)00132-1. doi: 10.1016/j.bpobgyn.2014.07.008. [Epub ahead of print] PMID: 25108498*

The successful treatment of women with vestibulodynia and its associated chronic pelvic floor dysfunctions requires interventions that address a broad field of possible pain contributors. Pelvic floor muscle hypertonicity was implicated in the mid-1990s as a trigger of major chronic vulvar pain. Painful bladder syndrome, irritable bowel syndrome, fibromyalgia, and temporomandibular jaw disorder are known common comorbidities that can cause a host of associated muscular, visceral, bony, and fascial dysfunctions. It appears that normalizing all of those disorders plays a pivotal role in reducing complaints of chronic vulvar pain and sexual dysfunction. Though the studies have yet to prove a specific protocol, physical therapists trained in pelvic dysfunction are reporting success with restoring tissue normalcy and reducing vulvar and sexual pain. A review of pelvic anatomy and common findings are presented along with suggested physical therapy management.

#### **COMPLEMENTARY AND ALTERNATIVE MEDICATIONS FOR CHRONIC PELVIC PAIN.**

*Leong FC. Obstet Gynecol Clin North Am. 2014 Sep;41(3):503-510. doi: 10.1016/j.ogc.2014.05.001. Epub 2014 Jul 14. PMID: 25155128*

Chronic pelvic pain is common, but rarely cured, thus patients seek both second opinions and alternative means of controlling their pain. Complementary and alternative medicine accounts for 11.2% of out-of-pocket medical expenditures for adults for all conditions in the United States. Although there are many treatments, rigorous testing and well-done randomized studies are lacking. Dietary changes and physical modalities such as physical therapy have often been included in the category of alternative medicine, but their use is now considered mainstream. This article concentrates on other sources of alternative and complementary medicine, such as dietary supplementation and acupuncture.

#### **ELECTRONIC HEALTHCARE**

##### **DEVELOPMENT OF TWO ELECTRONIC BLADDER DIARIES: A PATIENT AND HEALTHCARE PROFESSIONALS PILOT STUDY.**

*Mangera A, Marzo A, Heron N, Fernando D, Hameed K, Soliman AH, Bradley M, Hosking I, Abdel-Maguid M, Levermore M, Tindale WB, Chapple C. Neurourol Urodyn. 2014 Sep;33(7):1101-9. doi: 10.1002/nau.22469. Epub 2013 Sep 2. PMID: 24000163*

This is an interesting study bearing in mind that healthcare is becoming increasingly digital. The purpose was to assess patients' preferences in a pilot crossover study of two different electronic voiding diaries against a standard paper diary and assess urological health professional (HP) opinions on the electronic bladder diary reporting system. Two different electronic diaries were developed: (1) electronically read diary-a card with predefined slots read by a card reader and (2) e-diary-a handheld touch screen device. Data uploaded from either electronic diary produced an electronic report. Mangera and colleagues from Sheffield recruited 22 patients split into two cohorts for each electronic diary, 11 completed each type of electronic diary for 3 days either preceded or followed by a standard paper diary for 3 days. Both diaries were completed on the 7th day. Patients' perceptions of both diaries were recorded using a standardized questionnaire. An HP study recruited 22 urologists who were given the paper diary and the electronic reports. Time taken for analysis was recorded along with accuracy and HP preferences. The majority of patients (82%) preferred the e-diary and only 1/11 found it difficult to use. Patients had the same preference for the electronically read diary as the paper diary. The paper diary took 66% longer to analyze than the electronic report and was analyzed with an accuracy of 58% compared to 100%. Slightly more HP (9%) preferred the electronic report to the paper diary. The authors concluded that this proposed e-diary with its intuitive interface has overcome previous deficiencies in electronic diaries with most patients finding the format user-friendly. Electronic reports make analysis and interpretation by HP quicker and more accurate.

### DEVELOPMENT AND EVALUATION OF AN E-HEALTH SYSTEM TO CARE FOR PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Lee MH, Wu HC, Lin JY, Tan TH, Chan PC, Chen YF. *Int J Urol.* 2014 Apr;21 Suppl 1:62-8. doi: 10.1111/iju.12336. PMID: 24807502

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In this study from Taiwan, Internet intervention was used to care for bladder pain syndrome/interstitial cystitis patients to alleviate their pain and bothering symptoms. Healthcare education was carried out through the Internet by asking the patients, who were randomly divided into study (40 patients) and control (40 patients) groups, to check possible sensitive foods, habits, and behaviours weekly to remind and consolidate important rules for promoting quality of life. The symptom flares consultation through short message service with the Internet used to elevate healthcare efficiency was undertaken. Questionnaires, including Short Form 36 health survey, O'Leary-Sant symptom and problem indices, as well as visual analog scales pain and urgency scales, were used to evaluate quality of life and disease severity improvements before and after information and communication technology intervention. The outcome was evaluated at week 8. The E-health system was shown to be effective in improving quality of life of bladder pain syndrome/interstitial cystitis patients through intervention of Internet healthcare education and short message service for the consolidation of healthy behaviour and lifestyle in the 8-week follow up.

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