# International Painful Bladder Foundation

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

## IPBF e-Newsletter and Research Update

**Issue 43, September 2016**

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

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



## MEETING REVIEWS

### SOCIETAL IMPACT OF PAIN (SIP) SYMPOSIUM 2016 "TIME FOR ACTION"

Despite its impact on the economy, chronic pain tends to find itself relegated to a back-burner on the political agenda. The multi-stakeholder SIP symposium in Europe endeavours to rectify this. The SIP 2016 symposium with the theme Time for Action was held on 23 and 24 May 2016 in the European Parliament and Concert Noble in Brussels. Over 220 representatives of health care- and stakeholder- organisations from more than 28 countries attended SIP 2016, bringing together representatives of the European institutes including MEPs, policy makers, pain specialists, scientific researchers, patient representatives and other stakeholders. This makes it a unique meeting in Europe.

This year the programme included four working groups discussing four key issues related to the societal impact of pain:

1. Pain as a quality indicator for health care
2. Chronic Pain: a disease or multi-morbidity?
3. The relevance of pain in cancer care and rehabilitation
4. Pain, rehabilitation and reintegration of workers in the working force

Each working group produced specific policy recommendations addressing the societal impact of pain.

Patient representatives had the opportunity to attend an introduction to the official world of care in Brussels and the European Commission. Highly complex with multiple branches, but what seemed to be missing was an office to help patient organizations find their way through the maze.

A key topic in the symposium was the question as to whether chronic pain should be considered a symptom or a disease or condition in its own right. While there was a great deal of support for it to be considered a disease or condition in its own right, it was pointed out nevertheless by one speaker that we do not yet have the scientific evidence to state this categorically. However, scientific evidence is vital when presenting a case to the politicians. It is therefore essential to carry out focused research to find this evidence, and this means finding the money to fund the research.

Full details of the symposium and the recommendations can be found at:
https://www.sip-platform.eu/events/sip-2016/program.html and https://www.sip-platform.eu/events/sip-2016/materials.html

## SUCCESSFUL IC/BPS MEETING IN AHMEDABAD, INDIA HELD ON 14 AUGUST

A very successful IC/BPS meeting was held in Ahmedabad on 14 August organized by urologist and long-time IC/BPS pioneer in India Nagendra Mishra MD, and declared open by Balaka Basu, a patient from Mumbai. This meeting in Ahmedabad was attended by around 25 urologists and 8 patients with their relatives. All aspects of the disease received attention and delegates took part in lively discussions. The opportunity for interactive discussion is of course an added bonus of this size meeting and is not always possible in large conferences.
While most attendees came from Ahmedabad, some came from further afield. The most important message was that IC/BPS patients should not be taken lightly. Although the disease may be suspected from the history, cystoscopy is needed to rule out other diseases and disorders and to diagnose Hunner lesion which it is essential not to miss. A very important point discussed in relation to India was that bladder tuberculosis is not as common as IC/BPS.
There was a touch of nostalgia here too since it was 11 years ago in Ahmedabad at the 2005 annual USICON conference of the Urological Society of India that Dr Nagendra Mishra and Jane Meijlink - patient advocate and IPBF chair – first raised awareness of IC/BPS among the urologists of India and also organized a first patient meeting in Ahmedabad.

The annual ESSIC meeting in New Delhi in November (see upcoming events) is expected to further raise awareness and improve diagnosis and treatment of IC/BPS and associated disorders in India.

## PUBLICATIONS

### INTERNATIONAL CONTINENCE SOCIETY (ICS) PUBLISHES NEW STANDARD FOR TERMINOLOGY IN CHRONIC PELVIC PAIN SYNDROMES (SEE ALSO UNDER RESEARCH HIGHLIGHTS)

This long-awaited ICS standardization document – which should be seen as complementary to existing guidelines and standards - represents a new approach to chronic pelvic pain syndromes (including IC/BPS). In this document, the multidisciplinary working group, including a patient advocate, looks at the whole patient with known associated disorders. This holistic, patient-friendly document is hoped to make it easier for healthcare professionals to diagnose not only the syndromes but also recognize the possible presence of comorbidities, thereby ensuring that patients get referred to the right specialists at the earliest possible stage.
The document is currently on early view at Neurourology & Urodynamics.

*Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Homma Y, Garrido G, Gomes MJ, Elneil S, van de Merwe JP, Lin AT, Tomoe H.* A Standard for Terminology in Chronic Pelvic Pain Syndromes: A Report from the Chronic Pelvic Pain Working Group of the International Continence Society. *Neurourol Urodyn. 2016 Aug 26. doi: 10.1002/nau.23072. [Epub ahead of print] PMID: 27564065*

### NEWS FROM THE NATIONAL INSTITUTES OF HEALTH (NIH) IN THE USA:

The following link takes you to an interesting article about the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) **MAPP Network Study**:
The Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network: Yielding new insights into challenging urologic pain syndromes

Also of special interest to our field:
Pain expectations: altered brain responses in people with irritable bowel syndrome

### FREE OPEN ACCESS JOURNAL SPECIAL ISSUE PUBLICATIONS REMINDER

Open access articles and supplements are an ideal way for patients and their organizations to stay up to date with scientific developments in the field of IC/BPS and associated conditions. Below is a reminder of useful special issues with free access to the full text.

**- TRANSLATIONAL ANDROLOGY AND UROLOGY (TAU)**
**SUPPLEMENTS FOCUSED ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: PART I AND PART II**:

**PART I: TRANSLATIONAL ANDROLOGY AND UROLOGY VOL 4, NO 5 (OCTOBER 2015)**,
http://www.amepc.org/tau/issue/view/362. This link takes you to an overview of the articles with open access to HTML or pdf.

**PART II: TRANSLATIONAL ANDROLOGY AND UROLOGY VOL 4, NO 6 (DECEMBER 2015)**
http://tau.amegroups.com/issue/view/374 This link takes you to an overview of the articles with open access to HTML or pdf.

**- INTERNATIONAL JOURNAL OF UROLOGY**
**Special Issue: 3rd International Consultation on Interstitial Cystitis Japan (ICICJ) and International Society for the Study of Bladder Pain Syndrome (ESSIC) Joint Meeting, 21–23 March 2013, Kyoto, Japan**
**April 2014**
Volume 21, Issue Supplement S1 Pages 1–88, i–vi, A1–A25
Direct link: http://onlinelibrary.wiley.com/doi/10.1111/iju.2014.21.issue-s1/issuetoc

Please note that some new research articles listed under new research also have open access. See Research Highlights.

## CALENDAR OF UPCOMING EVENTS

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

13-16 September 2016, in Tokyo, Japan.
The ICS annual scientific meeting is increasingly becoming an important platform for chronic pelvic pain and IC/BPS and its 2016 meeting will include a number of research sessions on IC/BPS and chronic pelvic pain and a round table discussion on Interstitial Cystitis Revisited chaired by Professor Kuo from Taiwan as well as two workshops. The 2016 ICS meeting will be combined with the 6th International Consultation on Incontinence with sessions on many different conditions, including a session on IC/BPS chaired by Philip Hanno, MD. http://www.ics.org/2016.

### CONVERGENCES PP 2016 – CONVERGENCES IN PELVIPERENEAL PAIN

International meeting on chronic pelvic and abdominal pain, 15/16/17 September 2016, Palais des Congres, Aix en Provence, France for all stakeholders, including patient representatives. Simultaneous translation French/English/Spanish. Includes a session on IC/BPS. www.convergencespp.com. For the programme, go to: http://www.mcocongres.com/OUT/newsletter/convergencespp/convergencespp2016.pdf

### 3RD GLOBAL CONGRESS ON LUTD

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

### 16TH WORLD CONGRESS ON PAIN

The IASP World Congress on Pain, 26–30 September, 2016, Yokohama, Japan
http://www.iasp-pain.org/Yokohama?navItemNumber=593

### ESSIC ANNUAL MEETING 2016

ESSIC (International Society for the Study of IC/BPS) will hold its 2016 Annual Meeting at Four Points by Sheraton New Delhi, Airport Highway, in New Delhi, India, 17-19 Nov 2016. Further details including the programme are available at www.essic.eu.

### 1ST MEETING OF THE SOCIETY FOR PELVIC RESEARCH

The first meeting of the Society for Pelvic Research will be held 5-6 December, 2016 in Charleston, South Carolina. Venue: Marriott Charleston Historic District, 125 Calhoun Street, Charleston, SC 29401, USA. Website https://www.pelvicresearch.com/. Conference details: https://www.pelvicresearch.com/spr-meetings2.html

### 2017 IPPS & 3RD WORLD CONGRESS OF ABDOMINAL AND PELVIC PAIN

October 12 - 15, 2017, Renaissance Washington DC Downtown, Washington, DC
Further information: http://pelvicpain.org/meetings/details.aspx?id=114

## RESEARCH HIGHLIGHTS

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

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

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

### STANDARD TERMINOLOGY

**A STANDARD FOR TERMINOLOGY IN CHRONIC PELVIC PAIN SYNDROMES: A REPORT FROM THE CHRONIC PELVIC PAIN WORKING GROUP OF THE INTERNATIONAL CONTINENCE SOCIETY.**

*Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Homma Y, Garrido G, Gomes MJ, Elneil S, van de Merwe JP, Lin AT, Tomoe H. Neurourol Urodyn. 2016 Aug 26. doi: 10.1002/nau.23072. [Epub ahead of print] PMID: 27564065*

Terms used in the field of chronic pelvic pain (CPP) are poorly defined and often confusing. An International Continence Society (ICS) Standard for Terminology in chronic pelvic pain syndromes (CPPS) has been developed with the aim of improving diagnosis and treatment of patients affected by chronic pelvic pain syndromes. The standard aims to facilitate research, enhance therapy development and support healthcare delivery, for healthcare providers, and patients.

This document looks at the whole person and all the domains (organ systems) in a systematic way. A dedicated working group (WG) was instituted by the ICS Standardisation Steering Committee according to published procedures. The WG extracted information from existing relevant guidelines, consensus documents, and scientific publications. Medline and other databases were searched in relation to each chronic pelvic pain domain from 1980 to 2014. Existing ICS Standards for terminology were utilized where appropriate to ensure transparency, accessibility, flexibility, and evolution. Consensus was based on majority agreement. The multidisciplinary CPPS Standard reports updated consensus terminology in nine domains; lower urinary tract, female genital, male genital, gastrointestinal, musculoskeletal, neurological aspects, psychological aspects, sexual aspects, and comorbidities. Each is described in terms of symptoms, signs and further evaluation. The document presents preferred terms and definitions for symptoms, signs, and evaluation (diagnostic work-up) of female and male patients with chronic pelvic pain syndromes, serving as a platform for ongoing development in this field.

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

### SYMPTOM VARIABILITY AND EARLY SYMPTOM REGRESSION IN THE MAPP STUDY, A PROSPECTIVE STUDY OF UROLOGIC CHRONICPELVIC PAIN SYNDROME.

*Stephens-Shields AJ, Clemens JQ, Jemielita T, Farrar J, Sutcliffe S, Hou X, Landis JR; MAPP Research Network. J Urol. 2016 Apr 27. [Epub ahead of print]* PMID: 27131464

In this MAPP Research Network study, the authors examine symptom variability in men and women with urological chronic pelvic pain syndrome (UCPPS). They describe symptom fluctuations as related to early symptom regression and its effect on estimated one-year symptom change and then describe a method to quantify patient-specific symptom variability. They found that patients with UCPPS exhibit symptom variability. At enrolment, patients had, on average, worse symptoms, resulting in a regression effect that influenced the estimated proportion of improved or worse subjects. Prospective studies should include a run-in to account for regression to the mean and other causes of early symptom regression. Further, symptom variability may be quantified and used to characterize longitudinal UCPPS symptom profiles.

### URINARY METABOLOMICS IDENTIFIES A MOLECULAR CORRELATE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IN A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN (MAPP) RESEARCH NETWORK COHORT.

*Parker KS, Crowley JR, Stephens-Shields AJ, van Bokhoven A, Lucia MS, Lai HH, Andriole GL, Hooton TM, Mullins C, Henderson JP. EBioMedicine. 2016 May;7:167-74. doi: 10.1016/j.ebiom.2016.03.040. Epub 2016 Mar 31. PMID: 27322470*

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a poorly understood syndrome affecting up to 6.5% of adult women in the U.S. The lack of broadly accepted objective laboratory markers for this condition hampers efforts to diagnose and treat this condition. To identify biochemical markers for IC/BPS, this MAPP Research Network team applied mass spectrometry-based global metabolite profiling to urine specimens from a cohort of female IC/BPS subjects from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. These analyses identified multiple metabolites capable of discriminating IC/BPS and control subjects. Of these candidate markers, etiocholan-3α-ol-17-one sulfate (Etio-S), a sulfoconjugated 5-β reduced isomer of testosterone, distinguished female IC/BPS and control subjects with a sensitivity and specificity >90%. Among IC/BPS subjects, urinary Etio-S levels are correlated with elevated symptom scores (symptoms, pelvic pain, and number of painful body sites) and could resolve high- from low-symptom IC/BPS subgroups. Etio-S-associated biochemical changes persisted through 3-6months of longitudinal follow up. These results raise the possibility that an underlying biochemical abnormality contributes to symptoms in patients with severe IC/BPS.

## GUIDELINES

### CLINICAL GUIDELINES FOR INTERSTITIAL CYSTITIS AND HYPERSENSITIVE BLADDER UPDATED IN 2015.

*Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH, Oh SJ, Kim JC, Lee KS. Int J Urol. 2016 Jul;23(7):542-9. doi: 10.1111/iju.13118. Epub 2016 May 24. PMID: 27218442*

The clinical guidelines for interstitial cystitis and hypersensitive bladder from East Asia have been updated as of 2015. The guidelines define interstitial cystitis by the presence of hypersensitive bladder symptoms (discomfort, pressure or pain in the bladder usually associated with urinary frequency and nocturia) and bladder pathology, after excluding other diseases explaining symptoms. Interstitial cystitis is further classified by bladder pathology; either Hunner type interstitial cystitis with Hunner lesions or non-Hunner type interstitial cystitis with mucosal bleeding after distension in the absence of Hunner lesions. Hypersensitive bladder refers to a condition, where hypersensitive bladder symptoms are present, but bladder pathology or other explainable diseases are unproven. Interstitial cystitis and hypersensitive bladder severely affect patients' quality of life as a result of disabling symptoms and/or comorbidities. Reported prevalence suggestive of these disorders varies greatly from 0.01% to >6%. Pathophysiology would be an interaction of multiple factors including urothelial dysfunction, inflammation, neural hyperactivity, exogenous substances and extrabladder disorders. Definite diagnosis of interstitial cystitis and hypersensitive bladder requires cystoscopy with or

without hydrodistension. Most of the therapeutic options lack a high level of evidence, leaving a few as recommended therapeutic options.

## IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

### UROTHELIAL FUNCTIONAL PROTEIN AND SENSORY RECEPTORS IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME WITH AND WITHOUT HUNNER'S LESION.

*Jhang JF, Hsu YH, Kuo HC. Urology. 2016 Aug 26. pii: S0090-4295(16)30542-8. doi: 10.1016/j.urology.2016.08.029. [Epub ahead of print] PMID: 27575016*

The purpose of this study by Jhang and colleagues from Taiwan was to investigate the urothelium function and sensory receptors difference between interstitial cystitis/bladder pain syndrome (IC/BPS) patients with or without Hunner lesion. Fourteen female IC/BPS patients with Hunner's lesion (Hunner IC) and 14 age-matched IC/BPS patients without Hunner's lesions (non-Hunner IC) were enrolled. Bladder mucosa biopsies were obtained. Bladder inflammation, eosinophil infiltration, and urothelial denudation were graded on a 4-point scale after staining with hematoxylin and eosin stain. Adhesive protein E-cadherin, tryptase, and zonula occuldens-1 in the bladder tissues were assessed with immunofluorescence staining. Urothelial muscarinic receptors M2, M3, endothelial nitric oxide synthase (e-NOS) and purinergic receptor P2X3 were evaluated by western blotting. It was found that Hunner IC patients had a significantly higher mean visual analog scale pain score and smaller cystometric bladder capacity than non-Hunner IC patients. The Hunner IC bladder specimens showed more severe or moderate eosinophilic infiltration and urothelial denudation than the non-Hunner IC bladder specimens did. The E-cadherin expression was significantly lower, and e-NOS expression was significantly higher in the Hunner IC bladder samples than in non-Hunner IC samples. The other functional proteins or sensory receptors did not differ between groups. It was concluded that bladder inflammation and urothelial cell adhesion defects were more severe in the Hunner IC than that in non-Hunner IC patients. ENOS was significantly higher in the Hunner IC than non-Hunner IC bladder samples, suggesting that eNOS expression difference may implicate different pathogenesis in two types of IC.

### EFFICACY AND SAFETY OF BOTULINUM TOXIN INJECTION FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS.

*Shim SR, Cho YJ, Shin IS, Kim JH. Int Urol Nephrol. 2016 Aug;48(8):1215-27. doi: 10.1007/s11255-016-1295-y. Epub 2016 Apr 30. PMID: 27139498*

The purpose of this review from Korea was to investigate the overall treatment efficacy and safety of botulinum toxin type A (BoNTA) injections compared with placebo in interstitial cystitis/bladder pain syndrome (IC/BPS). Shim and colleagues conducted a systematic review and meta-analysis of the published literature in PubMed, Cochrane Library, and EMBASE on BoNTA use in IC/BPS. Outcome measures included changes of OLS, ICSI, ICPI, VAS, frequency, nocturia, FBC, Qmax, and PVR from baseline and also included adverse events. A total of five studies were included, with a total sample size of 252 subjects (133 subjects in the experimental group and 119 subjects in the control group). The duration of follow-up ranged from 8 to 12 weeks. The BoNTA dosage was from 50 to 200 U. The pooled overall SMD in the mean change of VAS for the BoNTA group versus the placebo group was -0.49 (95 % CI -0.74, -0.23). There were also significant improvements in ICPI and frequency. The other outcomes (ICSI, nocturia, Qmax, and FBC) were not statistically different between the two groups. Although BoNTA is not regulatory approved indication, this first evidence-based systematic review and meta-analysis of BoNTA injection for IC/BPS showed significant differences in efficacy of treatment compared with placebo, especially for pain control, and also showed no differences in the rate of procedure-related adverse events.

### STUDY OF THE APOPTOTIC EFFECT OF URINE AS A DIAGNOSTIC BIOMARKER IN PATIENTS WITH INTERSTITIAL CYSTITIS.

[Article in English, Spanish]

*Di Capua-Sacoto C, Sanchez-Llopis A, O'Connor E, Martinez A, Ruiz-Cerdá JL. Actas Urol Esp. 2016 May 9. [Epub ahead of print] PMID: 27174573*

The main objective of this Spanish study was to assess the apoptotic effect of urine from patients with interstitial cystitis (IC) in cell cultures and to study its value as a diagnostic biomarker for IC. A prospective

study was conducted between January 2010 and January 2015 and included 57 patients diagnosed with IC and 50 healthy patients from the Hospital Clinic of Barcelona and the La Paz University Hospital. The urine of these patients was exposed to cell cultures, and its ability to induce apoptosis in the cultures was analysed. Using flow cytometry, the authors then measured the degree of apoptosis, quantified by the percentage of cells of the cell cycle in phase sub G0. It was concluded that the urine of patients with IC exerts an apoptotic effect on tumour cell cultures that is significantly greater than that exerted by the urine of healthy control patients. A ≥10% cutoff for the apoptosis test presented very low sensitivity (40%) but had a very high specificity (96%), thereby able to confirm the diagnosis of IC when positive.

**INITIAL EXPERIENCE WITH SACRAL NEUROMODULATION FOR THE TREATMENT OF LOWER URINARY TRACT DYSFUNCTION IN BRAZIL.**

*Rios LA, Averbeck MA, Franca W, Sacomani CA, Almeida FG, Gomes CM. Int Braz J Urol. 2016 Mar-Apr;42(2):312-20. PMID: 27176186*

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Rios and colleagues from Brazil report on the short-term outcomes of sacral neuromodulation (SNM) for treatment of idiopathic lower urinary tract dysfunction in Brazil (procedures performed before 2014). Clinical data and surgical outcomes of patients who underwent SNM staged procedures were retrospective evaluated. Urological assessment included a focused medical history and physical examination, measurement of postvoid residual volumes, urodynamics, and bladder diaries. A successful test phase was defined by improvement of at least 50% of the symptoms, based on bladder diaries. It was concluded that SNM is a minimally invasive treatment option for patients with refractory idiopathic lower urinary tract dysfunction. The authors' initial experience with staged technique showed that tined-lead electrodes yielded a high rate of responders and favorable clinical results in the short-term follow-up. No severe complications were reported.

**BOTULINUM TOXIN A FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.**

*Chiu B, Tai HC, Chung SD, Birder LA. Toxins (Basel). 2016 Jul 1;8(7). PMID: 27376330*

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Botulinum neurotoxin A (BoNT-A), derived from Clostridium botulinum, has been used clinically for several diseases or syndromes including chronic migraine, spasticity, focal dystonia and other neuropathic pain. Chronic pelvic or bladder pain is the one of the core symptoms of bladder pain syndrome/interstitial cystitis (BPS/IC). However, in the field of urology, chronic bladder or pelvic pain is often difficult to eradicate by oral medications or bladder instillation therapy. Chiu and colleagues report that they are looking for new treatment modality to improve bladder pain or associated urinary symptoms such as frequency and urgency for patients with BPS/IC. Recent studies investigating the mechanism of the antinociceptive effects of BoNT A suggest that it can inhibit the release of peripheral neurotransmitters and inflammatory mediators from sensory nerves. In this review, the authors examine the evidence supporting the use of BoNTs in bladder pain from basic science models and review the clinical studies on therapeutic applications of BoNT for BPS/IC.

**TREATMENT EFFECT OF CYCLOSPORINE A IN PATIENTS WITH PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS: A SYSTEMATIC REVIEW.**

*Wang Z, Zhang L. Exp Ther Med. 2016 Jul;12(1):445-450. Epub 2016 Apr 27. PMID: 27347076*

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Cyclosporine A (CyA) is emerging as a potential therapeutic strategy for painful bladder syndrome/interstitial cystitis (PBS/IC), which is currently an incurable disease. The purpose of this systematic review was to evaluate the treatment effects of CyA in PBS/IC. Electronic and manual retrieval procedures were carried out to identify eligible references for the systematic review. The entire contents of the included articles were assessed, from study design to reported results. Eight studies, comprising three randomized controlled trials (RCTs), four prospective studies and one retrospective cohort study, were included, involving a total of 298 subjects. Meta-analysis was not implemented due to heterogeneity of the manner of reporting the outcome parameters. All studies reported an improvement in symptoms following treatment with CyA. The results of the three RCTs implied that the treatment effects of CyA were better than those of pentosan polysulfate sodium. Some adverse events, for example, elevation of serum creatinine levels and an increase in blood pressure, were

noted in five studies. In conclusion, the evidence from the studies implied that treatment of CyA can result in a long-term benefit in patients of PBS/IC; however, further evidence is required to verify this.

**EFFECTS OF HYPERBARIC OXYGEN THERAPY ON HYDROCHLORIC ACID-INDUCED INTERSTITIAL CYSTITIS IN RATS: A HISTOLOGICAL AND ULTRASTRUCTURAL STUDY.**

*Yilmaz M, Cakmak T, Yenilmez A, Baseskioglu B, Metin S. Undersea Hyperb Med. 2016 May-Jun;43(3):181-8. PMID: 27416685*

Yilmaz and colleagues investigated the therapeutic effects of hyperbaric oxygen ($HBO_2$) therapy in this syndrome in an experimental IC model through biochemical analyses and histopathological assessments. 24 Sprague Dawley rats were divided into three treatment groups sham (transurethral intravesical injection with sterile distilled water), rats with IC (induced by transurethral intravesical injection with hydrochloric acid), and rats with IC + $HBO_2$. After completion of experiments the animals were sacrificed and their urinary bladders were removed surgically. Tissues were evaluated by light and electron microscopy. Lesion index scoring system for IC was used to evaluate vesical injury. TNF-α levels were measured by ELISA test kit. Lesion index scores and TNF-α levels of the sham and IC + $HBO_2$ treatment groups were quite similar. Although $HBO_2$ treatment did not show any effect in reducing the number of mast cells, it reduced the mast cell activity. All parameters except mitochondrial damage were improved in the IC + $HBO_2$ treatment group compared to the IC without $HBO_2$ treatment group. The authors concluded that $HBO_2$ treatment may alleviate the inflammation, may lead to a certain degree of reversal of adverse histopathological changes, and is effective in enhancing the healing process in interstitial cystitis. They are of the opinion that $HBO_2$ treatment may be included as a weapon in the armamentarium against IC.

**IS URETHRECTOMY NECESSARY DURING CYSTECTOMY IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME?**

*Yang TX, Luo DY, Li H, Wang KJ, Shen H. Urology. 2016 Jul 13. [Epub ahead of print] PMID: 27424120*

The purpose of this study by Yang and colleagues was to assess the outcome of cystectomy and cystourethrectomy in patients with intractable IC/BPS, and to identify whether urethrectomy is necessary. During 2007 to 2014, 18 women were eligible and elected surgical treatment after conservative treatment failed. Seven cystectomies with ileal conduit urinary diversions, eight cystourethrectomies with ileal conduit urinary diversions, and three supratrigonal cystectomy with orthotopic ileocystoplasty were performed. Patient histories, perioperative medical records, and follow-up outcomes were evaluated and summarized. Patients reported subjectively improved social function and mental condition secondary to decreased urination frequency postoperatively. Pain also significantly decreased compared with baseline. To date, additional surgery to alleviate persistent symptoms or postoperative complications has not been necessary. Furthermore, there was no association between reported urethral pain and the initial transvaginal urethrectomy incidence. More operation time and longer postoperative hospitalization duration was recorded without better surgical outcomes in the urethrectomy group. The authors concluded that cystectomy and cystourethrectomy are effective and adequate treatment for IC/BPS, and their experience indicates that urethrectomy is not routinely needed. However, further long-term, prospective studies involving a larger study group are needed.

**ELEVATED LEVEL OF NERVE GROWTH FACTOR IN THE BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A META-ANALYSIS.**

*Chen W, Ye DY, Han DJ, Fu GQ, Zeng X, Lin W, Liang Y. Springerplus. 2016 Jul 13;5(1):1072. doi: 10.1186/s40064-016-2719-y. eCollection 2016. PMID: 27462520*

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The purpose of the study by Chen and colleagues was to elucidate the association between nerve growth factor (NGF) level and bladder pain syndrome/interstitial cystitis (BPS/IC) by conducting a meta-analysis. They conducted a systematic literature search to identify original studies of NGF level in BPS/IC before November 2015. Eligible studies were retrieved via both computer searches and manual review of references. The summary difference estimates between controlled group and BPS/IC group were calculated based on the weighted mean difference (WMD) with its 95 % confidence interval (CI). Sensitivity and publication analyses were performed after the pooled analysis. Meta-analysis of 10 original studies involving 295 cases and 290 normal controls showed an increased level of urinary NGF in BPS/IC patients. The combined WMD was 36.39.

There was significant difference between controlled group and BPS/IC patients in the term of NGF/Cr level. There was no significant publication bias in the included studies. The authors concluded that their results demonstrated that there was indeed an increased level of NGF in the BPS/IC patients.

**THE ROLE OF THE MUCOSA IN NORMAL AND ABNORMAL BLADDER FUNCTION.**

*Fry CH, Vahabi B. Basic Clin Pharmacol Toxicol. 2016 May 26. doi: 10.1111/bcpt.12626. [Epub ahead of print] PMID: 27228303*

Fry and Vahabi from Bristol UK report that the internal face of the detrusor smooth muscle wall of the urinary bladder is covered by a mucosa, separating muscle from the hostile environment of urine. However, the mucosa is more than a very low permeability structure and offers a sensory function that monitors the extent of bladder filling and composition of the urine. The mucosa may be considered as a single functional structure and comprises a tight epithelial layer under which is a basement membrane and lamina propria. The latter region itself is a complex of afferent nerves, blood vessels, interstitial cells and in some species including human beings a muscularis mucosae. Stress on the bladder wall through physical or chemical stressors elicits release of chemicals, such as ATP, acetylcholine, prostaglandins and nitric oxide that modulate the activity of either afferent nerves or the muscular components of the bladder wall. The release and responses are graded so that the mucosa forms a dynamic sensory structure, and there is evidence that the gain of this system is increased in pathologies such as overactive bladder and bladder pain syndrome. This system therefore potentially provides a number of drug targets against these conditions, once a number of fundamental questions are answered. These include how is mediator release regulated; what are the intermediate roles of interstitial cells that surround afferent nerves and blood vessels; and what is the mode of communication between urothelium and muscle - by diffusion of mediators or by cell-to-cell communication?

**UROTHELIAL ATP SIGNALING: WHAT IS ITS ROLE IN BLADDER SENSATION?**

*Takezawa K, Kondo M, Nonomura N, Shimada S. Neurourol Urodyn. 2016 Aug 19. doi: 10.1002/nau.23099. [Epub ahead of print] PMID: 27542121*

Bladder functional disorders are common health problems; however, their pathologies are poorly understood. Adenosine triphosphate (ATP) released from the urothelium has been suggested to have an essential role in the micturition reflex, and its involvement in bladder functional disorders has been intensively investigated. Takezawa and colleagues from Japan review the latest advances in research on urothelial ATP signalling. The authors report that recently conflicting evidence has led them to question the role of urothelial ATP signalling in normal micturition reflex. In contrast, under pathological conditions, it seems likely that enhanced urothelial ATP signaling mediates bladder hyperactivity. These recent findings suggest that the urothelial ATP signalling pathway is a potential therapeutic target for bladder functional disorders.

**IMPORTANT ROLE OF PHYSICIANS IN ADDRESSING PSYCHOLOGICAL ASPECTS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS): A QUALITATIVE ANALYSIS.**

*Kanter G, Volpe KA, Dunivan GC, Cichowski SB, Jeppson PC, Rogers RG, Komesu YM. Int Urogynecol J. 2016 Aug 31. [Epub ahead of print] PMID: 27581769*

Kanter and colleagues from Albuquerque report that interstitial cystitis/bladder pain syndrome (IC/BPS) is a poorly understood source of chronic pain causing significant morbidity, with variable treatment success. Despite the need to understand patient perspectives in chronic pain, there is a paucity of qualitative data for IC/BPS. Their aim was to acquire information regarding patient experience with IC/BPS symptoms and with their medical care to elicit suggestions to improve patient satisfaction with that care. Fifteen women with IC/PBS participated in a total of four focus groups. Sessions were recorded and transcribed and information deidentified. Focus groups were conducted until thematic saturation was reached. All transcripts were coded and analyzed by a minimum of three independent physician reviewers. Investigators identified emergent themes and concepts using grounded-theory methodology. They identified three emergent patient experience concepts: IC/PBS is debilitating, the disease course is unpredictable and unrelenting, and patients experience significant isolation. Importantly, suicidal ideation was expressed in each group. Patients voiced strong preference for physicians who provided education regarding the condition, an array of treatment options, organized treatment plans, and optimism and hope regarding treatment outcomes. They concluded that their

study presents novel findings of the importance of patient-physician interaction in IC/BPS and reinforces the tremendous disability and burden of this disease, which frequently manifests in suicidal ideation. Patients preferred organized treatment plans with diverse choices and providers who offered hope in dealing with their condition.

## BLADDER AND PELVIC HYPERSENSITIVITY

### INTRAVESICAL PAC1 RECEPTOR ANTAGONIST, PACAP(6-38), REDUCES URINARY BLADDER FREQUENCY AND PELVIC SENSITIVITY IN NGF-OE MICE.

*Girard BM, Malley SE, Mathews MM, May V, Vizzard MA. J Mol Neurosci. 2016 Jun;59(2):290-9. doi: 10.1007/s12031-016-0764-1. Epub 2016 May 4. PMID: 27146136*

Chronic NGF overexpression (OE) in the urothelium, achieved through the use of a highly urothelium-specific uroplakin II promoter, stimulates neuronal sprouting in the urinary bladder, produces increased voiding frequency and non-voiding contractions, and referred somatic sensitivity. Additional NGF-mediated pleiotropic changes might contribute to increased voiding frequency and pelvic hypersensitivity in NGF-OE mice such as neuropeptide/receptor systems including PACAP(Adcyap1) and PAC1 receptor (Adcyap1r1). Given the presence of PAC1-immunoreactive fibers and the expression of PAC1 receptor expression in bladder tissues, and PACAP-facilitated detrusor contraction, whether PACAP/receptor signalling contributes to increased voiding frequency and somatic sensitivity was evaluated in NGF-OE mice. Intravesical administration of the PAC1 receptor antagonist, PACAP(6-38) (300 nM), significantly increased intercontraction interval (2.0-fold) and void volume (2.5-fold) in NGF-OE mice. Intravesical instillation of PACAP(6-38) also decreased baseline bladder pressure in NGF-OE mice. PACAP(6-38) had no effects on bladder function in WT mice. Intravesical administration of PACAP(6-38) (300 nM) significantly reduced pelvic sensitivity in NGF-OE mice but was without effect in WT mice. PACAP/receptor signalling contributes to the increased voiding frequency and pelvic sensitivity observed in NGF-OE mice.

## OVERACTIVE BLADDER AND PAIN

### SOMATIC SYNDROMES AND CHRONIC PAIN IN WOMEN WITH OVERACTIVE BLADDER.

*Reynolds WS, Mock S, Zhang X, Kaufman M, Wein A, Bruehl S, Dmochowski R. Neurourol Urodyn. 2016 Jul 1. [Epub ahead of print] PMID: 27367486*

Mechanisms underlying pain perception and afferent hypersensitivity, such as central sensitization, may impact overactive bladder (OAB) symptoms. However, little is known about associations between OAB symptom severity, pain experience, and presence of comorbid chronic pain syndromes. This study examined relationships between OAB symptoms, somatic symptoms, and specific chronic pain conditions in which central sensitization is believed to play a primary role, in a community-based sample of adult women with OAB. The authors recruited adult women with OAB to complete questionnaires assessing urinary symptoms, pain and somatic symptoms, and preexisting diagnoses of central sensitivity syndromes. They analyzed the effects of overall bodily pain intensity, general somatic symptoms, and diagnoses of central sensitivity syndromes on OAB symptom bother and health-related quality of life. Of the 116 women in this study, over half (54%) stated their urge to urinate was associated with pain, pressure, or discomfort. Participants reported a wide range of OAB symptoms and health-related quality of life. There was a significant, positive correlation between OAB symptoms and somatic symptoms as well as overall pain intensity. Only 7% of women met diagnostic criteria for fibromyalgia; yet these women demonstrated significantly increased OAB symptom burden and decreased OAB quality of life compared to those without fibromyalgia. Women with more severe OAB symptoms reported increased general somatic symptom burden and increased overall body pain intensity, especially women with fibromyalgia. These findings suggest that attributes of pain and co-morbidity with chronic pain conditions may impact the experience of OAB symptoms for many women.

### DOES CENTRAL SENSITIZATION HELP EXPLAIN IDIOPATHIC OVERACTIVE BLADDER?

*Reynolds WS, Dmochowski R, Wein A, Bruehl S. Nat Rev Urol. 2016 Aug;13(8):481-91. Epub 2016 Jun 1. PMID: 27245505*

The pathophysiological mechanisms underlying overactive bladder syndrome (OAB) can include dysfunction of sensory pathways of the peripheral and central nervous systems, resulting in bladder hypersensitivity. Central sensitization describes an induced state of spinal hypersensitivity that is associated with a variety of chronic pain disorders that share many attributes with OAB, albeit without the presence of pain. As such, the concept of central sensitization might be relevant to understanding the mechanisms and clinical manifestations of OAB syndrome. An understanding of the pathophysiology and clinical manifestations of central sensitization, and the evidence that supports a role of central sensitization in OAB, including the potential implications of mechanisms of central sensitization for the treatment of patients with OAB could provide a novel approach to the treatment of patients with this disease. Such an approach would be especially relevant to those patients with central sensitization-related comorbidities, and has the potential to improve the outcomes of these patients in particular.

## URETHRAL SYNDROME

**[URETHRAL SYNDROME AND URETHRAL PAIN: DO WE TREAT PEOPLE OR DIAGNOSES?].**

[Article in German]

*Doggweiler R, Reitz A, Kirschner-Hermanns R. Aktuelle Urol. 2016 Aug;47(4):315-20. doi: 10.1055/s-0042-106662. Epub 2016 Aug 8. PMID: 27500850*

The urethral syndrome with urethral pain and bladder voiding disorders is a diagnosis of exclusion. Possible aetiologies are diverse and include organic, functional and inflammatory pathologies of the urethra. Infections, inflammation of the paraurethral glands, spasms of the sphincter muscle and/or of the pelvic floor muscles, oestrogen deficiency, trauma, neuropathies, hypersensitivity and psychosomatic issues have been investigated as possible causes. Patients with urethral syndrome must be viewed, evaluated and treated holistically. They need a lot of time and attention during their evaluation and treatment.

## KETAMINE CYSTITIS

**THE ROLE OF IMMUNOGLOBULIN E IN THE PATHOGENESIS OF KETAMINE RELATED CYSTITIS AND ULCERATIVE INTERSTITIAL CYSTITIS: AN IMMUNOHISTOCHEMICAL STUDY.**

*Jhang JF, Hsu YH, Jiang YH, Kuo HC. Pain Physician. 2016 May;19(4):E581-7.* PMID: 27228524

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Jhang and colleagues report that a previous study revealed elevated serum Immunoglobulin E (IgE) in ketamine related cystitis (KC) patients. IgE might participate in the pathogenesis of different types of bladder pain syndromes, including KC and interstitial cystitis (IC). The aim of this study was to investigate the IgE expression in KC and IC bladder tissue. The authors investigated the bladder IgE with immunofluorescence staining and quantification. The active mast cells were measured using tryptase. The symptoms and urodynamic study results were recorded. Double immunofluorescence staining of tryptase and IgE was also performed. Sixteen KC patients, 10 ulcerative[lesion] IC patients, and 20 non-ulcerative [non-lesion] IC patients participated. The history and urodynamic parameters were investigated in these patients. The bladder mucosa was biopsied during cystoscopic hydrodistention. Bladder biopsies were also taken from 22 patients with bacterial cystitis and 12 healthy controls. Bladder IgE was positive in 15 (93.8%) KC patients, 9 (90%) ulcerative IC patients, one (5%) non-ulcer IC patient, 8 (36.4%) bacterialcystitis patients, and 2 (16.7%) controls ($P < .001$). The bladder IgE was greater in the patients with KC than in the others. After excluding KC patients, bladder IgE was significantly higher in the patients with ulcerative IC than the others. The bladder IgE was significantly correlated with pain on a visual analogue scale and maximum bladder capacity. Tryptase expression did not show a significant difference between KC, ulcer IC, and non-ulcer IC ($P = 0.222$). Double immunofluorescence staining showed co-expression of tryptase and IgE. The authors concluded that IgE-mediated inflammation played a significant role in the pathogenesis of KC and ulcerative [lesion] IC.

**EVALUATION OF URINARY BLADDER FIBROGENESIS IN A MOUSE MODEL OF LONG-TERM KETAMINE INJECTION.**

*Shen CH, Wang SC, Wang ST, Lin SM, Wu JD, Lin CT, Liu YW. Mol Med Rep. 2016 Sep;14(3):1880-90. doi: 10.3892/mmr.2016.5482. Epub 2016 Jul 7. PMID: 27431428*

Long-term ketamine abuse has been shown to affect the lower urinary tract and result in interstitial cystitis-like syndrome. However, the causative mechanism of ketamine-induced dysfunction remains unclear. The present study by Shen and colleagues aimed to investigate the physiological, histological and molecular changes on ketamine-associated cystitis (KC) in a mouse model. Both male and female Balb/c mice were separately distributed into the control group (normal saline) and ketamine group, which received ketamine hydrochloride (100 mg/kg/day) daily by intraperitoneal injection for a total period of 20 weeks. In each group, the urine was analyzed by gas chromatography-mass spectrometry to measure the concentration of ketamine and its metabolites. Urinary frequency and urine volume were examined to investigate the urinary voiding functions. Mice bladders were excised for cDNA microarray and hematoxylin and eosin (HE) staining. The ketamine and metabolites were detected only in ketamine-treated mice urine. The voiding interval was reduced in the male mice group after 20 weeks of ketamine administration. Additionally, the result of cDNA array analysis revealed a number of gene expression levels involved in chronic wound healing response and collagen accumulation, which were closely associated with fibrosis progression in the connective tissue. In HE staining of the bladder tissue, the ketamine-injected mice exhibited prominently denser blood vessel distribution in the submucosal layer. Based on the evidence in the present study, a mechanism that delineates fibrosis formation of urinary bladder induced by the pathogenesis of ketamine abuse can be constructed.

**MESENCHYMAL STEM CELLS PROTECT AGAINST THE TISSUE FIBROSIS OF KETAMINE-INDUCED CYSTITIS IN RAT BLADDER.**

*Kim A, Yu HY, Heo J, Song M, Shin JH, Lim J, Yoon SJ, Kim Y, Lee S, Kim SW, Oh W, Choi SJ, Shin DM, Choo MS. Sci Rep. 2016 Aug 2;6:30881. doi: 10.1038/srep30881. PMID: 27481042*

Abuse of the hallucinogenic drug ketamine promotes the development of lower urinary tract symptoms that resemble interstitial cystitis. The pathophysiology of ketamine-induced cystitis (KC) is largely unknown and effective therapies are lacking. Here, using a KC rat model, the authors show the therapeutic effects of human umbilical cord-blood (UCB)-derived mesenchymal stem cells (MSCs). Daily injection of ketamine to Sprague-Dawley rats for 2-weeks resulted in defective bladder function, indicated by irregular voiding frequency, increased maximum contraction pressure, and decreased intercontraction intervals and bladder capacity. KC bladders were characterized by severe mast-cell infiltration, tissue fibrosis, apoptosis, upregulation of transforming growth factor-β signalling related genes, and phosphorylation of Smad2 and Smad3 proteins. A single administration of MSCs ($1 \times 10(6)$) into bladder tissue not only significantly ameliorated the aforementioned bladder voiding parameters, but also reversed the characteristic histological and gene-expression alterations of KC bladder. Treatment with the antifibrotic compound N-acetylcysteine also alleviated the symptoms and pathological characteristics of KC bladder, indicating that the antifibrotic capacity of MSC therapy underlies its benefits. According to the authors, this study for the first-time shows that MSC therapy might help to cure KC by protecting against tissue fibrosis in a KC animal model and provides a foundation for clinical trials of MSC therapy.

**BDNF-ERK1/2 SIGNALING PATHWAY IN KETAMINE-ASSOCIATED LOWER URINARY TRACT SYMPTOMS.**

*Wang X, Peng B, Xu C, Gao Z, Cao Y, Liu Z, Liu T. Int Urol Nephrol. 2016 Sep;48(9):1387-93. doi: 10.1007/s11255-016-1315-y. Epub 2016 May 10. PMID: 27165402*

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Long-term ketamine abuse can affect the urinary system, resulting in lower urinary tract symptoms (LUTS), but the pathogenesis of this is still unknown. Previous studies have demonstrated that ketamine can change the expression of the brain-derived neurotrophic factor (BDNF) in the serum of ketamine abuse patients. The aim of the present study was to explore the mechanism of the ketamine-mediated BDNF signalling pathway in the bladder of rats on chronic ketamine treatment. Rats were randomly assigned to a control (normal saline) or ketamine (30 mg/kg) group, with five rats in each group. The experimental group was given ketamine via intraperitoneal injection daily, while the control group was treated with saline. After 12 weeks of treatment, bladders were excised and samples from the control and ketamine group were examined with transmission electron microscopy (TEM). Phosphoprotein and non-phosphoprotein purification, histopathology, immunohistochemistry, and western blot were carried out in all groups. Histological study showed hyperplastic epithelium and inflammatory cell infiltration in ketamine-treated rat bladders. TEM showed that chronic ketamine treatment results in structural damage to organelles. Immunohistochemical staining and

western blot showed that the expression of BDNF was significantly lower in the ketamine group. However, the expression of phosphorylated extracellular signal-regulated kinases ½ (ERK1/2) in the ketamine group was higher, whereas the total ERK1/2 was similar to the control group. It was concluded that long-term ketamine abuse reduces expression of BDNF, while inducing phosphorylation of ERK1/2 in the bladder wall. This may play an important role in the pathogenesis of ketamine-associated LUTS.

**MICROVASCULAR INJURY IN KETAMINE-INDUCED BLADDER DYSFUNCTION.**

*Lin CC, Lin AT, Yang AH, Chen KK. PLoS One. 2016 Aug 16;11(8):e0160578. doi: 10.1371/journal.pone.0160578. PMID: 27529746*

The pathogenesis of ketamine-induced cystitis (KC) remains unclear. In this study from Taiwan, bladder microvascular injury was investigated as a possible contributing mechanism. A total of 36 KC patients with exposure to ketamine for more than 6 months, and 9 control subjects, were prospectively recruited. All participants completed questionnaires, including the O'Leary-Sant interstitial cystitis symptom index (ICSI) and the interstitial cystitis problem index (ICPI). All KC patients received a urodynamic study and radiological exams. Bladder tissues were obtained from cystoscopic biopsies in the control group and after hydrodistention in the KC group. Double-immunofluorescence staining of N-methyl-d-aspartate receptor subunit 1 (NMDAR1) and the endothelial marker, cluster of differentiation 31 (CD31), was performed to reveal the existence of NMDAR1 on the endothelium. Electron microscopy (EM) was applied to assess the microvascular change in the urinary bladder and to measure the thickening of the basement membrane (BM). A proximity ligation assay (PLA) was used to quantify the co-localization of the endothelial CD31 receptor and the mesenchymal marker [fibroblast-specific protein 1 (FSP-1)]. The Mann-Whitney U test and Spearman's correlation coefficient were used for statistical analysis. The mean ICSI and ICPI scores of the KC group were significantly higher than those (0 and 0, respectively) of the control group. The KC patients had decreasing cystometric bladder capacity (CBC) with a mean volume of 65.38 mL. NMDAR1 was expressed on endothelial cells in both groups under immunofluorescence staining. Moreover, KC patients had significant BM duplication of microvessels in the mucosa of the urinary bladder under EM. The co-expression of the endothelial marker CD31 and mesenchymal marker FSP1 was significantly stained and calculated under PLA. In conclusion, microvascular injury and mesenchymal phenotypic alteration of endothelial cells can potentially contribute to KC-induced bladder dysfunction.

## CHRONIC PAIN / CHRONIC PELVIC PAIN

**A REVIEW OF CHRONIC PAIN IMPACT ON PATIENTS, THEIR SOCIAL ENVIRONMENT AND THE HEALTH CARE SYSTEM.**

*Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. J Pain Res. 2016 Jun 28;9:457-67. doi: 10.2147/JPR.S105892. eCollection 2016. PMID: 27418853*

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Chronic pain (CP) seriously affects the patient's daily activities and quality of life, but few studies on CP have considered its effects on the patient's social and family environment. In this work from Spain, through a review of the literature, Dueñas and colleagues assessed several aspects of how CP influences the patient's daily activities and quality of life, as well as its repercussions in the workplace, and on the family and social environment. Finally, the consequences of pain on the health care system are discussed. On the basis of the results, they concluded that in addition to the serious consequences on the patient's life, CP has a severe detrimental effect on their social and family environment, as well as on health care services. Thus, they wish to emphasize the need to adopt a multidisciplinary approach to treatment so as to obtain more comprehensive improvements for patients in familial and social contexts. Accordingly, it would be beneficial to promote more social- and family-oriented research initiatives.

**MEASURING THE QUALITY OF PUDENDAL NERVE PERINEURAL INJECTIONS.**

*Antolak S Jr, Antolak C, Lendway L. Pain Physician. 2016 May;19(4):299-306. PMID: 27228517*

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Pudendal neuropathy is a tunnel syndrome characterized by pelvic pain and may include bowel, bladder, or sexual dysfunction or a combination of these. One treatment method, pudendal nerve perineural injections

(PNPIs), uses infiltration of bupivacaine and corticosteroid around the nerve to provide symptom relief. Bupivacaine also anesthetizes the skin in the receptive field of the nerve that is injected. Bupivacaine offers rapid pain relief for several hours while corticosteroid provides delayed pain control often lasting 3 to 5 weeks. Not all pudendal nerve blocks may provide complete pain relief but long-term pain control from the steroid appears to be associated with immediate response to bupivacaine. The authors offer a method of evaluating the quality of a pudendal block on the day it is performed using pinprick sensation evaluation. The aim of this study from private practice in the USA was to demonstrate that pinprick sensory changes provide a simple and rapid method of measuring response to local anesthetic andpain reduction provided by a PNPI on the day it is performed. This response defines the quality of each PNPI. The authors report that PNPIs relieve pain. Anesthesia affected all 6 pudendal nerve branches in only 13.2% of patients. Complete pain relief occurred in 39.2%. This argues against use of perineural pudendal blockade as a diagnostic test. Pain relief after PNPI is associated with number of nerve branches that are anesthetized. At 2 hours after a PNPI its quality (the number of the 6 nerve branches with reduced response to pinprick from the perineural local anesthetic) is associated with subjective reduction of pain.

## CENTRAL SENSITIZATION

### THE GREAT DECEIVER: A CASE OF CENTRAL SENSITIZATION PRESENTING AS CARCINOID SYNDROME.

*Ramos JA. A A Case Rep. 2016 Jun 1;6(11):364-5. doi: 10.1213/XAA.0000000000000318. PMID: 27144900*

Central sensitization defines a state of amplified sensory input within the nervous system across many organ systems; it overlaps syndromes as fibromyalgia, chronic fatigue, irritable bowel, and interstitial cystitis. Commonly, individuals will experience multiple syndromes during the course of their lifetime. A 62-year-old patient presented for evaluation of multiple medically unexplained symptoms postsurgically including chronic left chest wall and flank pain with concomitant diarrhea, abdominal pain, and facial flushing. After extensive multidisciplinary evaluations, he was diagnosed as having central sensitization in which the initial presentation mimicked carcinoid syndrome. He was subsequently treated with extensive multidisciplinary pain rehabilitation, and it did well.

## PAIN MANAGEMENT

### ANTI-NERVE GROWTH FACTOR IN PAIN MANAGEMENT: CURRENT EVIDENCE.

*Chang DS, Hsu E, Hottinger DG, Cohen SP. J Pain Res. 2016 Jun 8;9:373-83. PMID: 27354823*

Chang and colleagues report that there continues to be an unmet need for safe and effective pain medications. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) dominate the clinical landscape despite limited effectiveness and considerable side-effect profiles. Although significant advancements have identified myriad potential pain targets over the past several decades, the majority of new pain pharmacotherapies have failed to come to market. The discovery of nerve growth factor (NGF) and its interaction with tropomyosin receptor kinase A (trkA) have been well characterized as important mediators of pain initiation and maintenance, and pharmacotherapies targeting this pathway have the potential to be considered promising methods in the treatment of a variety of nociceptive and neuropathic pain conditions. Several methodologic approaches, including sequestration of free NGF, prevention of NGF binding and trkA activation, and inhibition of trkA function, have been investigated in the development of new pharmacotherapies. Among these, NGF-sequestering antibodies have exhibited the most promise in clinical trials. However, in 2010, reports of rapid joint destruction leading to joint replacement prompted the US Food and Drug Administration (FDA) to place a hold on all clinical trials involving anti-NGF antibodies. Although the FDA has since lifted this hold and a number of new trials are under way, the long-term efficacy and safety profile of anti-NGF antibodies are yet to be established.

## FIBROMYALGIA

### PATIENT-REPORTED OUTCOMES AND FIBROMYALGIA.

*Williams DA, Kratz AL. Rheum Dis Clin North Am. 2016 May;42(2):317-32. doi: 10.1016/j.rdc.2016.01.009. Epub 2016 Mar 17. PMID: 27133492*

Fibromyalgia (FM) is classified as a chronic pain condition accompanied by symptoms of fatigue, sleep problems, problems with cognition, negative mood, limited functional status, and the presence of other chronic overlapping pain conditions. Comprehensive assessment of all of these components can be challenging. This paper from Michigan USA provides an overview of patient-reported approaches that can be taken to assess FM in the contexts of diagnosis, symptom monitoring, phenotyping/characterization, and for purposes of clinical trials.

**PROGRESSION OF FIBROMYALGIA: RESULTS FROM A 2-YEAR OBSERVATIONAL FIBROMYALGIA AND CHRONIC PAIN STUDY IN THE US**.
*Adams EH, McElroy HJ, Udall M, Masters ET, Mann RM, Schaefer CP, Cappelleri JC, Clair AG, Hopps M, Daniel SR, Mease P, Silverman SL, Staud R. J Pain Res. 2016 Jun 1;9:325-36. PMID: 27330325*
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A previous fibromyalgia (FM) research reports that 20%-47% of diagnosed patients may not meet the study definition of FM 1-2 years after diagnosis. The aim of this study was to gain a better understanding of the progression of FM in a geographically diverse cohort over a 2-year time period. This cohort study followed 226 subjects recruited online to assess FM and chronic widespread pain (CWP) diagnosis stability over time. Seventy-six FM+CWP+ subjects completed assessments at both time points; 56 (73.7%) met the FM study definition at follow-up. Twenty subjects no longer met the FM study definition (eleven became FM-CWP- and nine became FM-CWP+). Ten subjects (two from FM-CWP- and eight from FM-CWP+) transitioned into the FM+CWP+ group at follow-up; they reported more tender points and pain interference with sleep and worse physical function at baseline compared with subjects who did not transition to FM+CWP+. Most (76.7%) of the subjects who transitioned into/out of FM+CWP+ experienced changes in CWP, number of positive tender points, or both. The results suggest that some FM+CWP+ patients experience fluctuation in symptoms over time, which may reflect the waxing and waning nature of FM and affect diagnosis and treatment.

**IDENTIFYING THE SYMPTOM AND FUNCTIONAL DOMAINS IN PATIENTS WITH FIBROMYALGIA: RESULTS OF A CROSS-SECTIONAL INTERNET-BASED SURVEY IN ITALY.**
*Salaffi F, Mozzani F, Draghessi A, Atzeni F, Catellani R, Ciapetti A, Di Carlo M, Sarzi-Puttini P. J Pain Res. 2016 May 13;9:279-86. PMID: 27257392*
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The aims of this cross-sectional study were to investigate the usefulness of using an Internet survey of patients with fibromyalgia in order to obtain information concerning symptoms and functionality and identify clusters of clinical features that can distinguish patient subsets. An Internet website has been used to collect data. Fibromyalgia Impact Questionnaire Revised version, self-administered Fibromyalgia Activity Score, and Self-Administered Pain Scale were used as questionnaires. Hierarchical agglomerative clustering was applied to the data obtained in order to identify symptoms and functional-based subgroups. Three hundred and fifty-three patients completed the study (85.3% women). The highest scored items were those related to sleep quality, fatigue/energy, pain, stiffness, degree of tenderness, balance problems, and environmental sensitivity. A high proportion of patients reported pain in the neck (81.4%), upper back (70.1%), and lower back (83.2%). A three-cluster solution best fitted the data. The variables were significantly different among the three clusters: cluster 1 (117 patients) reflected the lowest average scores across all symptoms, cluster 3 (116 patients) the highest scores, and cluster 2 (120 patients) captured moderate symptom levels, with low depression and anxiety. Three subgroups of fibromyalgia samples in a large cohort of patients have been identified by using an Internet survey. This approach could provide rationale to support the study of individualized clinical evaluation and may be used to identify optimal treatment strategies.

## VULVODYNIA/VULVAL PAIN SYNDROME

**COMMITTEE OPINION NO 673: PERSISTENT VULVAR PAIN.**
*[No authors listed] Obstet Gynecol. 2016 Sep;128(3):e78-84. doi: 10.1097/AOG.0000000000001645. PMID: 27548558*

Persistent vulvar pain is a complex disorder that frequently is frustrating to the patient and the clinician. It can be difficult to treat and rapid resolution is unusual, even with appropriate therapy. Vulvar pain can be caused by a specific disorder or it can be idiopathic. Idiopathic vulvar pain is classified as vulvodynia. Although optimal treatment remains unclear, consider an individualized, multidisciplinary approach to address all physical and emotional aspects possibly attributable to vulvodynia. Specialists who may need to be involved include sexual counsellors, clinical psychologists, physical therapists, and pain specialists. Patients may perceive this approach to mean the practitioner does not believe their pain is "real"; thus, it is important to begin any treatment approach with a detailed discussion, including an explanation of the diagnosis and determination of realistic treatment goals. Future research should aim at evaluating a multimodal approach in the treatment of vulvodynia, along with more research on the etiologies of vulvodynia.

**IS THE DSM-V LEADING TO THE NONDIAGNOSIS OF VULVODYNIA?**

*Vieira-Baptista P, Lima-Silva J. J Low Genit Tract Dis. 2016 Aug 9. [Epub ahead of print] PMID: 27508984*

The authors from Porto, Portugal express their concern about the impact that the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition "genito-pelvic pain/penetration disorder" may have on vulvodynia, namely, its non-diagnosis or assumption that it is a merely psychological issue. A review of the concepts of "genito-pelvic pain/penetration disorder," "vaginismus," "dyspareunia," and "vulvodynia" was performed to understand if the suspicion that the more recent and broader DSM concept can have a negative impact on vulvodynia patients. The authors found that the definition and referred associated conditions of the "genito-pelvic pain/penetration disorder" overlap those of provoked vestibulodynia, a form of vulvodynia characterized by mechanical allodynia localized to the vulvar vestibule. Despite the footnote that the diagnosis of the former is made after the exclusion of a better explanation for the complaints, the authors believe that a significant number of vulvodynia patients will be included in the "genito-pelvic pain/penetration disorder," thus risking an inappropriate therapeutic approach. "Vaginismus" and "dyspareunia" may occur together, but it is not always the case; assuming otherwise may have a negative impact in the treatment of these women. The authors concluded that the "genito-pelvic pain/penetration disorder" diagnosis may help the clinical approach of women with dyspareunia and/or an increased pelvic muscle tonus. However, it may have a significant negative impact in the approach and treatment of affected women: treatment cannot be "one size fits all." A significant number of women with this diagnosis will have vulvodynia, and an exclusively psychological/psychiatric approach would be suboptimal for the condition.

## SJOGREN'S SYNDROME

**NEW TREATMENT GUIDELINES FOR SJÖGREN'S DISEASE.**

*Vivino FB, Carsons SE, Foulks G, Daniels TE, Parke A, Brennan MT, Forstot SL, Scofield RH, Hammitt KM. Rheum Dis Clin North Am. 2016 Aug;42(3):531-51. PMID: 27431353*

Sjögren's disease is associated with a high burden of illness, diminished quality of life, and increased health care costs. The Sjögren's Syndrome Foundation developed the first US clinical practice guidelines for management of the oral, ocular, and rheumatologic or systemic manifestations. Guideline recommendations were reviewed by a consensus expert panel using a modified Delphi process. This initiative should improve the quality and consistency of care for Sjögren's disease in the United States, guide insurance reimbursement, and define areas for future study. Guidelines will be periodically reviewed and revised as new information becomes available.

**RECURRENT ATTACKS OF HYPOKALEMIC QUADRIPARESIS: AN UNUSUAL PRESENTATION OF PRIMARY SJÖGREN SYNDROME.**

*Seirafian S, Shafie M, Abedini A, Pakzad B, Roomizadeh P. Intern Med. 2016;55(13):1797-800. doi: 10.2169/internalmedicine.55.6453. Epub 2016 Jul 1. PMID: 27374687*

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Seirafian and colleagues from Iran report the case of a 64-year old woman with recurrent attacks of hypokalemic quadriparesis which resulted from distal renal tubular acidosis (dRTA) secondary to Sjögren syndrome. The patient presented with sudden onset quadriparesis. A physical examination showed symmetric weakness of all four limbs. Severe hypokalemia (1.8 mEq/L), accompanied by normal anion gap

metabolic acidosis, a positive urine anion gap and an inappropriately high urine pH pointed toward the diagnosis of dRTA. Further investigations disclosed primary Sjögren syndrome, which had not previously been recognized. On the basis of the current report and a review of the literature they suggest investigating the possibility of Sjögren syndrome in all patients with clinically unexplained dRTA.

**SMALL FIBER NEUROPATHY: GETTING BIGGER!**

*Chan AC, Wilder-Smith EP. Muscle Nerve. 2016 May;53(5):671-82. doi: 10.1002/mus.25082. Epub 2016 Mar 12. PMID: 26872938*

Etiological and clinical heterogeneity of small fiber neuropathy (SFN) precludes a unifying approach and necessitates reliance on recognizable clinical syndromes. Symptoms of SFN arise from dysfunction in nociception, temperature, and autonomic modalities. This review focuses on SFN involving nociception and temperature, examining epidemiology, etiology, clinical presentation, diagnosis, pathophysiology, and management. Prevalence of SFN is 52.95 per 100,000 population, and diabetes and idiopathic are the most common etiologies. Dysesthesia, allodynia, pain, burning, and coldness sensations frequently present in a length-dependent pattern. Additional autonomic features in gastrointestinal, urinary, or cardiovascular systems are frequent but poorly objectified. SFN is diagnosed by intraepidermal nerve fiber density and quantitative sensory and autonomic tests in combination with normal nerve conduction. Pathophysiological understanding centers on sodium channel dysfunction, and genetic forms are beginning to be understood. Treatment is directed at the underlying etiology supported by symptomatic treatment using antidepressants and anticonvulsants. Little is known about long-term outcomes, and systematic cohort studies are needed.

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