

# 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 34, October 2013

*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 Meetings
- Patient Organisation News
- Books
- Research Highlights
- Donations & Sponsoring

### MEETING REVIEWS

#### REVIEW OF THE ICS ANNUAL SCIENTIFIC MEETING, 26-30 AUGUST 2013, BARCELONA SPAIN

It was perhaps not so surprising to find that this year's ICS annual scientific meeting held at the International Convention Centre Barcelona in Spain was well attended by Spanish and Latin American health professionals, with even more Latin American delegates this year since the next annual scientific meeting in 2014 will be held in Latin America, in Brazil. Since the ICS is a multi-disciplinary society, this meeting is attended by nurses, physiotherapists, doctors, specialists and others with an interest in urinary and faecal incontinence and pelvic floor dysfunction and pain from around the world. This is a group of professionals with a great interest in obtaining the latest information about bladder and pelvic pain and hypersensitivity. The International Painful Bladder Foundation (IPBF) consequently had an exceptionally busy booth at this meeting and distributed huge piles of brochures, leaflets, flyers and CDs on IC/BPS and associated disorders. The IPBF also displayed a poster on its booth with clear images of Hunner lesions (courtesy of Professor Andrey Zaitcev from Moscow and ESSIC). This generated great interest and it was evident that many urologists felt uncertainty and a lack of confidence with regard to identifying lesions in clinical practice. It would be useful to have a workshop dedicated specifically to this topic.

**The images used for the IPBF's Barcelona Hunner lesion poster can be found on the ESSIC website at: <http://www.essic.eu/videomenu.html> along with a large number of videos showing lesions on cystoscopy with hydrodistension.**

This year many abstracts on IC/BPS were submitted from all parts of the world and particularly from East Asia where much research is taking place. Once again, everyone was using different terminology and studies presented included patients diagnosed on the basis of a wide variety of criteria, often with no distinction between patients with or without lesions, leading to some confusion. This once again underlined how vital it is for agreement to be reached worldwide on diagnostic criteria, terminology and definitions. Similar terminology confusion could be seen this year in the ketamine-associated cystitis studies, with many different terms in use.

A brief overview of abstracts presented in Barcelona related to our field can be found on our website. [Click here](#). Some were on basic science, some on treatment including a number of trials with hyaluronic acid, chondroitin sulphate, botox, triamcinolone and mirabegron, while one interesting abstract from Leuven, Belgium reported that the study team had identified BK polyoma virus (BKPyV) in the urine of virtually all their patients with the classic lesion form of PBS/IC, suggesting that it might be a potential new therapeutic target.

One abstract looks at the controversial issue of glomerulations. The abstract summaries have been divided into two sections, first IC/BPS and secondly abstracts on ketamine including studies comparing ketamine and IC/BPS.

The next [ICS annual scientific meeting](#) will be held in Rio de Janeiro, Brazil, 20-24 October 2014.

**UroToday** has a podcast by Dr Christopher Payne on ICS 2013 and IC/BPS: [ICS 2013 - Podcast: Christopher K. Payne, MD, FACS discusses highlights of the bladder pain/interstitial cystitis sessions from the Annual Scientific Meeting of the International Continence Society](#).

#### **UROLOGY ROUNDTABLE MEETING HELD 25 SEPTEMBER 2013 AT THE EUROPEAN PARLIAMENT IN BRUSSELS. "HOW TO PROVIDE THE RIGHT PREVENTION AND TREATMENT TO THE RIGHT PATIENT AT THE RIGHT TIME".**

This roundtable, attended by IPBF chair Jane Meijlink, was co-organised by the European Alliance for Personalised Medicine (EAPM) and the European Association of Urology (EAU) and hosted by Petru Lohan, Romanian MEP and active health campaigner. More than a dozen speakers addressed the broader issues of personalised medicine in terms of urology (although mainly from the viewpoint of urologic cancer).

Petru Lohan, MEP: *"Since personalised medicine requires an unprecedented level of cooperation and collaboration across the healthcare system, we need to continue to tackle the challenge of breaking barriers and learning to speak the same language.*

*Meanwhile, substantial education and training efforts are needed to ensure that knowledge and good practice concerning novel technologies and scientific approaches are shared.*

*New discoveries will not get us very far unless we know how to address the challenge of generating knowledge and developing the right tools.*

*And this is equally true when it comes to meeting the challenge of translating new knowledge to medical applications with direct benefit for the patients, including qualifying and validating biomarkers and developing new designs for clinical trials".*

However, there was no mention of the fact that due to the current economic crisis, national health authorities are now radically cutting back on reimbursable treatments, particularly hitting IC/BPS patients very hard. This means that far from having a situation where each patient receives individualised treatment, the very drugs that may be ideal for some patients are being cut out of the reimbursement package.

Only one speaker fleetingly mentioned the word "adherence" to treatment, while issues such as debilitating side-effects and drug intolerance - leading to expensive non-compliance - were not raised at all. Bearing in mind the cost of all these wasted non-tolerated drugs, one would expect this aspect to be top of the agenda in Brussels.

Further information about the EAPM and its activities may be found at <http://euapm.eu>.

#### **IAPO: HOW CAN PATIENT-CENTRED ACCESS TO HEALTHCARE BE REALISED IN LATIN AMERICA?**

Mexico City, Mexico, 24 September 2013 – *"To achieve patient-centred access to healthcare in Latin America, patients need to be informed, empowered and involved in shaping our healthcare systems"* stated Eva Maria Ruiz de Castilla, IAPO Governing Board Member. This echoed the discussions of the participants at the International Alliance of Patients' Organizations (IAPO) multi-stakeholder seminar *'Patient-centred access to healthcare in Latin America'* held on 24 September. The seminar brought together over 70 participants, including patient group representatives from across Latin America, policy-makers, healthcare professionals, civil society and industry. The seminar addressed three key issues related to access to healthcare in Latin America: non-communicable diseases (NCDs), health technology assessment (HTA) and biological and biosimilar medicines. Dr Luis Ruben Durán Fontes, Under Secretary of Integration and Development of the Health Sector, gave the opening address and welcomed participants to Mexico. Speakers included: Dr Osvaldo Artaza Barrios, Pan American Health Organization/World Health Organization Mexico; Ricardo Pérez Cuevas, Inter-American Development Bank; Dra Mireya López Gamboa, the Centre for Research and Advanced Studies of the Instituto de Cancerología de México; KP Tsang, IAPO Chair; Gisela Ayala, Mexican Diabetes Federation and Gustavo Adolfo Campillo, Antioquia Social Support Network Foundation, Colombia. During the seminar, participants discussed the significant issues which prevent patients gaining access to safe, quality and affordable healthcare from prevention, through diagnosis and treatment. Issues highlighted included the differences in the regulatory processes between countries, the challenges with and need for better pharmacovigilance and educating patients and healthcare professionals to promote dialogue and engagement with policy processes. As Gustavo Adolfo Campillo, Antioquia Social Support Network Foundation, Colombia

said “We need to educate in order to empower, educate to have a stronger dialogue”. The conclusion of the seminar was that patient-centred access cannot be realised without patients being fully informed, empowered and involved in all decision-making processes to ensure they meet the needs of patients. The seminar was part of a week-long series of IAPO events which also include a two day workshop for the IAPO Latin American network of patients’ organizations and a half day meeting for Mexican patients’ organizations led by Red de Acceso.

**Further information on IAPO’s activities in Latin America: [www.patientsorganizations.org/latinamerica](http://www.patientsorganizations.org/latinamerica).**

## **UPCOMING MEETINGS**

### **IAPO 6TH GLOBAL PATIENTS CONGRESS 29-31 MARCH 2014, ASCOT UK: ‘BETTER ACCESS, BETTER HEALTH: A PATIENT-CENTRED APPROACH TO UNIVERSAL HEALTH COVERAGE’.**

The International Alliance of Patients’ Organizations (IAPO) is a unique global alliance representing patients of all nationalities across all disease areas and promoting patient-centred healthcare around the world. Its members are patients’ organizations working at international, regional, national and local levels to represent and support patients, their families and carers.

Registration is now open for IAPO’s 6<sup>th</sup> Global Patients’ Congress to be held 29-31 March 2014 at Macdonald Berystede Hotel & Spa, Ascot, UK. This is an important international event for patient leaders and others working to improve healthcare systems globally. Open to IAPO members and invited guests only.

The theme of the 6<sup>th</sup> Global Congress is: Better access, better health: a patient-centred approach to universal health coverage. The congress will bring together expertise and experience in how to build patient-centred healthcare globally. It provides a global platform for high level policy debate, knowledge and skills building and opportunities for exchange and networking. The programme features plenary sessions with keynote speakers and a range of parallel sessions including papers submitted through the open call process.

Further information: <http://www.patientsorganizations.org/congress>

### **ECRD 2014 : THE EUROPEAN CONFERENCE ON RARE DISEASES & ORPHAN PRODUCTS 8-10 MAY 2014, ANDEL'S HOTEL, BERLIN, GERMANY**

EURORDIS has announced that the European Conference on Rare Diseases and Orphan Products will be held in Berlin in 2014. The European Conference on Rare Diseases & Orphan Products (ECRD) is the unique platform/forum across all rare diseases, across all European countries, bringing together all stakeholders: patients’ representatives, academics, health care professionals, industry, payers, regulators and policy makers. ECRD covers research, development of new treatments, healthcare, social care, information, public health and support at European, national and regional levels. ECRD provides the state of the art of the rare disease environment, monitoring and benchmarking initiatives.

For further information and registration, go to: <http://www.rare-diseases.eu/>

#### **Additional upcoming meetings:**

##### **International Pelvic Pain Society (IPPS) 2013 Annual Meeting**

October 17-19, 2013

The Peabody Hotel

Orlando, FL

<http://www.pelvicpain.org/meetings/default.aspx>

##### **29th Annual EAU Congress**

11-15 April, 2014

Stockholm, Sweden

[www.eaustockholm2014.org](http://www.eaustockholm2014.org)

##### **ESSIC Annual Meeting**

June 2014, Philadelphia, USA

<http://www.essic.eu>

##### **3<sup>rd</sup> International Neuro-Urology Meeting**

28-30 August, 2014

Zurich, Switzerland  
 In honour of the retirement of Professor Jean-Jacques Wyndaele  
[www.swisscontinencefoundation.ch](http://www.swisscontinencefoundation.ch)

### **Convergences PP 2014 -Convergences in Pelvipерineal Pain**

Simultaneous translation French/English  
 Palais des Congres-Congress Centre, Aix-en-Provence, France  
 2-4 October 2014  
[www.convergencespp.com](http://www.convergencespp.com)

### **15<sup>th</sup> World Congress on Pain**

6-11 October 2014  
 La Rural Convention Center, Buenos Aires, Argentina  
<http://www.iasp-pain.org/Content/NavigationMenu/WorldCongressonPain2/15thWorldCongressonPain/default.htm>

## **GUIDELINES**

### **GUIDELINE ON INCONTINENCE MANAGEMENT FROM NICE (NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE) IN THE UK**

While this NICE guideline on “Urinary incontinence: The management of urinary incontinence in women” does not specifically cover IC/BPS, it does include overactive bladder and contains information that IC/BPS patients may find useful. [Click here](#) for further details or go to <http://www.nice.org.uk/nicemedia/live/14271/65143/65143.pdf> for a pdf file of the guideline.

## **PATIENT ORGANISATION NEWS**

### **SURVEYS FOR PATIENTS**

#### **- PATIENT SURVEY FROM THE CYSTITIS & OVERACTIVE BLADDER FOUNDATION (COBF)**

<http://www.cobfoundation.org/>

The COB Foundation has asked us to help raise aware of bladder illness by completing their online survey if you suffer from a bladder condition. Go to <http://www.cobfoundation.org/news/cob-foundation-survey> where you will find 4 categories of bladder condition for the survey. Any patient anywhere in the world is welcome to participate.

#### **- UK RESEARCHER SURVEY FOR PATIENTS**

A group of researchers in London is keen to hear from patients worldwide with bladder pain syndrome/interstitial cystitis regarding their experience with the illness. They would like to know about your symptoms, diagnosis and management in order to identify how the condition is assessed and managed so as to improve the service clinicians provide. Go to: <https://es.surveymonkey.com/s/BSPspatientsurvey>

#### **NEW LiRIS STUDY REPORTED BY ICA**

The Interstitial Cystitis Association (ICA) recently reported that TARIS Biomedical® has initiated a second Phase 2a study investigating LiRIS in women with Interstitial Cystitis (IC). LiRIS is designed to continuously provide lidocaine over an extended period in the bladder. The study is currently active at 12 study centers across the United States, and will ultimately include up to 20 study centers in the US and Canada. LiRIS is an investigational product which combines the local anesthetic lidocaine with a small, flexible delivery device. LiRIS is inserted into the bladder via a cystoscope, and remains in the bladder for 14 days where it is designed to continuously deliver treatment. At the end of this period, LiRIS is removed via a second cystoscopic procedure. For more details, go to [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Use trial identifier NCT01824303.

#### **INFORMATION ON VULVODYNIA**

A reminder to new readers of our e-Newsletter that the National Vulvodynia Association (NVA), a non-profit organisation set up in the United States in 1994, provides a wealth of information on all forms and aspects of vulvodynia on its website for both patients and professionals, including the latest scientific studies and insights: <http://www.nva.org>.

## IPBF UPDATED BROCHURES AND LEAFLETS.

Our newly updated 57 page IPBF brochure can be found at:

[http://www.painful-bladder.org/pdf/Diagnosis&Treatment\\_IPBF.pdf](http://www.painful-bladder.org/pdf/Diagnosis&Treatment_IPBF.pdf)

The IPBF has also compiled a first (pilot) fact sheet on Ketamine Abuse and the Urinary Tract. This fact sheet is also available on the IPBF website. [Click here...](#) or go to the home page [www.painful-bladder.org](http://www.painful-bladder.org)

## EDUCATION

### SPANISH COURSE ON PELVIC FLOOR: CURSO DE FORMACIÓN ESPECÍFICA “SUELO PLVIANO II”

A Spanish course on all aspects of the pelvic floor and pelvic pain, organised by Prof. María Fernanda Lorenzo Gómez, will be held in the beautiful city of Salamanca, Spain in November 2013. The course is for pre- and post-graduates: doctors, nurses and physiotherapists. The online brochure provides full details of the programme and registration. [Click here for brochure.](#)

## BOOKS

### The Bliss of Continence Restored

By Professor Peter Petros, Joan McCredie and Dr Patricia M. Skilling MB ChB. Published (e-book) September 5, 2013. Obtainable from Amazon.

## RESEARCH HIGHLIGHTS

### A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS 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. When reviewing the article, we generally use the terminology used by the authors.

### TREATMENT COSTS OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS IN AUSTRIA: A PHARMACOECONOMIC APPROACH FOLLOWING CURRENT GUIDELINES.

Riedl C, Engelhardt P, Schwarz B. *Clin Drug Investig.* 2013 Oct;33(10):737-42. PMID: 23921624

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic disease with a significant impact on quality of life. A broad range of therapies are used to treat this condition, and patients are often excluded from receiving more expensive and more effective therapies because of cost issues. The objective of this study from Austria was to assess the mid- and long-term costs (over 1, 5 and 10 years) of various therapies for BPS/IC. Costs in an open-access health system (Austria) for three BPS/IC-specific therapies (intravesical hyaluronan, pentosanpolysulfate and amitriptyline), taken from the American Urological Association guidelines, were evaluated and compared with those of non-specific symptomatic therapies. Response rates for the different therapies were taken from peer-reviewed publications and used to define the need for therapy maintenance with regard to symptom improvement. Despite the highest initial costs, the reduced need for further therapy in patients with long-term symptom remission after hyaluronan therapy resulted in the lowest total treatment costs at all three timepoints. Hyaluronan was cost saving against all alternatives in standard assumptions and in all sensitivity analyses. As a limitation, treatment costs in this study are specific for Austria. However, the template used for calculation of treatment costs can be transferred to all countries by inserting local prices. Disease-specific therapies with high remission rates result in significantly lower long-term costs in BPS/IC. Non-specific symptomatic therapies are most expensive. Long-term cost effectiveness is crucial in the treatment of chronic diseases to limit expenses in individual healthcare systems.

### COMBINED INTRAVESICAL SODIUM HYALURONATE/CHONDROITIN SULFATE THERAPY FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A PROSPECTIVE STUDY.

Giberti C, Gallo F, Cortese P, Schenone M. *Ther Adv Urol.* 2013 Aug;5(4):175-9. doi: 10.1177/1756287213490052. PMID: 23904856

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

The aim of this study from Savona, Italy was to verify the efficacy and safety of intravesical treatment combining sodium hyaluronate (HA) and chondroitin sulfate (CS) in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Between February 2010 and May 2011, 20 consecutive women with IC/BPS were treated with intravesical instillations containing sodium HA (1.6%; 800 mg/50 ml) and sodium CS (2%; 1 g/50 ml) weekly for the first month, biweekly for the second month, and then monthly for at least 3 months. No cases of side effects or complications were observed. The mean follow up was 5 months. Despite the limitations of this study, the authors concluded that the outcomes confirmed the role of combination therapy with HA and CS as a safe and effective option for the treatment of IC/BPS. Further randomized controlled studies with a higher number of patients and a longer follow-up period are needed to confirm these results.

#### **THE USE OF BOTULINUM TOXIN FOR THE TREATMENT OF UROLOGIC PAIN.**

Russell A, Kavia R, Dasgupta P, Sahai A. *Curr Opin Urol.* 2013 Sep 17. [Epub ahead of print]. PMID: 24047648

Russell and colleagues from London note that botulinum toxin injections into the bladder have become established in the management of refractory detrusor overactivity and overactive bladder. Mechanism of action of the toxin appears to involve both efferent and afferent nerve pathways, as well as having an antinociceptive effect. Over the years, several reports of its use in refractory bladder pain syndrome and interstitial cystitis have emerged. They review the literature with a view to assessing efficacy and adverse events in this setting. Small open-labelled studies have suggested botulinum neurotoxin serotype A (BoNT-A) to be an effective treatment for the majority of patients with refractory bladder pain syndrome/interstitial cystitis. A single set of injections result in demonstrable improvements in symptom scores and bladder pain, although some studies suggest repeated injections may be better. BoNT-A is more effective in nonulcer-type patients. In chronic pelvic pain syndrome, a recent placebo-controlled trial showed only a modest benefit for BoNT-A over placebo with a response rate of 30%. They are of the opinion that although botulinum neurotoxin for refractory bladder pain syndrome/interstitial cystitis appears promising, larger-scale studies with adequate follow-up and in particular randomized placebo-controlled studies are required to confirm these findings.

#### **BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS INCREASE THE RISK OF CORONARY HEART DISEASE.**

Chen HM, Lin CC, Kang CS, Lee CT, Lin HC, Chung SD. *Neurourol Urodyn.* 2013 Jun 27. doi: 10.1002/nau.22444. [Epub ahead of print]. PMID: 23813657

Chen and colleagues from Taipei, Taiwan note that a vascular factor has been proposed as being involved in the etiology of bladder pain syndrome/interstitial cystitis (BPS/IC). However, few studies have attempted to investigate the relationship between BPS/IC and cardiovascular disease. This study aimed to investigate the risk of coronary heart disease (CHD) among BPS/IC subjects during a 3-year follow-up period. Data for this retrospective matched-cohort study were retrieved from the Taiwan "Longitudinal Health Insurance Database 2000." There were 752 BPS/IC female subjects in the study cohort and 3,760 randomly selected female subjects in the comparison cohort. The authors individually tracked each subject for 3 years and identified each subject that received a subsequent diagnosis of CHD during that follow-up period. They concluded from their results that their study demonstrated an association between BPS/IC and a subsequent CHD diagnosis. They therefore advise clinicians to screen subjects with BPS/IC for modifiable risk factors for CHD.

#### **LONG-TERM EXPERIENCE WITH SODIUM CHONDROITIN SULFATE IN PATIENTS WITH PAINFUL BLADDER SYNDROME.**

[Article in English, Spanish]

Tornero JJ, Olarte H, Escudero F, Gómez G. *Actas Urol Esp.* 2013 Sep;37(8):523-526. doi: 10.1016/j.acuro.2013.01.008. Epub 2013 Jun 14. PMID: 23769895

The aim of this study from Murcia, Spain was to assess the response of patients diagnosed with painful bladder syndrome to treatment with instillations of sodium chondroitin sulfate. A series of cases of 28 patients with painful bladder syndrome followed a bladder instillation protocol with sodium chondroitin sulfate, according to the centre's regimen. From the medical histories, 19.4% had suffered an infection of the urinary tract, 3.8% had suffered urinary tuberculosis, 7.6% received pelvic radiation therapy and 26.9% had taken anticholinergic drugs for overactive bladder syndrome. The authors concluded that treatment with sodium chondroitin sulfate through endovesical instillation in painful bladder syndrome improves pain, voiding frequency and quality of life in the long term.

**BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS IS ASSOCIATED WITH HYPERTHYROIDISM.**

*Chung SD, Liu SP, Lin CC, Li HC, Lin HC. PLoS One. 2013 Aug 21;8(8):e72284. doi: 10.1371/journal.pone.0072284. PMID: 23991081*

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

A common theme with BPS/IC patients is comorbid disorders which are related to the autonomic nervous system that connects the nervous system to end-organs. Nevertheless, no study to date has reported the association between hyperthyroidism and BPS/IC. In this study, Chung and colleagues from Taipei examined the association of IC/BPS with having previously been diagnosed with hyperthyroidism in Taiwan. Data in this study were retrieved from the Longitudinal Health Insurance Database. The study consisted of 736 female cases with BPS/IC and 2208 randomly selected female controls. They performed a conditional logistic regression to calculate the odds ratio (OR) for having previously been diagnosed with hyperthyroidism between cases and controls. Their study results indicated an association between hyperthyroidism and BPS/IC. They suggest that clinicians treating female subjects with hyperthyroidism be alert to urinary complaints in this population.

**UROPLAKIN PEPTIDE-SPECIFIC AUTOIMMUNITY INITIATES INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME IN MICE.**

*Izgi K, Altuntas CZ, Bicer F, Ozer A, Sakalar C, Li X, Tuohy VK, Daneshgari F. PLoS One. 2013 Aug 16;8(8):e72067. doi: 10.1371/journal.pone.0072067. PMID: 23977210*

A major shortcoming in IC/PBS research has been the lack of an appropriate animal model. In this study from Cleveland, Izgi and colleagues show that the bladder specific uroplakin 3A-derived immunogenic peptide UPK3A 65-84, which contains the binding motif for IA(d) MHC class II molecules expressed in BALB/c mice, is capable of inducing experimental autoimmune cystitis in female mice of that strain. A highly antigen-specific recall proliferative response of lymph node cells to UPK3A 65-84 was observed, characterized by selectively activated CD4+ T cells with a proinflammatory Th1-like phenotype, including enhanced production of interferon  $\gamma$  and interleukin-2. T cell infiltration of the bladder and bladder-specific increased gene expression of inflammatory cytokines were observed. Either active immunization with UPK3A 65-84 or adoptive transfer of peptide-activated CD4+ T cells induced all of the predominant IC/PBS phenotypic characteristics, including increased micturition frequency, decreased urine output per micturition, and increased pelvic pain responses to stimulation with von Frey filaments. The authors conclude that this study demonstrates the creation of a more specific experimental autoimmune cystitis model that is the first inducible model for IC/PBS that manifests all of the major symptoms of this debilitating condition.

**AN ENDOGENOUS PAIN CONTROL SYSTEM IS ALTERED IN SUBJECTS WITH INTERSTITIAL CYSTITIS.**

*Ness TJ, Lloyd LK, Fillingim RB. J Urol. 2013 Aug 20. pii: S0022-5347(13)05144-6. doi: 10.1016/j.juro.2013.08.024. [Epub ahead of print]. PMID: 23973521*

Multiple studies have demonstrated that in healthy subjects painful stimuli applied to one part of the body inhibit pain sensation in other parts of the body, a phenomenon referred to as conditioned pain modulation (CPM). CPM is related to the presence of endogenous pain control systems. Studies have demonstrated deficits in CPM-associated inhibition in many, but not all chronic pain disorders. The present study from Alabama sought to determine whether CPM was altered in subjects with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). Female subjects with and without the diagnosis of IC/BPS were studied psychophysically using quantitative cutaneous thermal, forearm ischemia and ice water immersion tests. CPM was assessed by quantifying the effects of immersion of the hand in ice water (conditioning stimulus) on threshold and tolerance of cutaneous heat pain (test stimulus) applied to the contralateral lower extremity. They concluded from their results that an endogenous pain inhibitory system normally observed with CPM was altered in subjects with IC/BPS. This identifies IC/BPS as similar to several other chronic pain disorders such as fibromyalgia and irritable bowel syndrome and suggests that a deficit in endogenous pain inhibitory systems may be a contributor to such chronic pain disorders.

**SYMPATHOMIMETIC AMINES EFFECTIVELY CONTROL PAIN FOR INTERSTITIAL CYSTITIS THAT HAD NOT RESPONDED TO OTHER THERAPIES.**

*Check JH, Cohen G, Cohen R, Dipietro J, Steinberg B. Clin Exp Obstet Gynecol. 2013;40(2):227-8. PMID: 23971244*

The purpose of this study from New Jersey was to further investigate the efficacy of treatment of interstitial cystitis that had been refractory to standard treatment with sympathomimetic amines. Dextroamphetamine sulfate sustained release capsules up to 30 mg per day were prescribed in women with refractory painful

bladder syndrome/interstitial cystitis in six new cases. The patients were carefully evaluated for relief of symptoms. All six women found marked relief in their painful bladder syndrome in a rather short length of time. The benefit persisted as long as the therapy was maintained. Temporary cessation resulted in prompt return of symptoms, but resumption of sympathomimetic amines again allowed good relief of bladder pain and related symptoms. The authors concluded that because of very few side-effects and no drug dependence in the dosage used, sympathomimetic amines should be considered for first-line therapy.

#### **THE URODYNAMIC CHARACTERISTICS AND PROGNOSTIC FACTORS OF PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.**

*Kuo YC, Kuo HC. Int J Clin Pract. 2013 Sep;67(9):863-9. doi: 10.1111/ijcp.12116. PMID: 23952465*

The role of urodynamic study (UDS) in diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) remains inconclusive, nor has the predictor for a treatment success been elucidated. They evaluated the diagnostic and prognostic values of UDS in patients with IC/BPS. In this study from Taiwan, IC/BPS patients with complete data of a symptom assessment, video UDS, potassium chloride (KCl) test, cystoscopic hydrodistention and treatment records were reviewed retrospectively. O'Leary-Sant symptom index and problem index (ICSI, ICPI) were available in part of the patients. The associations between UDS parameters with symptom scores, KCl test result, cystoscopy findings and treatment outcome were analysed. The UDS parameters, including first sensation of filling (FSF), first desire to void (FD), strong desire to void (SD), cystometric bladder capacity (CBC), maximum flow rate (Qmax), detrusor pressure at Qmax (Pdet), voided volume (VV) and postvoid residual (PVR). Univariate and multivariate logistic regression analyses were used to identify the variable predicting treatment success. Female gender and the volume at SD were found to be the independent predictors for treatment outcome. Kuo and colleagues concluded that their study demonstrated that there might be a role of UDS to help in diagnosis and prognostication for IC/BPS. Future prospective investigations are warranted.

#### **RETUBULARIZATION OF THE ILEOCYSTOPLASTY PATCH FOR CONVERSION INTO AN ILEAL CONDUIT.**

*Massaro PA, Gajewski JB, Bailly G. Can Urol Assoc J. 2013 Jul-Aug;7(7-8):E462-6. doi: 10.5489/cuaj.204. PMID: 23914260*

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

This study from Canada presents the outcomes and long-term follow-up of patients who underwent conversion to an ileal conduit urinary diversion using the retubularized patch from the initial augmentation ileocystoplasty. Massaro and colleagues reviewed the charts of all patients who underwent this surgery at our centre. The indications for surgery, workup, clinical outcomes and complication rates were assessed. Patient-reported symptom response based on global response assessment (GRA) was determined and used as a subjective measure of overall treatment effectiveness. They concluded that conversion to an ileal conduit using the retubularized ileocystoplasty patch offers several technical and therapeutic advantages over creating a urinary diversion from a new bowel segment. It should therefore be considered a viable treatment option in patients who have exhausted more conservative management of their LUTS.

#### **TRYPTASE ACTIVATION OF IMMORTALIZED HUMAN UROTHELIAL CELL MITOGEN-ACTIVATED PROTEIN KINASE.**

*Marentette JO, Hauser PJ, Hurst RE, Klumpp DJ, Rickard A, McHowat J. PLoS One. 2013 Jul 29;8(7):e69948. doi: 10.1371/journal.pone.0069948. PMID: 23922867*

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

The pathogenesis of interstitial cystitis/painful bladder syndrome (IC/PBS) is multifactorial, but likely involves urothelial cell dysfunction and mast cell accumulation in the bladder wall. Activated mast cells in the bladder wall release several inflammatory mediators, including histamine and tryptase. Marentette and colleagues determined whether mitogen-activated protein (MAP) kinases are activated in response to tryptase stimulation of urothelial cells derived from human normal and IC/PBS bladders. They conclude that activation of extracellular signal regulated kinase 1/2 (ERK 1/2) in response to tryptase stimulation may facilitate wound healing or cell motility in areas of inflammation in the bladder associated with IC/PBS.

#### **CHALLENGES AND CURRENT EVIDENCE ON THE MANAGEMENT OF BLADDER PAIN SYNDROME.**

*Chrysanthopoulou EL, Doumouchtsis SK. Neurourol Urodyn. 2013 Aug 14. doi: 10.1002/nau.22475. [Epub ahead of print]. PMID: 23946107*

The aim of this review from London was to critically appraise the current evidence on the diagnosis and management of BPS. They found that patients may experience pain and lower urinary tract symptoms for a long time before diagnosis, affecting their mental health and work, causing stress, sleep disturbance,

depression, and sexual dysfunction. BPS has been considered as one of a group of chronic pain syndromes rather than as primarily an inflammatory bladder disorder. Despite the wide range of treatments, most are empirical and inadequate, usually offering just symptom relief. There is often delay in commencing treatment, and this may result in worse prognosis. Efforts are focused on different pathways for the early identification of this syndrome, trying to elucidate the pathogenetic mechanism, as well as introducing effective treatments.

#### **PHENOTYPIC AND FUNCTIONAL CHARACTERIZATION OF CIRCULATING POLYOMAVIRUS BK VP1-SPECIFIC CD8+ T CELLS IN HEALTHY ADULTS.**

*van Aalderen MC, Remmerswaal EB, Heutinck KM, Ten Brinke A, Pircher H, van Lier RA, Ten Berge IJ. J Virol. 2013 Sep;87(18):10263-72. doi: 10.1128/JVI.01540-13. Epub 2013 Jul 17. PMID: 23864628*

The human polyomavirus BK virus (BKV) establishes a latent and asymptomatic infection in the majority of the population. In immunocompromised individuals, the virus frequently (re)activates and may cause severe disease such as interstitial nephritis and hemorrhagic cystitis. Currently, the therapeutic options are limited to reconstitution of the antiviral immune response. T cells are particularly important for controlling this virus, and T cell therapies may provide a highly specific and effective mode of treatment. However, little is known about the phenotype and function of BKV-specific T cells in healthy individuals. Using tetrameric BKV peptide-HLA-A02 complexes, they determined the presence, phenotype, and functional characteristics of circulating BKV VP1-specific CD8(+) T cells in 5 healthy individuals. Van Aalderen and colleagues show that these cells are present in low frequencies in the circulation and that they have a resting CD45RA(-) CD27(+) memory and predominantly CCR7(-) CD127(+) KLRG1(+) CD49d(hi) CXCR3(hi) T-bet(int) Eomesodermin(lo) phenotype. Furthermore, their direct cytotoxic capacity seems to be limited, since they do not readily express granzyme B and express only little granzyme K. They compared these cells to circulating CD8(+) T cells specific for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and influenza virus (Flu) in the same donors and show that BKV-specific T cells have a phenotype that is distinct from that of CMV- and EBV-specific T cells. Lastly, they show that BKV-specific T cells are polyfunctional since they are able to rapidly express interleukin-2 (IL-2), gamma interferon (IFN- $\gamma$ ), tumor necrosis factor  $\alpha$ , and also, to a much lower extent, MIP-1 $\beta$  and CD107a.

#### **ILEAL CONDUIT WITHOUT CYSTECTOMY MAY BE AN APPROPRIATE OPTION IN THE TREATMENT OF INTRACTABLE BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.**

*Norus T, Fode M, Nordling J. Scand J Urol. 2013 Sep 27. [Epub ahead of print]. PMID: 24070021*

The aim of this study from Denmark was to report the outcomes of urinary diversion for bladder pain syndrome/interstitial cystitis (BPS/IC) at a large university hospital over a period of more than 10 years. Chart reviews were performed for BPS/IC patients who had undergone ileal conduit with or without cystectomy. Questionnaires on quality of life, BPS/IC symptoms and pain were mailed to patients. Outcomes in the cystectomy and the non-cystectomy groups were compared with Fisher's exact test. Ileal conduit without cystectomy was performed in 20 patients. Two underwent a subsequent cystectomy owing to persistent symptoms. Three patients underwent ileal conduit with concomitant primary cystectomy. Nineteen patients were alive at the time of the study and 15 returned the questionnaires. Twelve responders had been treated with ileal conduit and three had undergone primary cystectomy. The quality of life in both the cystectomy and the non-cystectomy groups was comparable with that in the general population. Seven patients in the non-cystectomy group were free of specific BPS/IC symptoms. The remaining five patients had minimal symptoms. Two cystectomy patients were free of symptoms, while one still suffered from severe symptoms. Eleven patients reported having no pain while four patients had visual analogue scale (VAS) scores between 2 and 9.5. Three patients experiencing pain belonged to the non-cystectomy group. There was no difference between the cystectomy group and the non-cystectomy group with regard to the proportion of patients who were symptom free. It was therefore concluded by the authors that ileal conduit without cystectomy may be an appropriate option when performing urinary diversion in BPS/IC patients.

#### **BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS IS ASSOCIATED WITH ANXIETY DISORDER.**

*Chung KH, Liu SP, Lin HC, Chung SD. NeuroUrol Urodyn. 2013 Aug 22:0. doi: 10.1002/nau.22382. [Epub ahead of print]. PMID: 24038135*

Recent research has demonstrated that bladder pain syndrome/interstitial cystitis (BPS/IC) is associated with many coexisting physical and psychiatric conditions. In this study from Taiwan, Chung and colleagues explored the potential association between anxiety disorder (AD) and BPS/IC using a case-controlled population-based approach in Taiwan. Data on the sampled subjects analyzed in this study were retrieved from the Longitudinal Health Insurance Database 2000. The study included 396 female cases with BPS/IC and 1,980 randomly selected female controls. The authors excluded subjects who had a history of major psychosis (except AD) or a

substance-related disorder. A conditional logistic regression was performed to calculate the odds ratio (OR) for the association between a previous diagnosis of AD and IC/BPS. They found that there was an association between AD and BPS/IC, even after taking demographic characteristics, medical co-morbidities, and substance-related disorders into consideration. Results of this study should alert clinicians to evaluate and monitor the presence of BPS/IC in patients with AD.

## **KETAMINE AND THE URINARY TRACT**

### **INCREASED APOPTOSIS AND SUBUROTHELIAL INFLAMMATION IN PATIENTS WITH KETAMINE-RELATED CYSTITIS: A COMPARISON WITH NON-ULCERATIVE INTERSTITIAL CYSTITIS AND CONTROLS.**

*Lee CL, Jiang YH, Kuo HC. BJU Int. 2013 May 23. doi: 10.1111/bju.12256. [Epub ahead of print]. PMID: 23937072*

The purpose of this study from the Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan was to investigate the suburothelial inflammation and urothelial dysfunction that occurs with ketamine-related cystitis (KC) and interstitial cystitis/bladder pain syndrome (IC/BPS). Bladder tissues from 16 patients with KC, 17 patients with IC/BPS and 10 control subjects were analysed. Immunofluorescence staining of the junction protein E-cadherin was carried out, and tryptase levels and a TUNEL assay were used to assess mast-cell activation and urothelial apoptosis, respectively. The fluorescence intensity of E-cadherin was measured using the ImageJ method. The percentages of activated mast cells and apoptotic cells were calculated as positive cells per unit area (4  $\mu\text{m}^2$ ). The authors found that KC and IC/BPS tissues both showed defective junction protein, increased suburothelial inflammation and increased urothelial cell apoptosis. Decreased expression of E-cadherin and increased apoptosis were more severe in KC than in IC/BPS bladder tissues and these findings were associated with the clinical symptoms of KC and IC/BPS.

### **GENITOURINARY TOXICITY OF KETAMINE.**

*Wei YB, Yang JR, Yin Z, Guo Q, Liang BL, Zhou KQ. Hong Kong Med J. 2013 Aug;19(4):341-8. doi: 10.12809/hkmj134013. Epub 2013 Jul 8. PMID: 23832948*

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Wei and colleagues from China report that ketamine is a relatively new recreational drug used by youngsters in recent decades. Its toxic effects on the genitourinary system were first reported in 2007, and now attract extensive attention from urologists, pharmacologists, and toxicologists all over the world. As many front-line health professionals and medical social workers are still unaware of this new clinical entity and an increasing number of the drug users seek help for urological symptoms, this mini-review aimed to summarise the clinical features and possible mechanisms of ketamine-induced genitourinary toxicity. By raising public awareness of these toxic effects, the authors hope that the contents of this review will be widely disseminated not only to medical professionals, but also to relevant government departments and the general public.

### **AUGMENTATION ENTEROCYSTOPLASTY IS EFFECTIVE IN RELIEVING REFRACTORY KETAMINE-RELATED BLADDER PAIN.**

*Chung SD, Wang CC, Kuo HC. Neurorol Urodyn. 2013 Aug 29. doi: 10.1002/nau.22477. [Epub ahead of print]. PMID: 23996856*

The purpose of this article from Taiwan is to report their early results of augmentation enterocystoplasty (AE) for severe bladder pain associated with chronic ketamine cystitis (KC). Chung and colleagues performed AE for 14 patients with refractory KC-related bladder pain, which is based on the criteria including severe bladder pain, urgency and frequency and/or upper urinary tract damage such as bilateral hydronephrosis, and contracted bladder. Every patient had been treated conservatively with medication or cystoscopic hydrodistention for at least 1 year before they had received surgical intervention. Video-urodynamic studies were obtained before AE and 3-6 months after surgery. Outcome measurements included visual analogue score (VAS) for pain, cystometric bladder capacity (CBC), maximum urinary flow rate (Q<sub>max</sub>), post-void residual, and maximal detrusor pressure (P<sub>det</sub>). The patients' general satisfaction with regard to treatment outcome was also assessed by the Patient Perception of Bladder Condition (PPBC). A total of 4 men and 10 women underwent this procedure as indicated. The mean age was 26.7 (ranged 20-38) years old and the duration of ketamine abuse was 3.82 years (ranged 2-7). Contracted bladder was noted in all patients, hydronephrosis in nine and vesicoureteral reflux (VUR) in eight. This pilot study demonstrated that AE is effective in relieving refractory ketamine-related bladder pain and lower urinary tract symptoms.

## **NOCTURIA**

### **SURVEY ON LOWER URINARY TRACT SYMPTOMS AND SLEEP DISORDERS IN PATIENTS TREATED AT UROLOGY DEPARTMENTS.**

*Shimizu N, Nagai Y, Yamamoto Y, Minami T, Hayashi T, Tsuji H, Nozawa M, Yoshimura K, Ishii T, Uemura H, Oki T, Sugimoto K, Nose K, Nishioka T. Nat Sci Sleep. 2013; 5: 7–13. PMID: 23620688*

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This study from Osaka, Japan by Shimizu and colleagues examined the association between sleep disorders and lower urinary tract symptoms in patients who had visited urology departments. This was an independent cross-sectional, observational study. Outpatients who had visited the urology departments at the Kinki University School of Medicine or the Sakai Hospital, Kinki University School of Medicine, between August 2011 and January 2012 were assessed using the Athens Insomnia Scale and the International Prostate Symptom Score. In total, 1174 patients, with 895 men and 279 women, were included in the study. Approximately half of these patients were suspected of having a sleep disorder. The results demonstrated that the risk factors for sleep disorders could also include voiding, post-micturition, and storage symptoms, in addition to nocturia.

### **CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME**

#### **EFFECTS OF FOODS AND BEVERAGES ON THE SYMPTOMS OF CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME.**

*Herati AS, Shorter B, Srinivasan AK, Tai J, Seideman C, Lesser M, Moldwin RM. Urology. 2013 Aug 23. pii: S0090-4295(13)00854-6. doi: 10.1016/j.urology.2013.07.015. [Epub ahead of print]. PMID: 23978369*

Another interesting study from the food sensitivity team at the Arthur Smith Institute for Urology in the USA. The purpose of this study was to better elucidate the prevalence of perceived food sensitivity and characterize the sensitivity pattern in patients with clinically diagnosed chronic prostatitis/chronic pelvic pain syndrome. A total of 286 men meeting the National Institutes of Health criteria for chronic prostatitis were mailed a validated questionnaire designed to detect the effect of foods, beverages, and/or supplements on pelvic pain symptoms. The questionnaire assessed the effect of 176 individual comestibles on each patient's symptoms. The responses were numerically scored on a scale of -2 to +2, and the mean values were generated for each comestible. In addition, the participants were asked to complete the O'Leary-Sant Symptom and Problem Index and Chronic Prostatitis Symptom Index questionnaires. Of the 286 surveys, 95 were returned, yielding a response rate of 33.2%. Of those subjects who responded, 47.4% reported that the consumption of certain comestibles aggravated their symptoms, with the most aggravating being spicy foods, coffee, hot peppers, alcoholic beverages, tea, and chili. In contrast, the comestibles that alleviated the symptoms the most included docusate, psyllium, water, herbal teas, and polycarbophil. The authors concluded that many patients with chronic prostatitis/chronic pelvic pain syndrome have demonstrable food, beverage, and dietary supplement sensitivities and that dietary changes should be considered in the treatment of these patients.

### **FIBROMYALGIA**

#### **OVERLAPPING STRUCTURAL AND FUNCTIONAL BRAIN CHANGES IN PATIENTS WITH LONG-TERM EXPOSURE TO FIBROMYALGIA.**

*Jensen KB, Srinivasan P, Spaeth R, Tan Y, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Vitton O, Gracely R, Ingvar M, Kong J. Arthritis Rheum. 2013 Aug 27. doi: 10.1002/art.38170. [Epub ahead of print]. PMID: 23982850*

Jensen and colleagues note that there is vast evidence for brain aberrations in patients with fibromyalgia (FM) and it is possible that central plasticity is critical for the transition from acute to chronic pain. However, the relationship between brain structure and function is poorly investigated. This study from Boston, with 26 FM patients and 13 age- and gender-matched healthy controls, investigated the differences between patients and controls regarding functional connectivity during intermittent pressure pain and measures of brain structure. Magnetic resonance imaging (MRI) was used to obtain high-resolution anatomical images and functional MRI scans for measures of pain-evoked brain activity. FM patients displayed a distinct overlap between decreased cortical thickness, brain volumes and measures of functional regional coherence in the rostral anterior cingulate cortex. The morphometric changes were more pronounced with longer exposure to FM pain. In addition, they found associations between structural and functional changes in the mesolimbic areas of the brain and comorbid depressive symptoms in FM patients. The authors concluded that the combined integration of structural and functional measures allowed for a unique characterization of the impact of FM pain on the brain and that their data may lead to the identification of early structural and functional brain alterations in

response to pain, which could be used to develop markers to predict the development of FM and other pain disorders.

**ALTERATIONS IN EXCITATORY AND INHIBITORY BRAINSTEM INTERNEURONAL CIRCUITS IN FIBROMYALGIA: EVIDENCE OF BRAINSTEM DYSFUNCTION.**

*Kofler M, Halder W. Clin Neurophysiol. 2013 Sep 21. pii: S1388-2457(13)00992-9. doi: 10.1016/j.clinph.2013.08.009. [Epub ahead of print]. PMID: 24064248*

Patients with fibromyalgia syndrome (FMS) perceive stimuli differently and show altered cortical sensory representation maps following peripheral stimulation. Altered sensory gating may play a causal role. In this study from Austria, blink reflex, blink reflex excitability recovery, and prepulse inhibition of the blink reflex - representing brainstem excitability - were assessed in 10 female patients with FMS and 26 female healthy controls. They found that blink reflex is normal, whereas blink reflex excitability recovery is enhanced and blink reflex prepulse inhibition is reduced in patients with FMS, suggesting functional changes at the brainstem level in FMS. Reduced blink reflex prepulse inhibition concurs with altered sensory gating in patients with FMS.

**HIGH PREVALENCE OF FIBROMYALGIA-ASSOCIATED SYMPTOMS IN PATIENTS WITH HYPOTHALAMIC-PITUITARY DISORDERS.**

*Harbeck B, Süfke S, Harten P, Haas CS, Lehnert H, Mönig H. Clin Exp Rheumatol. 2013 Aug 26. [Epub ahead of print]. PMID: 23981240*

Various complaints of patients with fibromyalgia often resemble clinical features observed in patients with hypothalamic-pituitary diseases. The aim of this study from Lübeck, Germany was to evaluate whether patients with hypothalamic-pituitary diseases are at increased risk for fibromyalgia syndrome (FMS). A questionnaire for evaluating fibromyalgia-associated symptoms was sent to 121 patients with hypothalamic-pituitary disorders (HPD) (60 women, 61 men; mean age, 55.4 years; range, 21-83 years) of the endocrine outpatient clinic. 115 patients (57 women, 58 men; mean age 56.9 years; range, 21 to 82 years) with cardiovascular diseases (CD) served as controls. Fibromyalgia-associated symptoms regarding muscular complaints were significantly more frequent in the HPD group than in CD patients. In particular, they found a significant higher prevalence of autonomic symptoms in the HPD group as compared to the CD group regarding several qualities (cold hands, flatulence, tiredness). In addition, swollen and painful finger joints were reported more often in the HPD group than in the CD group. Of note, no differences regarding any fibromyalgia-associated symptom were detected when patients with hypothalamic-pituitary hormone excess syndromes were compared to those with a pituitary pathology without hormonal excess. Similarly, prevalence of fibromyalgia-associated symptoms was not related to the treatment modality of pituitary disease; i.e. surgical vs. conservative or any hormonal replacement therapy. They conclude that their data suggest that patients with hypothalamic-pituitary disorders may be at increased risk of developing fibromyalgia-associated symptoms.

**OBJECTIVE EVIDENCE THAT SMALL-FIBER POLYNEUROPATHY UNDERLIES SOME ILLNESSES CURRENTLY LABELED AS FIBROMYALGIA.**

*Oaklander AL, Herzog ZD, Downs HM, Klein MM. Pain. 2013 Jun 5. pii: S0304-3959(13)00294-7. doi: 10.1016/j.pain.2013.06.001. [Epub ahead of print]. PMID: 23748113*

Fibromyalgia is a common, disabling syndrome that includes chronic widespread pain plus diverse additional symptoms. No specific objective abnormalities have been identified, which precludes definitive testing, disease-modifying treatments, and identification of causes. In contrast, small-fiber polyneuropathy (SFPN), despite causing similar symptoms, is definitionally a disease caused by the dysfunction and degeneration of peripheral small-fiber neurons. SFPN has established causes, some diagnosable and definitively treatable, eg, diabetes. To evaluate the hypothesis that some patients labelled as having fibromyalgia have unrecognized SFPN that is causing their illness symptoms, Oaklander and colleagues from Boston analyzed SFPN-associated symptoms, neurological examinations, and pathological and physiological markers in 27 patients with fibromyalgia and in 30 matched normal controls. Patients with fibromyalgia had to satisfy the 2010 American College of Rheumatology criteria plus present evidence of a physician's actual diagnosis of fibromyalgia. The study's instruments comprised the Michigan Neuropathy Screening Instrument (MNSI), the Utah Early Neuropathy Scale (UENS), distal-leg neurodiagnostic skin biopsies, plus autonomic-function testing (AFT). They found that 41% of skin biopsies from subjects with fibromyalgia vs 3% of biopsies from control subjects were diagnostic for SFPN, and MNSI and UENS scores were higher in patients with fibromyalgia than in control subjects. Abnormal AFTs were equally prevalent, suggesting that fibromyalgia-associated SFPN is primarily somatic. Blood tests from subjects with fibromyalgia and SFPN-diagnostic skin biopsies provided insights into causes. All glucose tolerance tests were normal, but 8 subjects had dysimmune markers, 2 had hepatitis C

serologies, and 1 family had apparent genetic causality. These findings suggest that SOME patients with chronic pain labelled as fibromyalgia have unrecognized SFPN, a distinct disease that can be tested for objectively and sometimes treated definitively.

#### **TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) REDUCES PAIN, FATIGUE, AND HYPERALGESIA WHILE RESTORING CENTRAL INHIBITION IN PRIMARY FIBROMYALGIA.**

*Dailey Dana L, Rakel Barbara A, Vance Carol GT, Liebano Richard E, Anand Amrit S, Bush Heather M, Lee Kyoung S, Lee Jennifer E, Sluka Kathleen A. Pain. 2013 Jul 27. pii: S0304-3959(13)00411-9. doi: 10.1016/j.pain.2013.07.043. [Epub ahead of print]. PMID: 23900134*

Because TENS works by reducing central excitability and activating central inhibition pathways, they tested the hypothesis that TENS would reduce pain and fatigue and improve function and hyperalgesia in people with fibromyalgia who have enhanced central excitability and reduced inhibition. The current study from Iowa used a double-blinded randomized, placebo controlled cross-over design to test effects of a single treatment of TENS in people with fibromyalgia. Three treatments were assessed in random order: active TENS, placebo TENS, no TENS. The following measures were assessed before and after each TENS treatment: pain and fatigue at rest and movement, pressure pain thresholds (PPTs), 6 minute walk test (6MWT), range of motion (ROM), five time sit to stand test (FTSTS), and single leg stance (SLS). Conditioned pain modulation (CPM) was completed at end of testing. There was a significant decrease in pain and fatigue with movement for active TENS compared to placebo and no TENS. PPTs increased at site of TENS (spine) and outside site of TENS (leg) when compared to placebo TENS or no TENS. During Active TENS CPM was significantly stronger compared to placebo TENS and no TENS. No changes in functional tasks were observed with TENS. Thus, the current study suggests TENS has short-term efficacy in relieving symptoms of fibromyalgia while the stimulator is active. Future clinical trials should examine the effects of repeated daily delivery of TENS, similar to how TENS is used clinically, on pain, fatigue, function and quality of life in individuals with fibromyalgia

#### **RHEUMATOID ARTHRITIS AND THE URINARY TRACT**

##### **[UROLOGICAL COMORBIDITIES IN PATIENTS WITH RHEUMATOID ARTHRITIS : LITERATURE REVIEW.]**

*[Article in German]*

*Friedl A, Mustak M, Hörtl W, Erlacher L. Z Rheumatol. 2013 Aug 11. [Epub ahead of print]. PMID: 23934052*

Friedl and colleagues from Austria write that patients with rheumatoid arthritis (RA) have an increased risk of urolithiasis which is further negatively impacted by a reduced bone density. Interstitial cystitis also tends to occur more often in patients with rheumatic diseases. The high incidence of bacterial urogenital infections is influenced by the use of immunomodulating drugs. Many RA patients have to undergo numerous tests until a diagnosis is reached and are then treated as outpatients on a tightly controlled schedule. Despite a closely controlled rheumatological follow-up, urological screening and determination of a baseline prostate-specific antigen (PSA) value (in men over 45 years old) should not be neglected. In patients with an increased risk of renal and bladder neoplasms or when such a diagnosis is known, the benefit of long-term use of high doses of non-steroidal anti-inflammatory drugs (NSAID, aspirin type) should be carefully weighed up with a risk profile and after specialist urological assessment. Patients who suffer from sexual dysfunction due to physical limitations and prolonged medical therapy should undergo urological and gynecological assessment to exclude contributing causes. The use of aphrodisiacs and erection-enhancing drugs (e.g. PDE5 inhibitors, local injection with prostaglandins and vacuum therapy) require prior approval by a medical specialist and also cardiovascular stability. Acute urinary retention is more common in chronic inflammatory musculoskeletal diseases.

#### **ABDOMINAL PAIN, IRRITABLE BOWEL SYNDROME**

##### **IRRITABLE BOWEL SYNDROME IN FEMALE PATIENTS IS ASSOCIATED WITH ALTERATIONS IN STRUCTURAL BRAIN NETWORKS.**

*Labus J, Dinov ID, Jiang Z, Ashe-McNalley C, Zamanyan A, Shi Y, Hong JY, Gupta A, Tillisch K, Ebrat B, Hobel S, Gutman BA, Joshi S, Thompson PM, Toga AW, Mayer EA. Pain. 2013 Sep 25. pii: S0304-3959(13)00517-4. doi:*

Alterations in gray matter (GM) density/ volume and cortical thickness (CT) have been demonstrated in small and heterogeneous samples of subjects with different chronic pain syndromes, including irritable bowel syndrome (IBS). Aggregating across 7 structural neuroimaging studies conducted at UCLA between August 2006 and April 2011, Labus and colleagues from Los Angeles examined group differences in regional GM volume in 201 predominantly premenopausal female subjects (82 IBS, mean age: 32 ± 10 SD), 119 Healthy Controls [HCs], 30 ± 10 SD). Applying graph theoretical methods and controlling for total brain volume, global and regional

properties of large-scale structural brain networks were compared between IBS and HC groups. Relative to HCs, the IBS group had lower volumes in bilateral superior frontal gyrus, bilateral insula, bilateral amygdala, bilateral hippocampus, bilateral middle orbital frontal gyrus, left cingulate, left gyrus rectus, brainstem, and left putamen. Higher volume was found for the left postcentral gyrus. Group differences were no longer significant for most regions when controlling for Early Trauma Inventory global score with the exception of the right amygdala and the left post central gyrus. No group differences were found for measures of global and local network organization. Compared to HCs, the right cingulate gyrus and right thalamus were identified as significantly more critical for information flow. Regions involved in endogenous pain modulation and central sensory amplification were identified as network hubs in IBS. Overall, evidence for central alterations in IBS was found in the form of regional GM volume differences and altered global and regional properties of brain volumetric networks.

#### **IRRITABLE BOWEL SYNDROME AND MIGRAINE: BYSTANDERS OR PARTNERS?**

Chang FY, Lu CL. *J Neurogastroenterol Motil.* 2013 Jul;19(3):301-11. doi: 10.5056/jnm.2013.19.3.301. Epub 2013 Jul 8. PMID: 23875096

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

Chang and colleagues from Taipei, Taiwan observe that irritable bowel syndrome (IBS) and migraine are distinct clinical disorders. Apart from the characteristics of chronic and recurrent pain in nature, these pain-related disorders apparently share many similarities. For example, IBS is female predominant with community prevalence about 5-10%, whereas that of migraine is 1-3% also showing female predominance. They are often associated with many somatic and psychiatric comorbidities in terms of fibromyalgia, chronic fatigue syndrome, interstitial cystitis, insomnia and depression etc., even the IBS subjects may have coexisted migraine with an estimated odds ratio of 2.66. They similarly reduce the quality of life of victims leading to the social, medical and economic burdens. Their pathogeneses have been somewhat addressed in relation to biopsychosocial dysfunction, heredity, genetic polymorphism, central/visceral hypersensitivity, somatic/cutaneous allodynia, neurolimbic pain network, gonadal hormones and abuses etc. Both disorders are diagnosed according to the symptomatically based criteria. Multidisciplinary managements such as receptor target new drugs, melatonin, antispasmodics, and psychological drugs and measures, complementary and alternatives etc. are recommended to treat them although the used agents may not be necessarily the same. Finally, the prognosis of IBS is pretty good, whereas that of migraine is less fair since suicide attempt and stroke are at risk. In conclusion, both distinct chronic pain disorders to share many similarities among various aspects probably suggest that they may locate within the same spectrum of a pain-centered disorder such as central sensitization syndromes. The true pathogenesis to involve these disorders remains to be clarified in the future.

#### **PAIN/CHRONIC PELVIC PAIN**

##### **SUCCESSFUL MANAGEMENT OF CHRONIC PELVIC PAIN.**

Rhodin A. *J Pain Palliat Care Pharmacother.* 2013 Aug 2. [Epub ahead of print]. PMID: 23909900

Annica Rhodin from Sweden notes that chronic pelvic pain is a common, multifactorial complaint that affects both women and men, causing disability and frustration for patients. The exact aetiology remains unknown, although several theories have been proposed. Assessment should be undertaken with care and compassion, while considering the sensitive nature of the area. Management involves ruling out treatable pathology concomitant with strategies to control pain. Novel treatment approaches have been investigated for specific clinical scenarios. The more severe CPP cases are best managed using a multidisciplinary approach. Management requires good integration and knowledge of all pelvic organ systems and including musculoskeletal, neurologic and psychological mechanisms.

##### **CENTRAL SENSITIZATION IN UROGYNECOLOGICAL CHRONIC PELVIC PAIN: A SYSTEMATIC LITERATURE REVIEW.**

Kaya S, Hermans L, Willems T, Roussel N, Meeus M. *Pain Physician.* 2013 Jul-Aug;16(4):291-308. PMID: 23877446

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Chronic pelvic pain (CPP) is a complex pain syndrome. Since its pathogenesis is still poorly understood and structural alterations in pain related brain regions may be present, there is a greater acceptance that sensitization of the central nervous system (CNS) plays an important role in the development and maintenance of chronicity. The purpose of this study from Turkey and Belgium was to systematically review the scientific evidence regarding central sensitization (CS) in female patients with urogynecological CPP. A systematic

literature search was conducted in PubMed and Web of Science using different keyword combinations related to urogynecological CPP and central sensitization. Full text clinical reports addressing CS in adult women with urogynecological CPP were included and assessed for methodological quality by 2 independent reviewers. The level of evidence of retained studies is low due to the observational study designs and a wide range of diagnoses and assessment methods. They concluded that although the majority of the literature provides evidence for the presence of CS in urogynecological CPP with changes in brain morphology/function and sensory function, it is unclear whether these changes in central pain processing are secondary or primary to CPP, especially since evidence regarding the function of endogenous pain inhibition and the role of psychosocial pain facilitation is scarce. Further studies with good methodological quality are needed in order to clarify exact mechanisms.

#### **THE WORDS PATIENTS USE TO DESCRIBE CHRONIC PAIN: IMPLICATIONS FOR MEASURING PAIN QUALITY.**

*Jensen MP, Johnson LE, Gertz KJ, Galer BS, Gammaitoni AR. Pain. 2013 Aug 8. pii: S0304-3959(13)00439-9. doi: 10.1016/j.pain.2013.08.003. [Epub ahead of print]. PMID: 23933183*

In this study from Seattle, patients with low back pain, fibromyalgia, and headache were asked to describe their pain in their own words, and the words and phrases they used were then classified into seven global domains (e.g., "Pain Quality," "Pain Magnitude") and as many specific subdomains needed to capture all of the ideas expressed (e.g., under Pain Quality, subdomains such as "sharp", "achy", and "throbbing"). Fifteen pain quality subdomains were identified as most common. Nine of these demonstrated significant between-group differences in frequency. For example, patients with FM described their pain as "achy" more often than patients with LBP or HA; patients with HA described their pain as more "throbbing" than patients with LBP or FM; and patients with LBP described their pain as more "shooting" than patients with FM or HA. With the 15 pain quality subdomains representing the "universe" of most important pain qualities to assess, only two of eight descriptive measures of pain quality were determined to have content validity. The findings are generally consistent with a study that used similar procedures in other patient samples to identify the most common words patients use to describe pain, supporting their generalizability. The findings also support the use of pain quality measures for discriminating between chronic pain conditions. Finally, the findings have important implications for evaluating and modifying, as needed, pain quality measures.

#### **THE IMPACT OF COMMUNICATION ON ADHERENCE IN PAIN MANAGEMENT.**

*Butow P, Sharpe L. Pain. 2013 Aug 5. pii: S0304-3959(13)00416-8. doi: 10.1016/j.pain.2013.07.048. [Epub ahead of print]. PMID: 23928026*

Despite a high prevalence of acute and chronic pain and ongoing effort to understand and reduce pain, studies show that there remains considerable unmet need for pain relief and management. Some unmet need arises from the lack of effective interventions. However, even where the evidence indicates that interventions, such as medication, exercise or cognitive-behavioural therapy are effective, patients are not always adherent with these treatment recommendations. Butow and colleagues from Sydney, Australia ask how can we, as health professionals, improve adherence? There are numerous models in health psychology that aim to explain why people engage in health behaviours (or opt not to), such as the health belief model, self-regulation theory and the theory of planned behaviour. These all suggest that patients' beliefs about their health condition and the recommended behaviour are important predictors of adherence. Reviews of interventions to increase adherence identify two key factors in promoting adherence: (a) good health-care provider-patient communication; and (b) interventions that are tailored to individuals' reasons for non-adherence. Hence, communication skills that express a non-judgemental approach, allow open exploration of patient beliefs and concerns, and use a negotiative approach that fosters shared decision-making, are crucial. Randomised controlled trials of brief communication skills training have shown improved outcomes in primary care settings for patients with fibromyalgia and acute pain. Although treatment of chronic pain is challenging, good communication between health provider and patient can promote adherence to lifestyle changes and appropriate medical interventions that appear to result in important, clinically significant benefits for a range of pain conditions.

#### **THE COST OF CHRONIC PAIN: AN ANALYSIS OF A REGIONAL PAIN MANAGEMENT SERVICE IN IRELAND.**

*Gannon B, Finn DP, O'Gorman D, Ruane N, McGuire BE. Pain Med. 2013 Aug 14. doi: 10.1111/pme.12202. [Epub ahead of print]. PMID: 23944994*

The objective of this study from Leeds, UK was to collect data on the direct and indirect economic cost of chronic pain among patients attending a tertiary pain management clinic serving a mixed urban and rural area in the West of Ireland. Data were collected from 100 patients using the Client Services Receipt Inventory and

focused on direct and indirect costs of chronic pain. Patients were questioned about health service utilization, payment methods, and relevant sociodemographics. Unit costs were multiplied by resource use data to obtain full costs. Cost drivers were then estimated. The study showed a cost per patient of US\$24,043 over a 12-month period. Over half of this was attributable to wage replacement costs and lost productivity in those unable to work because of pain. Hospital stays and outpatient hospital services were the main drivers for health care utilization costs, together accounting for 63% of the direct medical costs per study participant attending the pain clinic. The cost of chronic pain among intensive service users is significant, and when extrapolated to a population level, these costs represent a very substantial economic burden.

#### **COMBINATION PHARMACOTHERAPY FOR MANAGEMENT OF CHRONIC PAIN: FROM BENCH TO BEDSIDE.**

*Gilron I, Jensen TS, Dickenson AH. Lancet Neurol. 2013 Sep 24. pii: S1474-4422(13)70193-5. doi: 10.1016/S1474-4422(13)70193-5. [Epub ahead of print]. PMID: 24074723*

Gilron and colleagues from Kingston, Canada note that chronic pain, a frequently neglected problem, is treated with different classes of drugs. Current agents are limited by incomplete efficacy and dose-limiting side-effects. Knowledge of pain processing implicates multiple concurrent mechanisms of nociceptive transmission and modulation. Thus, synergistic interactions of drug combinations might provide superior analgesia and fewer side-effects than monotherapy by targeting of multiple mechanisms. Several trials in neuropathic pain, fibromyalgia, arthritis, and other disorders have assessed various two-drug combinations containing antidepressants, anticonvulsants, non-steroidal anti-inflammatories, opioids, and other agents. In some trials, combined treatment showed superiority over monotherapy, but in others improved benefit or tolerability was not seen. Escalating efforts to develop novel analgesics that surpass the efficacy of current treatments have not yet been successful; therefore, combination therapy remains an important beneficial strategy. Methodological improvements in future translational research efforts are needed to maximise the potential of combination pharmacotherapy for pain.

#### **FUNCTIONAL MRI AND PAIN.**

*Fomberstein K, Qadri S, Ramani R. Curr Opin Anaesthesiol. 2013 Aug 29. [Epub ahead of print] PMID: 23995063*

This article from Yale reviews the current state of knowledge in functional MRI (fMRI) research related to pain with primary focus on clinical studies. The authors note that with fMRI the subjective effects of pain (sensory, affect, emotion, and motor components) can be objectively imaged. Although the conventional fMRI technique has been the isolation of regions in the brain transmitting and modulating pain, functional connectivity measurement can identify functionally linked regions associated with pain processing. The primary and secondary somatosensory cortex (S1 and S2), anterior cingulate cortex (ACC), and insula are the four regions (part of pain matrix) consistently activated in pain states. Functional connectivity between the prefrontal cortex (PFC), ACC, and insula correlates well with clinical pain measures. The dorsal medial PFC to insula connectivity can identify patients prone to persistent back pain. Default mode network (DMN) to insula connectivity is associated with spontaneous pain in fibromyalgia patients. In addition, the DMN encompasses the PFC. Techniques for fMRI analysis, templates, and standards for identifying the functional networks in the brain are evolving continuously. The activation pattern with analgesic agents seems to be specific to the class of drugs. They conclude by saying that as we learn more about fMRI related to pain, functional connectivity patterns could emerge as biomarkers for specific pain conditions.

### **SJÖGREN'S SYNDROME**

#### **ADVANCES IN UNDERSTANDING THE PATHOGENESIS OF PRIMARY SJÖGREN'S SYNDROME.**

*Nocturne G, Mariette X. Nat Rev Rheumatol. 2013 Sep;9(9):544-56. doi: 10.1038/nrrheum.2013.110. Epub 2013 Jul 16. PMID: 23857130*

Primary Sjögren's syndrome (pSS) is a prototypic autoimmune disorder, management of which has long suffered from a lack of knowledge of the underlying pathophysiological mechanisms; however, over the past decade major advances have been made in understanding the pathogenesis of pSS. The innate immune system has been demonstrated to have an important role at the early stage of the disease, notably through activation of the type I interferon (IFN) system. In addition, mechanisms of B-cell activation in pSS have become clearer, particularly owing to recognition of the involvement of the TNF family cytokine B-cell-activating factor, production of which is highly dependent on expression of type I and type II IFNs. Moreover, key inroads have been made in understanding lymphomagenesis, the most severe complication of pSS. IL-12 production and subsequent T-cell activation, mainly IFN- $\gamma$ -secreting type 1 T-helper cells, have also been implicated in disease pathogenesis. Furthermore, evidence implicates neuroendocrine system dysfunction in pSS pathogenesis.

These pathophysiological advances open new avenues of investigation. Indeed, the increased understanding of pSS pathogenesis has already led to the development of promising novel therapeutic strategies. This article from France summarizes recent findings regarding the pathogenic mechanisms involved in pSS and their implications.

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