

# 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 33, June 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, Videos, Websites**
- **Research Highlights**
- **Donations & Sponsoring**

## MEETING REVIEWS

### JOINT MEETING OF THE 3rd INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS JAPAN (ICICJ3) AND THE ESSIC ANNUAL MEETING 2013, 21-23 March 2013, Japan

This was the third time that Japan has organised a meeting of world experts in the field of interstitial cystitis/bladder pain syndrome and hypersensitive bladder, held on this occasion in 2013 as a joint meeting with the International Society for the Study of BPS (ESSIC) and with the support of the Society of Interstitial Cystitis of Japan (SICJ) and the Comfortable Urology Network (CUN) of Japan. Many thanks are due to Dr Tomohiro Ueda for once again organising this unique, thought-provoking meeting of experts. A total of 126 delegates from around the world came to Kyoto, with 22 invited speakers in the main programme and 21 speakers presenting posters in the research programme. Two patient representatives were present from Germany (ICA-Deutschland and the IPBF) and several Japanese patient representatives also attended. While it was an intensive 2½ day programme, plenty of time was allowed for questions and discussion. It was also the perfect opportunity to learn first-hand about the hypersensitive bladder concept of the East Asian countries Japan, Korea and Taiwan, with a special presentation on this topic by Professor Yukio Homma of Tokyo.

The proceedings will be published in a special supplement of the International Journal of Urology scheduled for January 2014.

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

### REVIEW OF THE AMERICAN UROLOGICAL ASSOCIATION ANNUAL MEETING, 4-8 MAY 2013, SAN DIEGO, USA

The AUA this year had quite a lot to offer in the form of courses, research abstracts and special sessions in the field of IC/BPS, CP/CPPS and chronic pelvic pain. A number of abstracts were presented with NIDDK MAPP study feedback and these can be found in our review on the IPBF

website. Where IC/BPS is concerned: the take-home message came over loud and clear that glomerulations are not specific, can occur in other disorders, their significance is as yet unknown, and therefore they should NOT be used for diagnostic purposes. Furthermore, the Hunner's lesion (ulcer) subtype clearly seems to be a different entity to non-lesion disease and it was suggested in San Diego (as previously also in Kyoto) that the historic term interstitial cystitis could perhaps be used for this lesion disease, with bladder pain syndrome being used for non-lesion patients, although we will have to wait and see what happens in this regard. On Monday, 6 May, there was a podium session specifically dedicated to infections/inflammation of the genitourinary tract: interstitial cystitis and more abstracts in other sessions. For further information, read our review: [http://www.painful-bladder.org/pdf/2013\\_AUA\\_SanDiego.pdf](http://www.painful-bladder.org/pdf/2013_AUA_SanDiego.pdf)

### **REVIEW OF THE 1<sup>ST</sup> WORLD CONGRESS ON ABDOMINAL & PELVIC PAIN, 30 MAY – 1 JUNE 2013, BEURS VAN BERLAGE, AMSTERDAM**

This 1<sup>st</sup> World Congress on Abdominal & Pelvic Pain, chaired by urologist/sexologist Dr B. Messelink from the Dutch University of Groningen, was held at the historic Beurs van Berlage in the heart of Amsterdam. Over 500 abdominal and pelvic pain professionals from 10 disciplines and no fewer than 46 countries descended on multicultural Amsterdam. This unique initiative was jointly organised by Convergences PelviPerineal (ConPP), the International Pelvic Pain Society (IPPS) and the IASP special interest group Pain of UroGenital Origin (PUGO) and supported by the International Association for the Study of Pain (IASP), EFIC and the European Society of Neurogastroenterology and Motility and they are to be congratulated on its success. The International Association for the Study of Pain launched its Global Year against Visceral Pain in October 2012 and this congress was held within the period of this global year campaign.

Photos, videos and interviews can be found on the congress home page ([www.pelvicpain-meeting.com](http://www.pelvicpain-meeting.com)), while those who were unable to attend can enjoy the slide presentations of speakers by going to "[scientific programme](#)". Simply click on the name of the speaker.

The scientific programme covered a wide range of areas of abdominal and pelvic pain, from basic science and neurology to every kind of therapy and pain treatment; phenotyping, terminology, taxonomy and standardisation; psychology, depression and stress; sexual dysfunction; societal impact of pain; comorbidities and overlapping disorders; education; and included plenty of time for question and answer sessions with lively discussions on controversial areas.

The congress also included a parallel patient organisation workshop, in coordination with the International Pelvic Pain Partnership (IPPP), for representatives of patient organisations on the Friday morning, with lively discussions between patient advocates and healthcare professionals, looking at gaps in care and research and prioritising aspects that need attention. Facilitators were Sally Crowe and Jenny Birch. Participants were representatives from patient groups/charities and healthcare professionals and researchers with interests in pelvic pain, with pharmaceutical representatives engaged in research as observers. A report on this patient workshop will be available in due course.

An official report of the 1<sup>st</sup> World Congress on Abdominal & Pelvic Pain 2013 proceedings will be published as a book by the IASP Press.

It is planned to hold this congress every two years in different countries, with the next meeting being organised in Paris in January/February 2015.

A more detailed review of this congress is available on the IPBF website, [click here...](#)

## **SUCCESSFUL SIP MEETING 14/15 MAY 2013 IN BRUSSELS: MOVING A STEP FORWARD TOWARDS CONCRETE POLICY ACTIONS**

This year's Societal Impact of Pain (SIP) Focus Groups on Quality Indicators and Best-Practices for Reintegrating Chronic Pain Patients into the Workplace discussed and agreed on two policy documents for future policy actions to improve pain management in Europe: The SIP Recommendations paper on the "European Implementation of Quality Indicators in Chronic, Non-Malignant Pain Management" (Focus Group 1) and the SIP Proposal for Action, using "European Best Practices for the Reintegration of Chronic Pain Patients into the Workforce" (Focus Group 2). Both documents will set the basis for future actions of the multi-stakeholder group which aims to raise awareness of the impact of chronic pain, to exchange information and share best-practices across the European Union and to develop and foster policy strategies and activities to improve pain care in Europe. For further information go to: <http://www.sip-platform.eu/sip-2013.html>

### **UPCOMING MEETINGS**

#### **International Continence Society (ICS) Annual Scientific Meeting**

26-30 August 2013,

Barcelona, Spain

<http://www2.kenes.com/ics/Pages/Home.aspx>

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

October 17-19, 2013

The Peabody Hotel

Orlando, FL

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

#### **IAPO's 6<sup>th</sup> Global Patients Congress in 2014**

29-31 March 2014 in London, UK.

#### **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>

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

Simultaneous translation French/English

Palais des Congrès-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>

## PATIENT ORGANISATION NEWS

### INTERNATIONAL PELVIC PAIN PARTNERSHIP (IPPP)

A relatively new alliance is the International Pelvic Pain Partnership (IPPP) which is committed to substantially improving education, early and accurate diagnosis, effective treatment/management, and realistic prognosis for neuropathic chronic and visceral pelvic and perineal pain. The Partnership aims to increase the participation in research and services development, so that these objectives are achieved in the next decade.

Key aspirations of the IPPP are:

- Better awareness, education, understanding and experience of physicians to take chronic pain seriously, diagnose and treat effectively.
- Better access to (integrative/interdisciplinary) pain management
- Improved quality of life and comfort, with more respect for the condition
- More women empowered to ask for better treatment and care (self management)
- More clarity regarding terminology and definitions
- Better research to underpin all of the above.

IPPP member organisations come from all fields of pelvic pain. For further information, please contact: [info@pelvicpain.org.uk](mailto:info@pelvicpain.org.uk)

### IAPO CALLS ON WHO TO DEFINE UNIVERSAL HEALTH COVERAGE

On 24 May 2013 in Geneva, the International Alliance of Patients' Organizations (IAPO) urged the World Health Organization (WHO) to define universal health coverage and support countries in its implementation worldwide. This request was central to an intervention made by Carol Bennett, IAPO Board Member, on universal health coverage at the Sixty-sixth session of the WHO World Health Assembly in Geneva, Switzerland. The following is taken from IAPO's statement:

"...Universal health coverage is critical to delivering better health care. Expanding universal health coverage is an opportunity to ensure health for all, tackle poverty and encourage sustainable development. However, what is meant by universal health coverage is often poorly understood. IAPO calls on WHO to more clearly define universal health coverage and to scale-up support for Members States to implement or expand it.

In addition, the definition of universal health coverage must reference patient-centred healthcare and acknowledge its key principles of respect for the patient, choice and empowerment, patient involvement in health policy, access to safe quality and appropriate services and treatments, support for patients' needs and information. Only with such an approach, will the goals of universal health coverage be achieved.

Access to essential medicines is vital in achieving universal health coverage and is one of the pillars of primary care. IAPO is pleased to see that the global monitoring framework for the prevention and control of non-communicable diseases includes a target of 80% availability of the affordable basic technologies and essential medicines, by 2025. With the expansion of universal health coverage, there is an opportunity to build on WHO's progress towards ensuring access to essential medicines in all WHO strategies, including the post-2015 development agenda.

IAPO will continue to support WHO and other interested stakeholders in their efforts to expand universal health coverage worldwide."

[View IAPO's comments on universal health coverage](#)

[View the press release as a PDF](#)

### IAPO CALLS FOR WHO MEMBER STATE ACTION ON COUNTERFEIT MEDICAL PRODUCTS

On 24 May 2013 in Geneva, the International Alliance of Patients' Organizations (IAPO) urged the World Health Organization (WHO) Member States to involve patients in strategies to tackle the proliferation of counterfeit medication products. This request was central to an intervention made by IAPO on Substandard/spurious/falsely-labelled/falsified/counterfeit medical products at the Sixty-sixth session of the WHO World Health Assembly in Geneva, Switzerland. The following is taken from IAPO's statement:

"...IAPO has prioritized the issue of substandard/spurious/falsely-labelled/falsified/counterfeit medical products as one of many patient safety issues that are a real danger to patients. These products pose a very real threat to the lives of patients worldwide and are one of many threats to the quality and safety of medicines available to patients.

IAPO is supportive of the 'member-state mechanism' to promote the prevention and control of counterfeit medical products and associated activities. In particular, IAPO is pleased to see the inclusion in its work plan, of actions towards strengthening and capacity building of national and regional regulatory authorities and quality control laboratories. Similarly, IAPO supports the commitment outlined to "communication, education and awareness raising with consumers, health professionals and industry". However, we would like to see more progress in taking this work forward.

Progress on a number of activities outlined in the work plan was achieved by the International Medical Products Anti-Counterfeiting Taskforce and we encourage Member States to *build* on that work, utilising the lessons learnt and resources pledged to tackle counterfeit medical products through the taskforce. In this regard, IAPO believes that the 'member state mechanism' needs to detail how the many stakeholders with expertise, or who may be affected by this threat, will be included. A multi-stakeholder approach is absolutely essential to ensuring success. There are many key stakeholders ranging from health professionals to regulators to patients themselves and it is essential that they are *all* involved meaningfully in this work.

We must not let substandard, spurious, falsely-labelled, falsified, counterfeit medical products undermine trust and confidence in our health systems and we must not delay our efforts to find effective solutions to this critical public health issue."

[View IAPO's comments on SSFFC](#)

[View the press release as a PDF](#)

### IAPO: PATIENTS CALL FOR A GREATER ROLE IN MEDICATION SAFETY

This call was made at a Side Meeting to the World Health Organization's (WHO) World Health Assembly in Geneva, Switzerland on 24 May 2013. The meeting entitled: Patient Engagement in Medication Safety, was hosted by the Government of Australia, the International Alliance of Patients' Organizations (IAPO) and was held in collaboration with the [WHO Patient Safety Programme \(PSP\)](#).

Unsafe medication is a major issue in both developed and developing countries, causing millions of patient injuries and costing billions of dollars to healthcare systems. Estimates from developed nations suggest that between 7.5% and 10.4% of patients in acute care settings and 13% in ambulatory settings experience adverse drug events. During the meeting Ed Kelley, WHO Patient Safety, announced that the 3rd WHO Global Patient Safety Challenge will be on medication safety and will need to feature patient engagement prominently.

Engaging patients in medication safety is essential to improve health outcomes and prevent patients from being harmed. The meeting raised awareness of the importance of patient engagement in improving medication safety; shared country experiences; and served as a call to action to promote patient and family engagement in the area of medication safety. Given that between 28-56% of adverse drug events are preventable, there is room for improvement. As Chair of the meeting, Sir Liam Donaldson, WHO Envoy for Patient Safety provided an overview of the situation: '...the number

of patients who die from medical error is unacceptable. Patient stories should be told, should be heard and the lessons learnt implemented, so that with confidence we can say, never again.'

'We have the ability to reduce the harm caused by medication safety incidents and improve the quality of life and health of patients and consumers worldwide but to make it happen, we need to listen.' IAPO Governing Board Member, Carol Bennett highlighted as she shared examples of how IAPO members have been supporting patient engagement in patient safety initiatives worldwide. Speakers from Australia, Canada and Germany discussed the many ways in which patients can become more involved in making healthcare safer, such as through health literacy initiatives, co-design of policies and procedures and sitting on policy-making boards. Professor Chris Baggoley, Chief Medical Officer for Australia, highlighted the importance of embedding patient engagement in healthcare systems and national health policy. The session concluded that to achieve improved medication safety strong partnerships with patients need to be developed based on the values of respect and equity.

[View the press release as a PDF](#)

## **BOOKS, VIDEOS & WEBSITES**

### **NIDDK IBS AWARENESS**

In April this year, the NIDDK drew our attention to the 16th annual Irritable Bowel Syndrome (IBS) Awareness Month, sponsored by the International Foundation for Functional Gastrointestinal Disorders. The NIDDK has very useful information for those suffering from IBS or other bowel disorders. Try the following links:

<http://digestive.niddk.nih.gov/ddiseases/pubs/ibs/index.aspx>

<http://www.digestive.niddk.nih.gov/ddiseases/pubs/yrdd/index.aspx>

### **ICS NEW WEBSITE**

The International Continence Society (ICS) website has been moved and can now be found at [www.ics.org](http://www.ics.org).

### **INCONTINENCE: 5th EDITION**

Editors: Paul Abrams, Linda Cardozo, Saad Khoury, Alan Wein

Publisher: ICUD-EAU, 2013,

ISBN: 978-9953-493-21-3

This is the 5<sup>th</sup> Edition of Incontinence from the International Consultation on Urological Diseases (ICUD). This edition incorporates the results of the 5th International Consultation on Incontinence, held in Paris in February 2012 and organised for the purpose of developing consensus statements for the diagnosis, evaluation and treatment of urinary incontinence, faecal incontinence, pelvic organ prolapsed and bladder pain syndrome. 200 experts divided into 23 committees presented their chapters, and received input from the audience. Committee 19 presents an update on bladder pain syndrome with an algorithm for diagnosis and treatment. The book includes a CD-Rom. The book can be ordered online via: <https://www.uroweb.org/publications/other-publications/>

### **BLADDER PAIN SYNDROME: A Guide for Clinicians**

Edited by Nordling J, Wyndaele, JJ, Van de Merwe JP, Bouchelouche P, Cervigni M, Fall M.

Published by Springer 2013-01-12

Price: E-book € 159.99. Hardcover € 180.15

E-book ISBN 978-1-4419-6929-3

Hardcover ISBN 978-1-4419-6928-6

A reminder about this new book which provides a comprehensive update on the pathophysiology, epidemiology, terminology, evaluation and treatment of patients with IC/BPS. Chapter contributors are experts from around the world, including two patient advocates. While intended as a guide for clinicians, patients will have no problems in reading this text. The book includes many interesting topics that have not really been considered before such as the chapter on Syndromes Associated with Bladder Pain Syndrome as Clues to its Pathogenesis. Particularly interesting is Chapter 19 on Diet and its Role in Bladder Pain Syndrome and Comorbid Conditions by well-known diet experts Justin I. Friedlander, Barbara Shorter and Robert M. Moldwin who note that it is clear that dietary advice must take into account comorbid conditions. A chapter on Physiotherapy will also be greatly appreciated by both physiotherapists and patients, along with the chapter on Pelvic Floor Dysfunction in BPS. These, together with the chapter on Complementary and Alternative Medical Treatments of BPS, help to make this book particularly comprehensive and a valuable aid to anyone treating this complex group of patients. For further information, [click here](#).

### **PAINFUL BLADDER SYNDROME**

#### **Controlling and Resolving Interstitial Cystitis through Natural Medicine**

By: Philip Weeks

Published by: Singing Dragon 2012, 192 pages

ISBN: 9781848191105

For those with an interest in the alternative route, herbalist and acupuncturist Philip Weeks has written this book on a holistic and natural way of treating IC/BPS, taking the reader through the process of managing symptoms using a combination of natural techniques, nutrition and herbal treatment. For further information, [click here](#).

### **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.

#### **METHODS AND INCENTIVES FOR THE EARLY DIAGNOSIS OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.**

*Fall M, Peeker R. Expert Opin Med Diagn. 2013 Jan;7(1):17-24. doi: 10.1517/17530059.2012.717069. Epub 2012 Aug 27. PMID: 23530841*

The concept of interstitial cystitis (IC) has changed dramatically during the last decades, ultimately representing a symptom complex with varying contents. In order to include all patients with bladder pain, the umbrella term 'bladder pain syndrome' (BPS) was suggested, incorporating the classic presentation of IC as a separate phenotype. This change of concepts has not been uncontroversial. Bladder pain syndrome often has a profound effect on the patients' quality of life. Recognition of this problem complex is often hindered by insufficient familiarity in the medical community. The correct diagnosis is often delayed by several years and may be preceded by multiple medical consultations and treatment attempts. There is no doubt that an early and correct diagnosis is of great significance

for the patient. This article presents a critical review of methods and means to approach the diagnosis, including some notes on current controversies. Expert opinion: The key to an early diagnosis is symptom recognition. We are dealing with a heterogeneous concept including various phenotypes. The successful treatment requires understanding and expedient use of objective means, such as cystoscopy, biopsy and input from the multidisciplinary team. In the literature, limited evidence exists for the management of BPS/IC, due to heterogeneity in methodology and description of the syndrome(s). A more consistent use of available methods is desirable. For the immediate future, better understanding of the etiology, pathogenesis and presentation of various BPS/IC phenotypes is indispensable.

#### **ESSIC CRITERIA FOR THE DIAGNOSIS OF BLADDER PAIN SYNDROME / INTERSTITIAL CYSTITIS (BPS/IC) AND COMPARISON WITH THE NIDDK CRITERIA.**

[Article in English, Spanish]

*Proaño A, Garde G, Garrido G, Mazza O. Arch Esp Urol. 2013 Mar;66(2):206-214. PMID: 23589598*

The aim of this Spanish study by Proaño and colleagues from Argentina was to apply the diagnostic criteria of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the criteria of the European Society for Study of Interstitial Cystitis (ESSIC) in their population with Bladder Pain Syndrome /interstitial cystitis (BPS/IC). A cohort of 36 patients with the endoscopic clinical diagnosis of BPS/IC was evaluated retrospectively in the Hospital de Clinicas José de San Martín and Urology Center CDU over a period of 5 years. Cystoscopy with diagnostic and therapeutic hydrodistention was applied to all patients. The NIDDK criteria were applied to the patients with endoscopic clinical diagnosis of BPS/IC. The new criteria proposed by the ESSIC were contrasted and results were compared. Of a total of 36 patients treated, 33 were women and 3 were men, with ages between 30 and 75 years, 100% presented pain or urgency. Glomerulation or Hunner lesions appeared in 30 patients (83%). 35 patients (97%) had urinary frequency >8/day, and 22 patients (61%) had bladder capacity <350cc. Only 22 patients (61%) completed the strict diagnostic criteria of the NIDDK. On the other hand, using the new criteria proposed by the ESSIC for the diagnosis of BPS/IC 35 patients (97%) were included in this pathology, with normal cystoscopy in 6 patients (17%) and 14 patients (39%) with bladder capacity >350cc. It was concluded that the widest diagnostic criteria of the ESSIC allow the inclusion of more patients in the certainty diagnosis of BPS/IC than the NIDDK criteria, facilitating the diagnosis of this strange urological disease.

#### **[THE CARE SITUATION OF PATIENTS WITH INTERSTITIAL CYSTITIS IN GERMANY : RESULTS OF A SURVEY OF 270 PATIENTS.]**[Article in German]

*Jocham D, Froehlich G, Sandig F, Ziegler A. Urologe A. 2013 May;52(5):691-702. doi: 10.1007/s00120-013-3130-8. PMID: 23459923*

Jocham and colleagues from Lübeck, Germany used a comprehensive questionnaire to record the care situation of 270 patients with interstitial cystitis (IC) and bladder pain syndrome in Germany. They note that despite comprehensive literature on IC (62,000 citations in PubMed) almost nothing is known of the everyday care and quality of patient care in Germany. 94 % of the patients were women and 6 % men, the average age of women was 53.5 years and that of men 67 years and 47.77 % of the patients felt that they were well or very well informed about the disease. In many cases, the internet was the source of information. Social networking is also leading to increased exchange of information among patients. The diagnosis of IC was made most frequently (62.22 %) by biopsy and histological examination followed by urodynamics, potassium test, hydrodistension and cystoscopy. The average duration of the diagnosis was 9 years, 46.67 % of the patients consulted a doctor more than 20 times before the diagnosis was made and 51.84 % had to urinate more than 14 times per day. Frequency, nocturia and pain were the main symptoms, with 25 % of the patients complaining of urge incontinence. Analgesics were the most frequent oral medications taken (61.7 %) followed by pentosan polysulfate, antidepressants, antiepileptic drugs, antispasmodics and



remedies for urinary urgency. In the self-assessment of the success of treatment with oral medications (helped very well and well), pentosan polysulfate, analgesics, antidepressants and antiepileptic drugs were considered to be the best. Medications that restore the glucosamine lining of the bladder were used predominantly for instillation into the bladder included hyaluronic acid, chondroitin sulphate and a combination of both and pentosan polysulphate. In the self-assessment of the success of treatment with instillation therapy (helped very well or well) the order was: chondroitin sulphate (62.69%), hyaluronic acid (55.77%), a combination of both (53.66%) and pentosan polysulphate (46.30%). The electromotive drug administration (EMDA) procedure with the use of direct current to introduce medications into the bladder wall was mentioned surprisingly often (by 119 patients). In the self-assessment, success (helped very well or well) was considered the best with intravesical procedures (61.34%). Compared with all drug procedures, instillation of medication into the bladder was mentioned 368 times and was assessed by the patients as having helped very well and noticeably by 53.53%, followed by special invasive procedures at 50.56%/271 mentions, alternative therapies at 41.11%/287 mentions and oral medication at 39.75%/1,024 mentions. Hyaluronic acid and chondroitin sulphate products, the combination of both of these and pentosan polysulfate (both oral and intravesical) are not reimbursed by the statutory health insurance in Germany. Over 40% of patients treated with these therefore discontinued the treatment for reasons of cost.

#### **QUALITY OF INFORMATION ON THE INTERNET RELATED TO BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW OF THE EVIDENCE.**

*Tirlapur SA, Leiu C, Khan KS. Int Urogynecol J. 2013 Apr 20. [Epub ahead of print]. PMID: 23604231*

Bladder pain syndrome (BPS) has an impact on quality of life and available treatments often only provide temporary symptomatic relief. The information provided by websites can be valuable for patient education and management. The hypothesis was to assess medical information available on the internet related to bladder pain syndrome in terms of accuracy, credibility, readability and quality. A search was performed in the meta-search engine Copernic Agent, using the search terms "bladder pain syndrome, interstitial cystitis, painful bladder syndrome and pelvic pain", which simultaneously captured websites from a range of engines. Websites in the English language that were open-access were included. The four quality assessments used were: credibility using a ten-point scale, accuracy based on the American Urological Association guidelines, quality using the DISCERN questionnaire and readability using the Flesch Reading Ease Score. Inter-rater agreement was tested by intra-class coefficient (ICC). Eighteen suitable websites were identified; 7 (39%) were specialist or specific to BPS. The combined mean scores for accuracy, quality, credibility and readability ranged from 83 to 144 for specialist websites and 76 to 137 for non-specialist ones, with a maximum possible score of 208. There was good inter-observer agreement for the assessments performed with an ICC ranging from 0.80 for DISCERN to 0.53 for readability. Specialist websites had higher quality scores and readability scores compared with non-specialist websites whereas credibility and accuracy scores were no different. The authors report that they found four websites that fulfilled their criteria for good quality information. These top four included our own IPBF website.

#### **A NATIONWIDE POPULATION-BASED STUDY ON BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS AND ED.**

*Chung SD, Keller J, Lin HC. Int J Impot Res. 2013 Apr 4. doi: 10.1038/ijir.2013.15. [Epub ahead of print]. PMID: 23552579*

As bladder pain syndrome/interstitial cystitis (BPS/IC) has been demonstrated to proceed through the inflammatory pathways to cause endothelial dysfunction, and endothelial dysfunction is a major factor in the development of ED, it is possible that BPS/IC may be associated with ED. This study by

Chung and colleagues from Taiwan set out to investigate the putative association between ED and BPS/IC by using a population-based data set and case-control design in Taiwan. They obtained the data from Taiwan's National Health Insurance Research Database. Cases included 32 856 ED patients and 164 280 matched controls. Conditional logistic regression analyses were performed to compare the odds ratios (OR) and corresponding 95% confidence intervals (CIs) of having been previously diagnosed with BPS/IC in cases and controls. Among the total sample of 197 136 subjects, the prevalence of prior BPS/IC was 0.05%. The prevalence of prior BPS/IC was 0.10% and 0.04% for cases and controls, respectively. Conditional logistic regression analysis revealed that when compared with controls, the OR of prior BPS/IC for cases was 1.75 after adjusting for monthly income, geographic location, hypertension, diabetes, coronary heart disease, hyperlipidemia, renal disease, obesity, depressive disorder, alcohol abuse/alcohol-dependence syndromes and the number of outpatient visits within 1 year before index date. Subjects aged between 18 and 39 were additionally found to have the highest ORs for prior BPS/IC among cases when compared with controls. There was an association between BPS/IC and ED. The youngest cases with ED were found to have the strongest magnitudes of association with BPS/IC.

#### **HYPERSENSITIVE BLADDER: TOWARDS CLEAR TAXONOMY SURROUNDING INTERSTITIAL CYSTITIS.**

*Homma Y. Int J Urol. 2013 Mar 21. doi: 10.1111/iju.12143. [Epub ahead of print] PMID: 23521051*

*No abstract available*

In this editorial from Tokyo, Y. Homma, MD writes that there is confusion surrounding the taxonomy of interstitial cystitis (IC) and its related symptom syndromes, painful bladder syndrome (PBS), bladder pain syndrome (BPS) and overactive bladder (OAB) syndrome. He points out that IC is a disease name long used in medical and patient societies, but that it lacks clear definition. Furthermore, PBS and BPS both include the word "pain", creating the impression that patients must have pain, although a substantial number do not. Common complaints are a persistent need to void due to discomfort and irritation when there is only very little in the bladder. Professor Homma believes that this is suggestive of increased sensation of the bladder or urothelium and proposes the term hypersensitive bladder.

#### **[EFFECTIVENESS OF ACUPUNCTURE AND MOXIBUSTION THERAPY FOR THE TREATMENT OF REFRACTORY INTERSTITIAL CYSTITIS].**

[Article in Japanese]

*Katayama Y, Nakahara K, Shitamura T, Mukai S, Wakeda H, Yamashita Y, Inoue K, Nose K, Kamoto T. Hinyokika Kyo. 2013 May;59(5):265-9. PMID: 23719132*

This study from the University of Miyazaki, Japan examined the efficacy of acupuncture and moxibustion treatment on eight female patients with refractory interstitial cystitis (IC) who had been treated conservatively with hydrodistension, intravesical instillation of dimethyl sulfoxide, or oral medication. These patients had received hydrodistension on an average of 2.3±1.8 times. Moxa needles were applied to Ciliao in bladder meridian 32 and Xialiao in bladder meridian 34, and electroacupuncture was performed on Zhongliao in bladder meridian 33 at 3 Hz for 20 min once a week. The bladder condition was assessed by the visual analogue scale (VAS) score, the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI), the Interstitial Cystitis Problem Index (ICPI), and the maximum voided volume (MVV). After 3 months, patients who showed a reduction of >2 in their VAS score, reduction of <30% of ICSI and ICPI, and increase of >100 ml MVV were considered responders. There were three responders, and after repeated therapy to maintain these effects, they no longer required hydrodistension. Two responders had no recurrence for 48 months or more. Acupuncture and moxibustion resulted in improvement in 38% of the patients (3/8) with refractory IC, and repeated therapy maintained the therapeutic effects. This therapy is traditional and relatively noninvasive. Although its precise mechanism of action is unclear, this study suggests that

acupuncture and moxibustion treatment may be a complementary and alternative therapeutic option for refractory IC.

#### **BOTULINUM TOXIN TREATMENT FOR BLADDER DYSFUNCTION.**

*Santos-Silva A, da Silva CM, Cruz F. Int J Urol 2013 May 2. doi: 10.1111/iju.12188. [Epub ahead of print]. PMID: 23634720*

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In this review article from Portugal, the authors report that Botulinum toxin A is available under three different protein complexes that are not interchangeable until appropriate comparative studies are undertaken. The best studied for the treatment of urinary incontinence as a result of neurogenic detrusor overactivity and overactive bladder/idiopathic detrusor overactivity is onabotulinum toxin A. This brand is only approved for the treatment of urinary incontinence as a result of neurogenic detrusor overactivity at a dose of 200 U and idiopathic detrusor overactivity at a dose of 100 U. In patients with detrusor overactivity as a result of spinal cord injury or multiple sclerosis, 200 U of onabotulinum toxin A should be injected in 30 different sites above the trigone. It was shown to be highly effective in curing or decreasing urinary symptoms of incontinence, increasing quality of life, increasing bladder capacity and decreasing maximal detrusor pressure. This effect was independent of the concomitant use of oral anticholinergic drugs. Adverse events were mild, mainly urinary tract infections and high postvoid residual requiring clean intermittent catheterization. In patients with overactive bladder/idiopathic detrusor overactivity, 100 U of onabotulinum toxin A should be injected in 20 sites above the trigone. It markedly decreases urinary incontinence and improves quality of life. Frequency and urgency episodes are also decreased. Adverse events are mild, mainly urinary tract infections and urinary retention. The latter occurred in just 5% of the patients. Candidates for onabotulinum toxin A treatment should be warned that the effect of the toxin is transient and that repeated injections will be required to maintain the effect in the long term. There is no evidence that repeated injections will have a decreased efficacy.

#### **BOTULINUM TOXIN-WHAT UROLOGIC USES DOES THE DATA SUPPORT?**

*Seth J, Khan MS, Dasgupta P, Sahai A. Curr Urol Rep. 2013 Apr 27. [Epub ahead of print]. PMID: 23625366*

Botulinum toxin-A (BTX-A) is well established in the management of various aspects of lower urinary tract dysfunction (LUTD). One formulation, OnabotulinumtoxinA has recently been licensed in many parts of the world for use in neurogenic detrusor overactivity (NDO), and in the US for idiopathic overactive bladder (OAB), in patient's refractory to antimuscarinics. This review article from London looks at recent clinical publications that examine the use of BTX-A for the treatment of LUTD with a focus on OAB, detrusor overactivity (DO), benign prostatic hyperplasia (BPH) and painful bladder syndrome/interstitial cystitis (PBS/IC). A literature review was conducted using the PubMed database and studies that were published within the time frame of January 2011 to present were included. Large randomised placebo controlled trials and a pooled analysis of patients with multiple sclerosis/spinal cord injury and NDO has suggested that BTX-A improved urinary incontinence (UI) episodes, urodynamic parameters and QoL in these patients. 200 U of OnabotulinumtoxinA appeared equivalent to 300 U. In patients with OAB, lower doses of 100 U OnabotulinumtoxinA, appear efficacious and with an acceptable adverse event profile. In one large phase III trial, de novo clean intermittent catheterisation rates were 6.1 %. Repeated injections in DO appear efficacious. Results from BPH studies are mixed, and the largest randomised study in this setting has shown significant improvements in a number of parameters for a variety of OnabotulinumtoxinA doses, but none of the doses were statistically better than placebo. Few studies have been conducted in PBS / IC and larger scale randomised placebo controlled trials are required to validate its use in this setting.

### **INTRAVESICAL BOTULINUM TOXIN A INJECTIONS DO NOT BENEFIT PATIENTS WITH ULCER TYPE INTERSTITIAL CYSTITIS.**

*Lee CL, Kuo HC. Pain Physician. 2013 Mar;16(2):109-16. PMID: 23511677*

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A great deal of research is being carried out in Taiwan into botulinum toxin. In this study from Hyalin, Lee et al report that ulcer/lesion type and non-ulcer/lesion type interstitial cystitis/bladder pain syndromes (IC/BPS) are considered different disease entities. Consequently, they suggest that intravesical botulinum toxin A (BoNT-A) treatment outcomes could differ for each entity. The purpose of this study was to evaluate and compare the treatment outcomes of BoNT-A injections for each IC/BPS type. Forty-four consecutive patients with IC/BPS who had failed conventional treatments were prospectively enrolled in this study. Patients were classified as having ulcer (10) or non-ulcer (30) IC/BPS based on their previous cystoscopic findings. The lack of a control arm in this study was a limitation. Repeated intravesical BoNT-A injections provided effective treatment outcomes at the end-point in half of the patients with non-ulcer IC/BPS, but did not benefit any patient with ulcer type IC/BPS. After failure of repeated BoNT-A injections, all 10 patients with ulcer IC/BPS underwent transurethral electrocauterization of their ulcers, which resulted in immediate pain relief. The authors concluded that ulcer type IC/BPS should be treated as a different disease than non-ulcer IC/BPS.

### **REPEATED INTRAVESICAL ONABOTULINUMTOXINA INJECTIONS ARE EFFECTIVE IN TREATMENT OF REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.**

*Kuo HC. Int J Clin Pract. 2013 May;67(5):427-34. doi: 10.1111/ijcp.12113. PMID: 23574103*

Taiwan has been very active in recent years in research into intravesical onabotulinumtoxinA (BoNT-A) injections for treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). The aim of this study by Professor HC Kuo from Hualien, Taiwan was to evaluate the efficacy and safety of repeated intravesical onabotulinumtoxinA (BoNT-A) injections for treatment of IC/BPS. Patients confirmed to have IC/BPS and refractory to conventional treatments were treated with intravesical injections of 100 U of BoNT-A plus hydrodistention every 6 months for up to four times. Primary end-point was 6 months after the fourth BoNT-A injection. Measured parameters included O'Leary-Sant symptom score (OSS) including symptom and problem indexes (ICSI/ICPI), visual analogue score (VAS) for pain, voiding diary variables, urodynamic parameters, maximal bladder capacity (MBC), glomerulation grade, and global response assessment (GRA). Multiple measurements and Wilcoxon rank-sum test were used for comparison between groups. In overall patients, GRA, OSS, ICSI and ICPI scores, VAS, functional bladder capacity (FBC) and cystometric bladder capacity (CBC) all showed significant improvement. Extended study revealed that persistent symptomatic improvement lasted 6-12 months in seven, 13-22 months in six and 23-51 months in six after the fourth BoNT-A injection. Five women who had GRA < 2 were found to have Hunner's ulcer. Lack of control is the main limitation of this study. Professor Kuo concluded from his findings that four repeated intravesical BoNT-A injections were safe and effective for symptom and pain relief and increased bladder capacity for treatment of IC/BPS.

### **MORPHOLOGICAL CHANGES OF BLADDER MUCOSA IN PATIENTS WHO UNDERWENT INSTILLATION WITH COMBINED SODIUM HYALURONIC ACID-CHONDROITIN SULPHATE (IALURIL®).**

*Costantini E, Lazzeri M, Pistoiesi D, Del Zingaro M, Frumenzio E, Boni A, Pietropaolo A, Fragalà E, Porena M. Urol Int. 2013 Mar 13. [Epub ahead of print]. PMID: 23485915*

The purpose of this study from Italy was to investigate what changes are endoscopically evident after glycosaminoglycans (GAGs) therapy by hyaluronic acid (HA) and chondroitin sulphate (CS) (Ialuril®) in female patients with bladder pain syndrome (BPS)/ interstitial cystitis (IC) or recurrent urinary tract infections (rUTIs). Patients and Methods: 21 female patients over 18 years affected by rUTIs or

BPS/IC received intravesical instillation of HA and CS (4 weekly instillations followed by 2 instillations every 2 weeks and 2 instillation monthly). Post-treatment evaluation included cystoscopy and patient assessment of improvement in symptoms and satisfaction on a visual analogue scale (VAS) from 0 to 10. Results: The post-treatment endoscopy showed a positive effect on bladder mucosa morphology. In 2 cases, treatment did not change endoscopic findings and clinical symptoms. In the other patients, when macroscopic features of the bladder mucosa normalized, the clinical picture improved. It was therefore concluded that GAG therapy by HA and CS (laluril) improves the morphology of bladder mucosa in patients with rUTI or BPS/IC.

**MAINTENANCE OF THE RESPONSE TO DIMETHYL SULFOXIDE TREATMENT USING HYPERBARIC OXYGEN IN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: A PROSPECTIVE, RANDOMIZED, COMPARATIVE STUDY.**

*Gallego-Vilar D, García-Fadrique G, Povo-Martin I, Salvador-Marin M, Gallego-Gomez J. Urol Int. 2013 Mar 13. [Epub ahead of print]. PMID: 23485788*

The objective of this study from Spain was to determine the efficacy of hyperbaric oxygen (HBO) therapy in the maintenance of response after the administration of intravesical dimethyl sulfoxide (DMSO). Gallego-Vilar and colleagues conducted an open, prospective, randomized, comparative pilot study with women diagnosed with IC/PBS according to the European Society for the Study of Interstitial Cystitis criteria. In the first phase, DMSO was given to all patients. In the second phase, they used 1:1 randomization and administered HBO to 10 women. The evaluated variables were pain (through a visual analog scale), frequency and urgency of voids, nocturia, and quality of life using the O'Leary-Sant Interstitial Cystitis Score/Problem Index and the King's Health Questionnaire. In the second phase, they measured the length of time that clinical improvement was maintained. Results: The mean age was 47.6 years (SD 18.4). Out of 20 patients, 14 experienced clinical improvement after DMSO in all of the evaluated symptoms ( $p < 0.05$ ; 95% CI). After the second phase, all patients who received HBO had a more substantive and prolonged maintenance of the effects of DMSO. It was concluded that in this study, HBO improved the maintenance of the beneficial effects of DMSO among women with IC/PBS.

**CHANGES IN SEXUAL FUNCTIONING IN WOMEN AFTER NEUROMODULATION FOR VOIDING DYSFUNCTION.**

*Yih JM, Killinger KA, Boura JA, Peters KM. J Sex Med. 013 Feb 27. doi: 10.1111/jsm.12085. [Epub ahead of print]. PMID: 23445354*

Sacral neuromodulation is a well-established treatment for urinary and bowel disorders with potential use for other disorders such as sexual dysfunction. The purpose of this study was to evaluate changes in sexual functioning in women undergoing neuromodulation for voiding symptoms. Patients enrolled in this prospective, observational neuromodulation database study were evaluated. Data were collected from medical records, and patient-completed Female Sexual Function Index (FSFI) and Interstitial Cystitis Symptom-Problem Indices (ICSI-PI) at baseline, 3, 6, and 12 months post-implant. Patients rated overall change in sexual functioning on scaled global response assessments (GRA) at 3, 6, and 12 months post-implant. Women were grouped by baseline FSFI scores: less (score  $< 26$ ) and more sexually functional (score  $\geq 26$ ). Data were analyzed with Pearson's Chi-square or Fisher's Exact test and repeated measures. Of 167 women evaluated, FSFI scores improved overall from preimplant to 12 months. At baseline and each follow-up point, ICSI-PI scores were similar between groups and improved through time. For patients in the FSFI  $< 26$  group there was improvement from baseline to 12-month scores. Improved FSFI domains included desire, orgasm, satisfaction, and pain. Furthermore, of the 74 subjects in this group not sexually active at baseline, 10 became sexually active during follow-up. In the FSFI  $\geq 26$  group there was slight but statistically significant decline in mean scores between baseline and 12 months; however one had

become sexually inactive. A significant decrease was seen in the satisfaction domain. It was concluded that many factors affect sexual functioning in women; however sexual function may improve along with urinary symptoms after neuromodulation.

#### **NERVE STIMULATION FOR CHRONIC PELVIC PAIN AND BLADDER PAIN SYNDROME: A SYSTEMATIC REVIEW.**

*Tirlapur SA, Vlismas A, Ball E, Khan KS. Acta Obstet Gynecol Scand. 2013 May 24. doi: 10.1111/aogs.12184. [Epub ahead of print]. PMID: 23710833*

Chronic pelvic pain (CPP) and bladder pain syndrome (BPS) can have a negative impact on quality of life. Neuromodulation has been suggested as a possible treatment for refractory pain. The aim of this study by Tirlapur and colleagues from London was to assess the effectiveness of tibial and sacral nerve stimulation in the treatment of BPS and CPP. The authors searched until July 2012: The Cochrane Library, EMBASE (1980-2012), Medline (1950-2012), Web of knowledge (1900-2012), LILACS (1982-2012) and SIGLE (1990-2012) with no language restrictions. They manually searched through bibliographies and conference proceedings of the International Continence Society. Randomized and prospective quasi-randomized controlled studies versus sham nerve stimulation treatment or usual care of patients with CPP and BPS who underwent sacral or tibial nerve stimulation were included. Any studies involving transcutaneous stimulation were excluded. The outcome was a cure or improvement in symptoms. Three studies with 169 patients treated with tibial nerve stimulation were included; two for CPP and one for BPS. There were improvements in pain, urinary and quality of life scores. There was no reported data for sacral nerve stimulation. The authors concluded that there is scanty literature reporting variable success of posterior tibial nerve stimulation in improving pain, urinary symptoms and quality of life in CPP and BPS. In view of the dearth of quality literature, a large multi-centred clinical trial investigating the effectiveness of electrical nerve stimulation to treat BPS and CPP along with the cost-analysis of this treatment is recommended.

#### **ON- AND POST-TREATMENT SYMPTOM RELIEF BY REPEATED INSTILLATIONS OF HEPARIN AND ALKALIZED LIDOCAINE IN INTERSTITIAL CYSTITIS.**

*Nomiya A, Naruse T, Niimi A, Nishimatsu H, Kume H, Igawa Y, Homma Y. Int J Urol. 2013 Feb 22. doi: 10.1111/iju.12120. [Epub ahead of print]. PMID: 23432185*

The purpose of this study by Nomiya and colleagues from Tokyo was to examine outcomes of intravesical instillations of heparin and alkalized lidocaine in patients with interstitial cystitis. Patients with interstitial cystitis refractory to conventional therapies were given a solution of 20 000 U heparin, 5 mL 4% lidocaine and 25 mL 7% sodium bicarbonate, intravesically, weekly for 12 weeks consecutively. The treatment was regarded as "effective", when patients rated "slightly improved" or "better" on a seven-graded scale of global response assessment. Other assessment measures included O'Leary and Sant's symptom index and problem index, visual analog scale for pain, and frequency volume chart variables. A total of 32 patients were enrolled in the study. The average age was 63.3 years. All participants had received hydrodistension 2.2 times on average, and fulfilled National Institute of Diabetes and Digestive and Kidney Diseases criteria. The therapy was effective in 60.0% of the patients at the fourth instillation, in 76.7% at the last instillation, and 90.0%, 46.7% and 16.7% at 1, 2 and 6 months after the last instillation, respectively. Most of other assessment measures improved significantly at the fourth instillation and further beyond until the end of therapy. On termination of therapy, the efficacy gradually diminished, yet mostly maintained statistical significance by 2 months post-instillation. No severe adverse events occurred. The authors concluded that a 12-week course of weekly intravesical instillations of heparin combined with alkalized lidocaine is safe and effective in relieving symptoms in interstitial cystitis patients. The effect of the treatment is maintained for 6 months. Further studies are required to optimize the

number of instillations and maintenance intervals in order to maximize the therapeutic potential of simple or combined instillations in the management of interstitial cystitis.

#### **EFFECT OF AMITRIPTYLINE IN TREATMENT INTERSTITIAL CYSTITIS OR BLADDER PAIN SYNDROME ACCORDING TO TWO CRITERIA: DOES ESSIC CRITERIA CHANGE THE RESPONSE RATE?**

Sun Y, Fang Z, Ding Q, Zheng J. *Neurourol Urodyn*. 2013 Jun 6. doi: 10.1002/nau.22407. [Epub ahead of print]. PMID: 23744795

The ESSIC recommended that interstitial cystitis (IC) should be replaced by bladder pain syndrome (BPS), which focused more attention on the painful or discomfort feeling related to bladder and weakened the importance of cystoscopy in diagnosis process. This study by Sun and colleagues from Shanghai, China aimed to explore whether this alteration changed the treatment outcomes of amitriptyline and whether cystoscopy was meaningful for the treatment of this disease. They conducted a retrospective study including 25 IC patients fulfilled the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) criteria and 42 BPS patients diagnosed according to ESSIC criteria. All the patients received amitriptyline with a self-up-titration protocol. They compared the response rates of two groups by a patient reported global response assessment after 3 months and reclassified all the 67 patients according to ESSIC criteria, the response rates of different BPS types were also assessed. They found that there was no significant difference of response rate between IC patients (12/25, 48%) and BPS patients (19/42, 45.2%) according to different criteria. The response rate of BPS type 1 (13/30, 43.3%) was similar to that of type 2 or 3 (18/37, 48.6%). It was therefore concluded that the ESSIC criteria did not decrease the response rate of amitriptyline treatment for BPS patients compared to IC patients with complaint of bladder pain or discomfort. Cystoscopy showed no predictive effect for the treatment outcome of amitriptyline.

#### **ADAPTATION OF THE O'LEARY-SANT AND THE PUF FOR THE DIAGNOSIS OF INTERSTITIAL CYSTITIS FOR THE BRAZILIAN CULTURE.**

[Article in English, Portuguese]

Victal ML, Lopes MH, D'Ancona CA. *Rev Esc Enferm USP*. 2013 Apr;47(2):312-319. PMID: 23743895

The aim of this study was to translate and adapt the instruments known as the O'Leary-Sant and PUF to the Brazilian culture used in the diagnosis of interstitial cystitis. Victal and colleagues followed the methodological steps recommended by the international literature for cultural adaptation. The steps of translation, synthesis of translations and back translation were performed satisfactorily and evaluation the versions of the synthesis by the panel of experts has resulted in some changes, ensuring the equivalence between the original and translated versions. The PUF was pre-tested among 40 subjects and the O'Leary-Sant in a sample of 50 individuals due to the need for adjustments due to the low education population. The translation and adaptation process was successful and the instruments, after some modifications, proved easy to understand and complete quickly. However, this is a study prior to the validation process and will be promoting the use of the instrument in new research to assess its measurement properties.

#### **INTERSTITIAL CYSTITIS: ANOTHER IGG4-RELATED INFLAMMATORY DISEASE?**

Crumley S, Ge Y, Zhou H, Shen SS, Ro JY. *Ann Diagn Pathol*. 2013 May 31. pii: S1092-9134(13)00030-0. doi: 0.1016/j.anndiagpath.2013.03.004. [Epub ahead of print]. PMID: 23732167

Inflammation is thought to play a key role in many IC patients, characteristically with an increase in mast cells within the detrusor muscle of the bladder. Crumley and colleagues observed that some patients with IC had prominent plasma cells in bladder tissue, which elicited our interest in their possible pathogenic role in patients with IC. A total of 44 cases of IC were collected, including 42 bladder biopsies and 2 cystectomies. Patient age ranged from 18 to 92 years (average age of 49.5 years) and included 7 male and 37 female patients. The histology and immunostains for IgG, IgG4 and

tryptase were examined, and the results were correlated with clinical and cystoscopic findings. Four cases showed a significant increase in IgG4-positive plasma cells, with greater than 30 IgG4 plasma cells per high-power field and an IgG4/IgG ratio greater than 0.5. In addition, statistically significant differences were found between IC with IgG4-positive plasma cells vs IgG4-negative cases. The IgG4-positive patients were of older age and had increased severe inflammation and decreased bladder capacity as compared with the IgG4-negative patients. The authors propose that a subset of patients with IC may have an IgG4-related disease, and further study including serum IgG4 measurement is required to better define this relationship.

#### **INCREASED MRNA EXPRESSION OF GENES INVOLVED IN PRONOCICEPTIVE INFLAMMATORY REACTIONS IN BLADDER TISSUE OF INTERSTITIAL CYSTITIS.**

*Homma Y, Nomiya A, Tagaya M, Oyama T, Takagaki K, Nishimatsu H, Igawa Y. J Urol. 2013 May 28. pii: S0022-5347(13)04414-5. doi: 10.1016/j.juro.2013.05.049. [Epub ahead of print]. PMID: 23727186*

In this study from Japan by Homma and colleagues, the mRNA expression of transient receptor potential (TRP) family of channels and acid-sensing ion channel 1 (ASIC1) was assayed in bladder tissue of interstitial cystitis (IC). Bladder biopsies of 1) non-classic IC, 2) non-ulcerative portions of classic IC, 3) ulcerative portions of classic IC, and 4) non-cancerous portions of bladder cancer (control), were placed immediately in ice-cold RNAlater and subjected to real-time reverse-transcription polymerase chain reaction. mRNA expression of TRP channels, ASIC1, nerve growth factor (NGF), chemokine ligand 9 (CXCL9) and uroplakin 3A (UPK3A) was compared with control and symptom severity. Specimens from 50 subjects (non-classic IC, 17; classic IC, 22; control, 11) were analyzed. In non-classic IC, TRPV2 and NGF showed significantly increased expression. In classic IC, non-ulcerative portions demonstrated a significant increase in expression of TRPA1, TRPM2, TRPM8, TRPV1, TRPV2, ASIC1, NGF and CXCL9, and a significant decrease in UPK3A and TRPV4. Ulcerative portions showed similar changes for TRPM2, TRPV1, TRPV2, TRPV4, CXCL9 and UPK3A. Increased expression of TRPM2, first demonstrated in IC tissue, was the most pronounced among TRP family. Symptom measures all correlated with TRPM2 and TRPV2 expression, and partially with other genes. It was concluded by the authors that the study demonstrated increased expression of genes involved in pronociceptive inflammatory reactions in IC, TRPM2 for the first time, and TRPV1, TRPV2, TRPV4, ASIC1, NGF and CXCL9. Different expression pattern suggests distinct pathophysiology for classic and non-classic IC. The genes and their products are potential candidates for biomarkers or novel therapy targets.

#### **THE CENTRAL SENSITIZATION INVENTORY (CSI): ESTABLISHING CLINICALLY SIGNIFICANT VALUES FOR IDENTIFYING CENTRAL SENSITIVITY SYNDROMES IN AN OUTPATIENT CHRONIC PAIN SAMPLE.**

*Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, Gatchel RJ. J Pain. 2013 May;14(5):438-45. doi: 10.1016/j.jpain.2012.11.012. Epub 2013 Mar 13. PMID: 23490634*

Central sensitization (CS) is a proposed physiological phenomenon in which central nervous system neurons become hyperexcitable, resulting in hypersensitivity to both noxious and non-noxious stimuli. The term central sensitivity syndrome (CSS) describes a group of medically indistinct (or nonspecific) disorders, such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, for which CS may be a common etiology. In a previous study, the Central Sensitization Inventory (CSI) was introduced as a screening instrument for clinicians to help identify patients with a CSS. It was found to have high reliability and validity. The present study investigated a cohort of 121 patients who were referred to a multidisciplinary pain centre, which specializes in the assessment and treatment of complex pain and psycho-physiological disorders, including CSSs. A large percentage of patients met clinical criteria for one or more CSSs, and CSI scores were positively correlated with the number of diagnosed CSSs. A receiver operating characteristic analysis determined that a CSI score of 40 out of 100 best distinguished between the CSS patient group and a nonpatient comparison



sample. The CSI is a new self-report screening instrument to help identify patients with CSSs, including fibromyalgia. The present study investigated CSI scores in a heterogeneous pain population with a large percentage of CSSs, and a normative nonclinical sample to determine a clinically relevant cut-off value.

#### **CYCLOPHOSPHAMIDE-INDUCED CYSTITIS REDUCES ASIC CHANNEL, BUT ENHANCES TRPV1 RECEPTOR FUNCTION IN RAT BLADDER SENSORY NEURONS.**

*Dang K, Bielefeldt K, Gebhart GF. J Neurophysiol. 2013 May 1. [Epub ahead of print]. PMID: 23636721*

Using patch-clamp techniques, Dang and colleagues from Iowa, USA studied plasticity of ASIC channel and TRPV1 receptor function in dorsal root ganglia (DRG) neurons retrogradely labelled from the bladder. Saline (control) or cyclophosphamide (CYP) was given intraperitoneally on days 1, 3 and 5. On day 6, lumbosacral (LS, L6-S2) or thoracolumbar (TL, T12-L2) DRG were removed and dissociated. Bladders and bladder DRG neurons from CYP-treated rats showed signs of inflammation (greater myeloperoxidase activity; lower intramuscular wall pH) and increased size (whole cell capacitance), respectively, compared with controls. Most bladder neurons (>90%) responded to both protons and capsaicin. Protons produced multi-phasic currents with distinct kinetics whereas capsaicin always triggered a sustained response. The TRPV1 receptor antagonist A425619 abolished capsaicin-triggered currents and raised the threshold of heat-activated currents. Prolonged exposure to an acidic environment (pH range: 7.2 - 6.6) inhibited proton-evoked currents, potentiated the capsaicin-evoked current and reduced the threshold of heat-activated currents in LS and TL bladder neurons. CYP treatment reduced density, but not kinetics of the multi-phasic currents triggered by pH 5. In contrast, CYP-treatment was associated with an increased current density in response to capsaicin in LS and TL bladder neurons. Correspondingly, heat triggered current at a significantly lower temperature in bladder neurons from CYP-treated rats compared with controls. These results reveal that cystitis differentially affects TRPV1- and ASIC-mediated currents in both bladder sensory pathways. Acidification of the bladder wall during inflammation may contribute to changes in nociceptive transmission mediated through the TRPV1 receptor, suggesting a role for TRPV1 in hypersensitivity associated with cystitis.

#### **IDENTIFICATION OF NOVEL PYRAZOLOQUINAZOLINECARBOXYLATE ANALOGUES TO INHIBIT NERVE GROWTH FACTOR IN VITRO.**

*Eibl JK, Strasser BC, Ross GM. Eur J Pharmacol. 2013 May 15;708(1-3):30-7. doi: 10.1016/j.ejphar.2013.03.029. Epub 2013 Mar 22. PMID: 23528360*

Nerve growth factor (NGF) is known to regulate the development and survival of select populations of neurons via its binding/activation of the TrkA and p75<sup>NTR</sup> receptors. However, in some physiological circumstances NGF dysregulation can result in debilitating pathologies, including diabetic neuropathies, interstitial cystitis and fibromyalgia. Thus, the identification of small molecules which inhibit NGF signalling has significant therapeutic potential. PD 90780, Ro 08-2750, and ALE 0540 are small molecules that have been reported to bind and inhibit NGF activity. Importantly, the docking site of these compounds is hypothesized to occur at the loop I/IV cleft of NGF - a region which is required for efficient and selective binding of this neurotrophin to its receptor(s). Molecular modelling predicts a number of previously reported NGF antagonists (PD 90780, ALE 0540, and Ro 08-2750) share conserved molecular features, and these drug-like small molecules have the ability to bind and modify the molecular topology of NGF. In order to understand the putative mechanism of binding, Eibl and colleagues from Canada synthesized a pyrazoloquinazolinecarboxylate analogue series and tested each compound in an NGF-dependent PC12 cell differentiation assay. In vitro data confirms that the pyrazoloquinazolinecarboxylate analogues functionally inhibit NGF's effects on PC12 cell differentiation. The results of this study provide evidence to refine the docking mode of pyrazoloquinazolinecarboxylate based compounds for the purposes of inhibiting NGF in vitro. In

addition, they identified series analogue PQC 083 ( $IC_{50}=7.0\mu M$ ;  $CI=5.4-10.1\mu M$ ) which displays markedly higher potency than previously described NGF antagonists.

#### **VISCERAL HYPERSENSITIVITY IN FEMALE BUT NOT IN MALE SEROTONIN TRANSPORTER KNOCKOUT RATS.**

Galligan JJ, Patel BA, Schneider SP, Wang H, Zhao H, Novotny M, Bian X, Kabeer R, Fried D, Swain GM. *Neurogastroenterol Motil.* 2013 Jun;25(6):e373-81. doi: 10.1111/nmo.12133. Epub 2013 Apr 17. PMID: 23594365

Visceral hypersensitivity occurs in irritable bowel syndrome (IBS), particularly in women. Serotonin signaling, including reduced serotonin transporter (SERT) expression, may be disrupted in IBS patients. Galligan and colleagues from Michigan State University studied SERT gene knockout (KO) rats to determine if they exhibited sex-related alterations in visceral sensitivity. They measured serotonin in the colonic mucosa using HPLC and amperometric microelectrode techniques. Visceral sensitivity was assessed using the electromyographic visceromotor response (VMR) in response to colorectal balloon distention (CRD). They studied the electrophysiologic properties of colon projecting sensory neurons in vitro using whole-cell recordings. They found that increased colonic extracellular serotonin in female SERT KO rats is associated with visceral hypersensitivity and hyperexcitability of colon projecting sensory neurons. The SERT KO rat is a model for studying interactions between serotonin, sex and visceral sensation.

#### **LOCAL IMMUNE RESPONSE IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS ESSIC TYPE 3C.**

Gamper M, Viereck V, Eberhard J, Binder J, Moll C, Welter J, Moser R. *Int Urogynecol J.* 2013 May 14. [Epub ahead of print]. PMID: 23670165

Bladder pain syndrome/interstitial cystitis (BPS/IC) is identified based on subjective symptoms which lead to heterogeneous patient populations. Previous studies using gene expression arrays for BPS/IC with Hunner's lesions [European Society for the Study of Interstitial Cystitis (ESSIC) type 3C], a subtype of the condition discernible by cystoscopy, have revealed characteristic immune responses and urothelial abnormalities. This current study by Gamper and colleagues from Switzerland aimed to further characterize this subtype using a gene expression panel, hypothesizing that B-cell activation with high levels of urinary antibody concentration would be found. Cold-cup bladder biopsies, catheterized urine and blood were collected from 15 BPS/IC ESSIC type 3C patients, 11 non-inflammatory overactive bladder (OAB) patients and eight healthy controls. Gene expression in biopsies was quantified by real-time quantitative polymerase chain reaction (RT-qPCR), immunohistochemistry was performed on bladder tissue and urinary immunoglobulins G and A were quantified by enzyme-linked immunosorbent assay. Statistical analyses included the Kruskal-Wallis test for non-parametric data and post hoc tests identified differences between groups. High expression of T- and B-cell markers (CTLA4, CD20, CD79A, IGH@), low expression of urothelial markers (KRT20, UPK1B, UPK3A), focal lymphoid aggregates in the submucosa and high immunoglobulin concentration in urine were found exclusively in BPS/IC ESSIC type 3C patients. Results for OAB were in intermediate ranges between the other two groups and UPK1B even reached significantly lower expression when compared to healthy controls. The authors concluded from their findings that BPS/IC ESSIC type 3C is characterized by a local adaptive immune response with elevated urinary antibody concentrations. Quantification of urinary immunoglobulin levels could be used for a non-invasive diagnosis of BPS/IC ESSIC type 3C.

#### **REPEATED VARIATE STRESS (RVS) IN MALE RATS INDUCES INCREASED VOIDING FREQUENCY, SOMATIC SENSITIVITY AND URINARY BLADDER NGF EXPRESSION.**

Merrill L, Malley SE, Vizzard MA. *Am J Physiol Regul Integr Comp Physiol.* 2013 May 8. [Epub ahead of print]. PMID: 23657640

Merrill and colleagues from Vermont note that stress exacerbates symptoms of functional lower urinary tract disorders including interstitial cystitis (IC)/bladder pain syndrome (BPS) and overactive bladder (OAB) in humans, but mechanisms contributing to symptom worsening are unknown. These studies address stress-induced changes in the structure and function of the micturition reflex using an animal model of stress in male rats. Rats were exposed to 7 days of repeated variate stress (RVS). Target organ (urinary bladder, thymus, adrenal gland) tissues were collected and weighed following RVS. Evans blue (EB) concentration and histamine, MPO, NGF, BDNF, and CXCL12 protein content (ELISA) were measured in the urinary bladder, and somatic sensitivity of the hindpaw and pelvic regions was determined following RVS. Bladder function was evaluated using continuous, open outlet intravesical infusion of saline in conscious rats. Increases in body weight gain were significantly ( $p \leq 0.01$ ) attenuated by day 5 of RVS and adrenal weight was significantly ( $p \leq 0.05$ ) increased. Histamine, MPO, NGF, and CXCL12 protein expression was significantly ( $p \leq 0.01$ ) increased in the urinary bladder following RVS. Somatic sensitivity of the hindpaw and pelvic regions was significantly ( $p \leq 0.01$ ) increased at all monofilament forces tested (0.1 to 4 g) following RVS. Intercontraction interval, infused volume, and void volume were significantly ( $p \leq 0.01$ ) decreased following RVS. According to the authors, these studies demonstrate increased voiding frequency, histamine, MPO, NGF and CXCL12 bladder content and somatic sensitivity after RVS suggesting an inflammatory component to stress-induced changes in bladder function and somatic sensitivity.

#### **URGE PERCEPTION INDEX OF BLADDER HYPERSENSITIVITY.**

*Fujihara A, Ukimura O, Honjo H, Iwata T, Ueda T, Matsugasumi T, Kamoi K, Okihara K, Kawauchi A, Miki T. J Urol. 2013 May;189(5):1797-803. doi: 10.1016/j.juro.2012.11.117. Epub 2012 Nov 28. PMID: 23201494*

By analyzing bladder diaries with patient self-reported urinary perception grades, Fujihara and colleagues from Kyoto developed the urge perception index, a quantitative measure of bladder hypersensitivity. They evaluated the impact of the urge perception index on the definition of overactive bladder severity. They retrospectively evaluated the records of 69 female patients who visited their outpatient clinic with storage symptoms. Patients were asked to complete the overactive bladder symptom score and a 3-day bladder diary with self-reported grading of urinary perception on a range of 1 to 5 per void. Overactive bladder was diagnosed in 43 patients and nonoveractive bladder was diagnosed in 26. The urge perception index was defined as voided volume divided by the urinary perception grade at each void. They analysed 1,578 reported voids. According to the urinary perception grade, urge perception index values for overactive bladder were significantly lower than those for nonoveractive bladder. The average  $\pm$  SD urge perception index in 3-day bladder diaries was lower in overactive than in nonoveractive bladder cases. The most severe (lowest) single urge perception index value during the 3 days was significantly lower in patients with overactive than with nonoveractive bladder. There were negative linear correlations of the urge perception index with total overactive bladder symptom scores and with an urgency symptom score. They concluded from their findings that the urge perception index, an integrated parameter of patient reported bladder perception and voided volume, could be promising to quantify the severity of overactive bladder or bladder hypersensitivity by bladder diary analysis.

#### **CONFORMATIONAL DETERMINANTS OF THE ACTIVITY OF ANTIPROLIFERATIVE FACTOR GLYCOPEPTIDE.**

*Mallajosyula SS, Adams KM, Barchi JJ, Mackerell AD. J Chem Inf Model. 2013 May 24;53(5):1127-37. doi: 10.1021/ci400147s. Epub 2013 May 15. PMID: 23627670*

The antiproliferative factor (APF) involved in interstitial cystitis is a glycosylated nonapeptide (TVPAVVVA) containing a sialylated core 1  $\alpha$ -O-disaccharide linked to the N-terminal threonine. The chemical structure of APF was deduced using spectroscopic techniques and confirmed using total

synthesis. The synthetic APF provided a platform to study amino acid modifications and their effect on APF activity, based on which a structure-activity relationship (SAR) for APF activity was previously proposed. However, this SAR model could not explain the change in activity associated with minor alterations in the peptide sequence. Presented is computational analysis of 14 APF derivatives to identify structural trends from which a more detailed SAR is obtained. The APF activity is found to be dictated by the close interplay between carbohydrate-peptide and peptide-peptide interactions. The former involves hydrogen bond and hydrophobic interactions, and the latter is dominated by hydrophobic interactions. The highly flexible hydrophobic peptide adopts collapsed conformations separated by low energy barriers. APF activity correlates with hydrophobic clustering associated with amino acids 4A, 6V, and 8V. Peptide conformations are highly sensitive to single point mutations, which explain the experimental trends. The presented SAR will act as a guide for lead optimization of more potent APF analogues of potential therapeutic utility.

#### **NITRIC OXIDE AS A MARKER FOR EVALUATION OF TREATMENT EFFECT OF CYCLOSPORINE A IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS TYPE 3C.**

*Ehrén I, Hallén Grufman K, Vrba M, Sundelin R, Lafolie P. Scand J Urol. 2013 Apr 22. [Epub ahead of print]. PMID: 23600529*

This study evaluated whether luminal nitric oxide (NO) could be used as a marker for evaluation of therapeutic outcome in BPS/IC type 3C treated with the immunosuppressive agent cyclosporine A (CsA). Ten patients with BPS/IC type 3C were given CsA for 16 weeks, initially at 3 mg/kg/day, and after 12 weeks the dose was scaled down. Formation of NO was measured in the urinary bladder with a silicone catheter, and symptom and bother score related to the disease were evaluated with the Interstitial Cystitis Symptom and Problem Index, every second week. All patients had elevated NO levels in the bladder initially and NO levels decreased during treatment with CsA. When the dose of CsA was lowered NO formation increased and after 2 weeks without medication, the NO formation was the same as before the study began. The results indicate that measurement of NO is a tool for evaluating the response to anti-inflammatory treatment in patients with BPS/IC type 3C. NO could serve as a marker for assessing the activity of the inflammation.

#### **EXPRESSION AND FUNCTION OF CCL2/CCR2 IN RAT MICTURITION REFLEXES AND SOMATIC SENSITIVITY WITH URINARY BLADDER INFLAMMATION.**

*Arms L, Girard BM, Malley SE, Vizzard MA. Am J Physiol Renal Physiol. 2013 Apr 17. [Epub ahead of print]. PMID: 23594826*

Chemokines are pro-inflammatory mediators of the immune response and there is growing evidence for chemokine/receptor signalling involvement in nociception. Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a chronic pain syndrome characterized by pain, pressure or discomfort perceived to be bladder related with at least one urinary symptom. Arms and colleagues from Vermont have explored the expression and functional roles of CCL2 (monocyte chemoattractant protein-1) and its high-affinity receptor, CCR2, in micturition reflex function and somatic sensitivity in rats with urinary bladder inflammation induced by cyclophosphamide (CYP) treatment of varying duration (4 h, 48 h, chronic). Real-time qRT-PCR, ELISAs and immunohistochemistry demonstrated significant ( $p \leq 0.01$ ) increases in CCL2 and CCR2 expression in the urothelium and in Fastblue-labelled bladder afferent neurons in lumbosacral dorsal root ganglia with CYP-induced cystitis. Intravesical infusion of RS504393 (5  $\mu$ M), a specific CCR2 antagonist, reduced voiding frequency and increased bladder capacity and void volume in rats with CYP-induced cystitis (4 h) as determined with open outlet, conscious cystometry. In addition, CCR2 blockade, at the level of the urinary bladder, reduced referred somatic sensitivity of the hindpaw and pelvic region in rats with CYP treatment as determined with von Frey filament testing. The authors provide evidence of functional roles for CCL2/CCR2 signalling at the level of the urinary bladder in reducing voiding frequency and somatic

sensitivity following CYP-induced cystitis (4 h). These studies suggest that chemokines/receptors may be novel targets with therapeutic potential in the context of urinary bladder inflammation.

## CHRONIC PAIN

### **STRUCTURAL BRAIN ANOMALIES AND CHRONIC PAIN: A QUANTITATIVE META-ANALYSIS OF GRAY MATTER VOLUME.**

*Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, Williams DA, Schmidt-Wilcke T, Farrell MJ, Eickhoff SB, Robin DA. J Pain. 2013 May 16. pii: S1526-5900(13)00905-X. doi: 10.1016/j.jpain.2013.03.001. [Epub ahead of print] PMID: 23685185*

The diversity of chronic pain syndromes and the methods employed to study them make integrating experimental findings challenging, these authors report. This very interesting study by Smallwood and colleagues from San Antonio performed coordinate-based meta-analyses using voxel-based morphometry imaging results to examine gray matter volume (GMV) differences between chronic pain patients and healthy controls. There were 12 clusters where GMV was decreased in patients compared with controls, including many regions thought to be part of the "pain matrix" of regions involved in pain perception, but also including many other regions that are not commonly regarded as pain-processing areas. The right hippocampus and parahippocampal gyrus were the only regions noted to have increased GMV in patients. Functional characterizations were implemented using the BrainMap database to determine which behavioural domains were significantly represented in these regions. The most common behavioural domains associated with these regions were cognitive, affective, and perceptual domains. Because many of these regions are not classically connected with pain and because there was such significance in functionality outside of perception, it is proposed that many of these regions are related to the constellation of comorbidities of chronic pain, such as fatigue and cognitive and emotional impairments. Further research into the mechanisms of GMV changes could provide a perspective on these findings. Quantitative meta-analyses revealed structural differences between brains of individuals with chronic pain and healthy controls. These differences may be related to comorbidities of chronic pain.

### **THE PREVALENCE OF WIDESPREAD CENTRAL HYPERSENSITIVITY IN CHRONIC PAIN PATIENTS.**

*Schliessbach J, Siegenthaler A, Streitberger K, Eichenberger U, Nüesch E, Jüni P, Arendt-Nielsen L, Curatolo M. Eur J Pain. 2013 May 23:1-20. doi: 10.1002/j.1532-2149.2013.00332.x. [Epub ahead of print]. PMID: 23703952*

Chronic pain is associated with generalized hypersensitivity and impaired endogenous pain modulation (conditioned pain modulation; CPM). Despite extensive research, their prevalence in chronic pain patients is unknown. This study from Switzerland investigated the prevalence and potential determinants of widespread central hypersensitivity and described the distribution of CPM in chronic pain patients. Schliessbach and colleagues examined 464 consecutive chronic pain patients for generalized hypersensitivity and CPM using pressure algometry at the second toe and cold pressor test. Potential determinants of generalized central hypersensitivity were studied using uni- and multivariate regression analyses. Prevalence of generalized central hypersensitivity was calculated for the 5th, 10th and 25th percentile of normative values for pressure algometry obtained by a previous large study on healthy volunteers. CPM was addressed on a descriptive basis, since normative values are not available. Depending on the percentile of normative values considered, generalized central hypersensitivity affected 17.5-35.3% of patients. 23.7% of patients showed no increase in pressure pain threshold after cold pressor test. Generalized central hypersensitivity was more frequent and CPM less effective in women than in men. Unclearly classifiable pain syndromes showed higher frequencies of generalized central hypersensitivity than other pain syndromes. It was concluded that although prevalent in chronic pain, generalized central hypersensitivity is not present

in every patient. An individual assessment is therefore required in order to detect altered pain processing. The broad basic knowledge about central hypersensitivity now needs to be translated into concrete clinical consequences, so that patients can be offered an individually tailored mechanism-based treatment.

## **ABDOMINAL PAIN, IBS**

### **ABDOMINAL PAIN IS ASSOCIATED WITH ANXIETY AND DEPRESSION SCORES IN A SAMPLE OF THE GENERAL ADULT POPULATION WITH NO SIGNS OF ORGANIC GASTROINTESTINAL DISEASE.**

*Walter SA, Jones MP, Talley NJ, Kjellström L, Nyhlin H, Andreasson AN, Agréus L. Neurogastroenterol Motil. 2013 May 21. doi: 10.1111/nmo.12155. [Epub ahead of print]. PMID: 23692044*

Abdominal pain is common in the community, but only a subset meet diagnostic criteria for irritable bowel syndrome (IBS). Although anxiety and depression have been linked to IBS, the role of mood disturbances in the remainder with symptoms remains unclear. In this study from Sweden, Walter and colleagues aimed to study the associations between abdominal pain, anxiety, depression, and quality of life in the general population who were free of organic colonic disease by colonoscopy.

Two hundred and seventy-two randomly selected subjects from the general population, mean age 54 years (27-71), were clinically evaluated, had a colonoscopy and laboratory investigations to exclude organic gastrointestinal (GI) disease. All subjects completed GI symptom diaries for 1 week, the Rome II modular questionnaire, the Hospital Anxiety and Depression Scale, and Short Form 36. Twenty-two subjects were excluded due to organic disease; 1532 daily symptom records were available for analysis in the remainder. Thirty-four percent recorded at least one episode of abdominal pain on the diary. Twelve percent fulfilled Rome II criteria for IBS. Both anxiety and depression scores were higher in subjects who reported abdominal pain vs those who did not. Anxiety and depression scores independently from IBS diagnosis (Rome II) predicted pain reporting and also correlated positively with pain burden. Quality of life scores were generally lower in subjects with abdominal pain. It was concluded that anxiety and depression are linked to functional abdominal pain, not only in subjects with IBS but also in otherwise healthy people with milder, subtle GI symptoms.

### **MUCOSAL MAST CELL COUNT IS ASSOCIATED WITH INTESTINAL PERMEABILITY IN PATIENTS WITH DIARRHEA PREDOMINANT IRRITABLE BOWEL SYNDROME.**

*Lee H, Park JH, Park DI, Kim HJ, Cho YK, Sohn C, Jeon WK, Kim BI, Chae SW. J Neurogastroenterol Motil. 2013 Apr;19(2):244-50. doi: 10.5056/jnm.2013.19.2.244. Epub 2013 Apr 16. PMID: 23667756*

Although mucosal mast cell tryptase is known to significantly increase intestinal permeability, the relationship between mucosal mast cells and intestinal permeability remains unclear. The objective of this study by Lee and colleagues from Seoul, Korea was to evaluate the correlation among intestinal permeability, tryptase activity and mucosal mast cell count. Rectal biopsies from 16 patients with diarrhoea-predominant irritable bowel syndrome (IBS-D) and 7 normal subjects were assessed for tryptase activity and macromolecular permeability using horseradish peroxidase in Ussing chambers. In addition, mucosal mast cell levels were immunohistochemically quantified via image analysis. Rectal biopsy of tissues from IBS-D patients showed significantly increased permeability compared with those from normal controls. Tryptase activity was also substantially higher in rectal biopsy samples from IBS-D patients than those from normal controls. Mucosal mast cell counts were not significantly different between the 2 groups. However, correlation analysis revealed that only mucosal mast cell count was significantly correlated with intestinal permeability in IBS-D patients. The authors suggest that this study demonstrates a positive correlation between the number of mucosal mast cells and intestinal permeability, suggesting that mucosal mast cells play an important role for increased intestinal permeability in patients with IBS-D.

## FIBROMYALGIA

### **COGNITIVE IMPAIRMENT IN FIBROMYALGIA.**

*Bertolucci PH, de Oliveira FF. Curr Pain Headache Rep. 2013 Jul;17(7):344. PMID: 23709236*

Bertolucci and De Oliveira from Sao Paulo, Brazil report that cognitive and behavioral impairments are core manifestations of fibromyalgia and may be more disabling than pain itself. Involvement of the central nervous system is ascertained by the fact that frontoparietal and limbic cortices are often functionally and structurally affected along the course of this disease. Even though neuroimaging has brought some experimental evidence to support such network disruption, there are currently no clinically effective biomarkers that detect and quantify cognitive and behavioral disturbances in fibromyalgia; thus, traditional scales and tests of neuropsychiatric assessment remain the most important diagnostic tools. This review addresses the most common cognitive and behavioral impairments in people with fibromyalgia, while explaining their pathophysiological basis and currently available therapeutic options.

## CHRONIC PELVIC PAIN

### **ASSOCIATION BETWEEN CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME AND ANXIETY DISORDER: A POPULATION-BASED STUDY.**

*Chung SD, Lin HC. PLoS One. 2013 May 15;8(5):e64630. doi: 10.1371/journal.pone.0064630. Print 2013. PMID: 23691256*

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This case-control study from Taipei, Taiwan utilized a population-based dataset to examine the association of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) with prior anxiety disorder (AD) by comparing the risk of prior AD between subjects with CP/CPPS and matched controls in Taiwan. Chung and colleagues used data sourced from the Taiwan Longitudinal Health Insurance Database. The cases comprised 8,088 subjects with CP/CPPS and 24,264 randomly matched subjects as controls. They used a conditional logistic regression to calculate the odds ratio (OR) for having been previously diagnosed with AD between subjects with and without CP/CPPS. Of the 24,264 sampled subjects, 2309 (7.1%) had received an AD diagnosis before the index date; AD was found in 930 (11.5%) cases and 1379 (5.7%) controls. The conditional logistic regression analysis revealed that compared to controls, the OR for prior AD among cases was 2.10 after adjusting for diabetes, hypertension, hyperlipidemia, and sexually transmitted diseases. Our results show that CP/CPPS was consistently and significantly associated with prior AD in all age groups (18~39, 40~59, and >59 years). In particular, subjects aged 40~59 years had the highest adjusted OR (of 2.53) for prior AD among cases compared to controls. They concluded that CP/CPPS is associated with previously diagnosed AD. Urologists should be alert for the association between CP/CPPS and AD in subjects suffering from AD.

### **THE 2013 EAU GUIDELINES ON CHRONIC PELVIC PAIN: IS MANAGEMENT OF CHRONIC PELVIC PAIN A HABIT, A PHILOSOPHY, OR A SCIENCE? 10 YEARS OF DEVELOPMENT.**

*Engeler DS, Baranowski AP, Dinis-Oliveira P, Elneil S, Hughes J, Messelink EJ, van Ophoven A, Williams AC. Eur Urol. 2013 Apr 28. pii: S0302-2838(13)00420-X. doi: 10.1016/j.eururo.2013.04.035. [Epub ahead of print]. PMID: 23684447*

Progress in the science of pain has led pain specialists to move away from an organ-centred understanding of pain located in the pelvis to an understanding based on the mechanism of pain and integrating, as far as possible, psychological, social, and sexual dimensions of the problem. This change is reflected in all areas, from taxonomy through treatment. However, deciding what is adequate investigation to rule out treatable disease before moving to this way of engaging with the

patient experiencing pain is a complex process, informed by pain expertise as much as by organ-based medical knowledge. The purpose of this paper is to summarise the evolving changes in the management of patients with chronic pelvic pain by referring to the 2012 version of the European Association of Urology (EAU) guidelines on chronic pelvic pain. The working panel highlights some of the most important aspects of the management of patients with chronic pelvic pain emerging in recent years in the context of the EAU guidelines on chronic pelvic pain. The guidelines were completely updated in 2012 based on a systematic review of the literature from online databases from 1995 to 2011. According to this review, levels of evidence and grades of recommendation were added to the text. A full version of the guidelines is available at the EAU office or Web site ([www.uroweb.org](http://www.uroweb.org)). The previously mentioned issues are explored in this paper, which refers throughout to dilemmas for the physician and treatment team as well as to the need to inform and engage the patient in a collaborative empirical approach to pain relief and rehabilitation. These issues are exemplified in two case histories. Chronic pelvic pain persisting after appropriate treatment requires a different approach focusing on pain. This approach integrates the medical, psychosocial, and sexual elements of care to engage the patient in a collaborative journey towards self-management.

#### **MALE CHRONIC PELVIC PAIN SYNDROME AND THE ROLE OF INTERDISCIPLINARY PAIN MANAGEMENT.**

*Baranowski AP, Mandeville AL, Edwards S, Brook S, Cambitzi J, Cohen M. World J Urol. 2013 May 9. [Epub ahead of print]. PMID: 23657353*

This paper is a team collaboration which aims to describe the multidisciplinary chronic pelvic pain (CPP) service for men in a major London teaching hospital. Evidence from the European Association for Urology Guidelines and the small pool of relevant psychological literature is reviewed as well as results from this team's own pelvic pain programme (LINK) in association with a description of the programme. Treatment targets for men with CPP are outlined. The roles of the consultant in pain management, clinical nurse specialist, clinical psychologist and specialist physiotherapist in delivering treatment are described. This includes the journey from initial consultation through treatment options. Finally, they describe our pelvic pain programme (LINK) which aims to deliver an effective multidisciplinary intervention via single sex groups. This programme links all significant treatment dimensions as well as connecting groups of patients to reduce their sense of isolation. Evidence is presented from the formal evaluation of the programme.

#### **VULVODYNIA**

#### **LATENT CLASS ANALYSIS OF COMORBIDITY PATTERNS AMONG WOMEN WITH GENERALIZED AND LOCALIZED VULVODYNIA: PRELIMINARY FINDINGS.**

*Nguyen RH, Veasley C, Smolenski D. J Pain Res. 2013 Apr 18;6:303-9. doi: 10.2147/JPR.S42940. Print 2013. PMID: 23637555*

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The pattern and extent of clustering of comorbid pain conditions with vulvodynia is largely unknown. However, elucidating such patterns may improve our understanding of the underlying mechanisms involved in these common causes of chronic pain. In this interesting study, Nguyen and colleagues from Minneapolis sought to describe the pattern of comorbid pain clustering in a population-based sample of women with diagnosed vulvodynia. A total of 1457 women with diagnosed vulvodynia self-reported their type of vulvar pain as localized, generalized, or both. Respondents were also surveyed about the presence of comorbid pain conditions, including temporomandibular joint and muscle disorders, interstitial cystitis, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, endometriosis, and chronic headache. Age-adjusted latent class analysis modelled extant



patterns of comorbidity by vulvar pain type, and a multigroup model was used to test for the equality of comorbidity patterns using a comparison of prevalence. A two-class model (no/single comorbidity versus multiple comorbidities) had the best fit in individual and multigroup models. For the no/single comorbidity class, the posterior probability prevalence of item endorsement ranged from 0.9% to 24.4%, indicating a low probability of presence. Conversely, the multiple comorbidity class showed that at least two comorbid conditions were likely to be endorsed by at least 50% of women in that class, and irritable bowel syndrome and fibromyalgia were the most common comorbidities regardless of type of vulvar pain. Prevalence of the multiple comorbidity class differed by type of vulvar pain: both (37.6% prevalence, referent), generalized (21.6% prevalence, adjusted odds ratio 0.41, 95% confidence interval 0.27-0.61), or localized (12.5% prevalence, adjusted odds ratio 0.31, 95% confidence interval 0.21-0.47). The authors concluded that this novel work provides insight into potential shared mechanisms of vulvodynia by describing that a prominent comorbidity pattern involves having both irritable bowel syndrome and fibromyalgia. In addition, the prevalence of a multiple comorbidity class pattern increases with increasing severity of vulvar pain.

#### **VULVODYNIA AND FUNGAL ASSOCIATION: A PRELIMINARY REPORT.**

*Ventolini G, Gygax SE, Adelson ME, Cool DR. Med Hypotheses. 2013 May 23. pii: S0306-9877(13)00224-7. doi: 10.1016/j.mehy.2013.04.043. [Epub ahead of print]. PMID: 23707510*

Vulvodynia (vulvar pain syndrome) is a chronic multifactorial disease affecting almost 13million women in the USA and can lead to morbidity and a reduced quality of life. Ventolini and colleagues hypothesize that an initial microbiological insult in the vagina causes modifications in the biological vaginal milieu and/or an alteration on the lactobacilli flora. The vaginal milieu responds to the insult by developing an inflammatory reaction with abnormal cytokine production. These hypotheses were tested quantifying vaginal lactobacillus and cytokines, in patients with vulvodynia compared to matched healthy controls. Their preliminary data suggest a vaginal flora alteration and an immunological response involving *Candida* in patients with vulvodynia. Ongoing studies will assist them to clarify these findings.

#### **SUCCESSFUL THERAPY OF VULVODYNIA WITH LOCAL ANESTHETICS: A CASE REPORT.**

*Weinschenk S, Brocker K, Hotz L, Strowitzki T, Joos S. Forsch Komplementmed. 2013;20(2):138-43. doi: 10.1159/000350023. Epub 2013 Apr 15. PMID: 23636033*

Summary Background: Vulvodynia often occurs with unexplained vulvar pain and hyperesthesia, sexual dysfunction, and psychological disability, lacking an organic or microbiological substrate. In this case report from Germany, a 25-year-old woman with generalized, unprovoked vulvodynia for 12 years was treated repeatedly with procaine 1% for 14 sessions after she had previously had numerous unsatisfying multidisciplinary treatments. The authors observed a decrease in pain scores on the visual analogue scale (VAS) from initially 8-9 to presently 0-2. Injection sites were: Head's zones and trigger points of the lower abdomen, regional hypogastric ganglia, bilateral maxillary sinus, and scars of the lower jaw. No major adverse events were observed. Injections to remote sites improved symptoms more strongly than local or regional therapy. After a 3-year follow-up the patient is free of symptoms. Conclusion: Therapy with local anesthetics (TLA, neural therapy) can be a useful additional therapy in complicated cases of vulvodynia. Further studies on the underlying mechanism of injections into remote foci (interference field, stoerfeld) and the effectiveness of TLA in chronic pain syndromes should be performed.

#### **AUGMENTED CENTRAL PAIN PROCESSING IN VULVODYNIA.**

*Hampson JP, Reed BD, Clauw DJ, Bhavsar R, Gracely RH, Haefner HK, Harris RE. J Pain. 2013 Apr 8. pii: S1526-5900(13)00805-5. doi: 10.1016/j.jpain.2013.01.767. [Epub ahead of print] PMID: 23578957*

Vulvodynia (VVD) is a chronic pain disorder wherein women display sensitivity to evoked stimuli at the vulva and/or spontaneous vulvar pain. Hampson and colleagues report their previous work suggests generalized hyperalgesia in this population; however, little is known about central neurobiological factors that may influence pain in VVD. Here they investigated local (vulvar) and remote (thumb) pressure-evoked pain processing in 24 VVD patients compared to 13 age-matched, pain-free healthy controls (HCs). As a positive control they also examined thumb pressure pain in 24 fibromyalgia patients. The VVD and fibromyalgia patients displayed overlapping insular brain activations that were greater than HCs in response to thumb stimulation. Compared to HCs, VVD participants displayed greater levels of activation during thumb stimulation within the insula, dorsal midcingulate, posterior cingulate, and thalamus. Significant differences between VVD subgroups (primary versus secondary and provoked versus unprovoked) were seen within the posterior cingulate with thumb stimulation and within the precuneus region with vulvar stimulation (provoked versus unprovoked only). The augmented brain activation in VVD patients in response to a stimulus remote from the vulva suggests central neural pathology in this disorder. Moreover, differing central activity between VVD subgroups suggests heterogeneous pathologies within this diagnosis. The presence of augmented brain responses to pressure stimuli remote from the vulva was observed in vulvodynia patients. These findings may guide treatment decisions for better response, as brain mechanisms may be a factor in some VVD patients.

## ENDOMETRIOSIS

### **PREVALENCE OF PAIN SYNDROMES, MOOD CONDITIONS, AND ASTHMA IN ADOLESCENTS AND YOUNG WOMEN WITH ENDOMETRIOSIS.**

Smorgick N, Marsh CA, As-Sanie S, Smith YR, Quint EH. *J Pediatr Adolesc Gynecol.* 2013

Adult women with endometriosis are often diagnosed with comorbid pain, mood, and autoimmune conditions. This study (retrospective review of medical records) from Ann Arbor, Michigan aims to describe the occurrence of pain syndromes, mood conditions, and asthma in adolescents and young women with endometriosis evaluated at their medical centre. Participants were 138 adolescents/young women, less than age 24 years at the time of their initial visit at the medical centre, whose surgical diagnosis of endometriosis was made at this institution or by outside institutions by the age of 21. Main outside measures were: Prevalence of comorbid pain syndromes (defined as interstitial cystitis, irritable bowel syndrome, chronic headaches, chronic low back pain, vulvodynia, fibromyalgia, temporomandibular joint disease, and chronic fatigue syndrome), mood conditions (defined as depression and anxiety), and asthma. Comorbid pain syndromes were found in 77 (56%) women, mood conditions in 66 (48%) women, and asthma in 31 (26%) women. Comparing endometriosis patients with and without comorbid pain syndromes, no differences were found in age at time of diagnosis, endometriosis symptoms, and endometriosis stage. Patients with comorbid pain syndromes were more likely to report mood conditions and smoking, underwent more surgeries for endometriosis, and were more likely to undergo appendectomy or cholecystectomy. It was concluded that comorbid pain syndromes, mood conditions and asthma are common in adolescents and young women with endometriosis.

### **THE 'EVIL TWIN SYNDROME' IN CHRONIC PELVIC PAIN: A SYSTEMATIC REVIEW OF PREVALENCE STUDIES OF BLADDER PAIN SYNDROME AND ENDOMETRIOSIS.**

Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS. *Int J Surg* 2013;11(3):233-7. doi: 10.1016/j.ijssu.2013.02.003. Epub 2013 Feb 15. PMID: 23419614

Chronic pelvic pain (CPP) may be due to bladder pain syndrome (BPS) or the co-existence of BPS and endometriosis, known as the 'evil twins syndrome'. The purpose of this study from London was to estimate the prevalence of BPS and the co-existence of BPS and endometriosis in women with CPP.

Nine studies were included with 1016 patients with CPP. Study quality and diagnostic assessment varied. The mean prevalence of BPS was 61%. The mean prevalence of endometriosis was 70% and co-existing BPS and endometriosis was 48%. It was concluded that almost two thirds of women presenting with CPP have BPS. Large variations in prevalence may be due to variable study selection and quality. Clinicians need to actively investigate patients for BPS, a condition that appears to co-exist with endometriosis.

## APNEA

### **OBSTRUCTIVE SLEEP APNEA INCREASES THE RISK OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A POPULATION-BASED MATCHED-COHORT STUDY.**

*Chung SD, Lin CC, Liu SP, Lin HC. NeuroUrol Urodyn. 2013 Mar 28. doi: 10.1002/nau.22401. [Epub ahead of print]. PMID: 23553652*

Previous studies indicated a possible association between bladder pain syndrome/interstitial cystitis (BPS/IC) and sleep disorders including sleep abnormalities with delayed onset of sleep, waking up before needed, and snoring. Nevertheless, no previous study has reported the association between obstructive sleep apnea (OSA) and BPS/IC. In this retrospective cohort study, Chung and colleagues from Taipei, Taiwan examined the risk of BPS/IC among subjects with OSA during a 3-year follow-up in Taiwan using a population-based dataset. This study comprised 2,940 study subjects with OSA, and 29,400 randomly selected comparison subjects. The authors individually followed-up each sampled subject (n = 32,340) for a 3-year period to identify those subjects who subsequently received a diagnosis of BPS/IC. A Cox proportional hazards regression model was constructed to estimate the risk of subsequent BPS/IC following a diagnosis of OSA. Incidences of BPS/IC during the 3-year follow-up period were 13.61 and 3.60 for subjects with and those without OSA, respectively. After adjusting for diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraines, sicca syndrome, allergies, endometriosis, asthma, tobacco use disorder, and alcohol abuse, the stratified Cox proportional hazards regressions revealed that the hazard ratio for BPS/IC among subjects with OSA was 3.71 that of comparison subjects. The authors concluded that this study provides epidemiological evidence of a link between OSA and a subsequent BPS/IC diagnosis. They suggest that clinical practitioners treating subjects with OSA be alert to urinary complaints in this population.

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