

# International Painful Bladder Foundation

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

## IPBF e-Newsletter and Research Update

Issue 32, February 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 syndrome, chronic pelvic pain and associated disorders.*

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

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## MEETING REVIEWS

### ESSIC BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A NEW INSIGHT INTO A PUZZLE, HELD 17 NOVEMBER 2012 IN ROME WAS A GREAT SUCCESS

Invited leading world experts in the field of Interstitial Cystitis / BPS met in Rome for a global consultation and conference, organized by ESSIC, the *International Society for the Study of Bladder Pain Syndrome* ([www.essic.org](http://www.essic.org)), to compare views and insights into nomenclature, definitions, criteria, research and therapies. On November 17, an open symposium for doctors and specialists was organised at which these world experts presented an overview of this disease in terms of diagnosis and therapy. The symposium was truly a great success and many thanks are due to Professor Mauro Cervigni and also especially Serena Bartezzi and the Italian IC patient organisation AICI for their hard work in organising this unique meeting. Discussions on definitions and nomenclature are continuing, in preparation for the joint ICICJ 3/ESSIC meeting in Kyoto in March. Further information will be published in due course.

#### **REVIEW OF UROGENITAL PAIN MEETING, HELD ON FRIDAY 18 JANUARY 2013 IN LONDON**

A meeting on Urogenital Pain was held on Friday 18 January 2013 at the Royal Society of Medicine in London. The purpose of this meeting, organised by urogynaecologist and uro-neurologist Sohier Elneil, MD, was to provide an overview of urogenital pain and how to manage this highly complex group of patients. It was aimed at doctors of different disciplines, nurses, physiotherapists, psychologists and patient liaison groups. Two patient advocates attended, Judy Birch from the Pelvic Pain Support Network in the UK and myself from the International Painful Bladder Foundation. The day was divided into three sections: chronic pelvic pain syndrome, urogenital pain conditions and therapeutic approaches. Panel discussions were included and plenty of time was allowed for questions and discussions following presentations. This made it a lively, interactive and thought-provoking meeting.

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#### **UPCOMING MEETINGS:**

#### **JOINT 3rd INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS JAPAN (ICICJ) AND THE ESSIC ANNUAL MEETING 21-23 MARCH 2013**

The Comfortable Urology Network (CUN) of Japan, the International Society for the Study of BPS (ESSIC) and the Society of Interstitial Cystitis of Japan (SICJ) have pleasure in announcing a joint meeting of the 3rd International Consultation on Interstitial Cystitis Japan (ICICJ) and the ESSIC annual meeting 2013 to be held in Kyoto, Japan 21-23 March, 2013 to mark the 10th Anniversary of the first ICICJ. The theme of this meeting will be: PHENOTYPING BLADDER PAIN BASED ON PATHOPHYSIOLOGY, an important step in a multi-stage international approach to phenotyping the disease based on the pathophysiology, and a redefinition of interstitial cystitis/bladder pain syndrome/hypersensitive bladder syndrome (IC/BPS/HBS) suitable for clinical and scientific use worldwide. The meeting website for this unique international event has full details of registration, programme and contact address: [http://www.hainyo-net.org/study/icicj/index\\_e.html](http://www.hainyo-net.org/study/icicj/index_e.html)

Poster programme download: <http://convention.jtbcom.co.jp/3icicj/program/poster.pdf>

Oral programme download: <http://convention.jtbcom.co.jp/3icicj/program/oral.pdf>

#### **SIP 2013 FOCUS GROUPS MEETING 14-15 MAY 2013**

Following three European SIP symposia between 2010 and 2012, this year for the first time the SIP (Societal Impact of Pain) Programme Committee has decided to organise the so-called "SIP Focus Groups" meeting which will take place on 14th and 15th May 2013 in Brussels. More information will follow shortly on the SIP website: <http://www.sip-platform.eu/home.html>

#### **1st WORLD CONGRESS ON ABDOMINAL & PELVIC PAIN, BEURS VAN BERLAGE, AMSTERDAM, 31 MAY-1 JUNE 2013**

The 1st World Congress on Abdominal and Pelvic Pain to be held 31 May - 1 June in Amsterdam at the historic "Beurs van Berlage" (<http://www.beursvanberlage.nl/welcome>), the former Stock Exchange in the very heart of Amsterdam, will be a unique opportunity for everyone involved in different aspects of abdominal and pelvic pain to get together and share the latest information and insights. This first world congress is being organized by the IASP PUGO special interest group, IPPS and ConPP, all of which are well-known associations in the abdominal and pelvic pain world. It is also being held in the middle of the Global Year Against Visceral Pain launched in October 2012 by the International Association for the Study of Pain (IASP). The organisers hope that this congress will contribute to raising further awareness and increase knowledge about these debilitating conditions. There has been a good response to abstracts and 50 high quality research papers have been selected for display on poster boards. Eight top papers will be orally presented and there will be plenty of

time to discuss research in the field of abdominal and pelvic pain. This makes this event the ideal international congress for all those involved in treating patients suffering from visceral pain. Please note that the early bird registration deadline is 1 March 2013.

Congress website for further information and registration: <http://www.pelvicpain-meeting.com>

#### **EURORDIS ANNUAL MEMBERSHIP MEETING, 30 MAY-1 JUNE 2013, DUBROVNIK, CROATIA**

EURORDIS is a non-governmental patient-driven alliance of patient organisations representing 544 rare disease patient organisations in 49 countries. EURORDIS is the voice of 30 million people affected by rare diseases throughout Europe. The 2013 EURORDIS Membership Meeting will take place in Dubrovnik, Croatia at Hotel Rixos Libertas, May 30 – June 1st, 2013. The meeting will include the EURORDIS General Assembly, plenary session, parallel workshops including EPIRARE workshop and satellite meetings (Help Lines, CNA workshop and RareConnect Online Patient Communities). The main theme of the meeting will be National Plans for Rare Diseases. For more information, please go to <http://www.eurordis.org/content/membership-meetings>

#### **INTERNATIONAL NEUROMODULATION SOCIETY (INS) 11<sup>TH</sup> WORLD CONGRESS, BERLIN, GERMANY, 8-13 JUNE 2013**

The INS 11th World Congress will be held in Berlin on 8-13 June 2013. The INS informs us that it will feature a session on treating painful bladder symptoms and dysfunction with neuromodulation/neurostimulation on Tuesday, 11 June, in the afternoon. Pre-Conference Sessions will be available on: Solving Problems at the Neural Interface and Innovations In Neuromodulation. Main Sessions will deal with: Pain, The Brain, Headache, The Heart, Gastrointestinal Dysfunction, Neurorehabilitation, Urological Dysfunction, Colorectal Dysfunction. Further information is available at:

[www.neuromodulation.com/ins-congress](http://www.neuromodulation.com/ins-congress)

Preliminary programme: <http://www.neuromodulation.com/10-june-2013>

#### ***Reminder to conference organisers - Registration fees are often too high for voluntary patient advocates***

*There are a number of upcoming meetings in the field of chronic pelvic/bladder pain which are of interest to both patients and healthcare professionals. A recurrent problem for patient advocates is the unaffordability of registration fees for many of these conferences. We would like to put in a plea to all conference organisers for fee waivers or low registration fees for voluntary patient representatives from non-profit organisations.*

## **SOCIETY NEWS**

#### **IAPO CALLS FOR A PATIENT-CENTRED APPROACH TO THE POST-2015 DEVELOPMENT AGENDA IN GENEVA**

IAPO is the only global alliance representing patients of all nationalities across all disease areas and promoting patient-centred healthcare worldwide. Its members are patients' organizations working at local, national, regional and international levels to represent and support patients, their families and carers. IAPO has over 200 members which span over 50 countries and 50 disease areas and through its membership represents an estimated 365 million patients worldwide.

On 25 January in Geneva, Switzerland, the International Alliance of Patients' Organizations (IAPO) urged the World Health Organization (WHO) to adopt a patient-centred approach to the post-2015 development agenda. This request was central to an intervention made by Jo Groves, IAPO CEO, on the agenda item: Monitoring the achievement of the health-related Millennium Development Goals (MDGs) at the 132nd Session of the WHO Executive Board session in Geneva, Switzerland. The following is taken from IAPO's statement:

“...The MDGs have been a powerful force in maintaining support for health as a crucial element of development. A solid framework with clear objectives has proven to be highly effective in bringing about improvements in health in low income countries. Now that the international community is looking ahead to health in the post-2015 development agenda, there is an opportunity to build on the huge strides that have been made in global development. There is an opportunity to put forward ambitious goals that sustain the work of the MDGs, ensure health for all, tackle poverty and integrate the economic, social and environmental pillars of sustainable development.

IAPO is pleased to see that the post-2015 development agenda is considering the societal and economic impact of non-communicable diseases (NCDs) and that WHO is advocating for a holistic approach to NCD prevention and management. However, the post-2015 agenda must be driven by the needs and experiences of people affected by ill-health and success defined in their terms. A patient-centred approach acknowledges that many aspects of a person’s life are affected by the burden of the disease and should be the starting point to meeting future health-related development goals. WHO is right to focus on health as a human right and we recognise the growing support in the international community for universal health coverage. Both are a positive step towards patient-centred healthcare and sustainable development.

IAPO welcomes the consultative process being undertaken in the post-2015 development process. Patients’ organizations are a key stakeholder and undertake vital work to support patients such as health literacy training, health promotion advice, support for managing conditions and accessing treatment. These are important initiatives that improve health outcomes and prevent individuals and families falling into poverty as a result.”

Furthermore, IAPO also expressed support for the WHO’s work to define and formalize the active engagement of NGOs as part of the WHO reform process. This message was central to an intervention made by Jo Groves, IAPO CEO, on WHO reform at the 132nd Session of the WHO Executive Board session in Geneva, Switzerland. The following is taken from IAPO’s statement:

“...IAPO recognises that the issue of reform is complex with considerable implications for global healthcare governance. IAPO commends WHO’s efforts so far, but we cannot stress enough the need for greater involvement of civil society and particularly patients’ organizations in shaping the reforms.

IAPO supports the WHO’s move towards a new policy that will better define and formalize the active engagement of NGOs, especially those serving patient interests. IAPO takes very seriously our mandate to support all patients’ organizations to effectively represent their members and constituents at all levels of decision-making, including the WHO. These organizations must be empowered to engage without prejudice and regardless of their financial and political resources.

IAPO has invested significant resources in educating and training patients’ organization representatives about the WHO processes and supporting informed participation at local, regional and international meetings. Patients’ organizations offer patients a direct voice in expressing their concerns and needs and also in understanding the options and obligations for sustainable healthcare. IAPO has developed a set of recommendations for moving this work forward which were shared with WHO in December 2012. These were based on the three areas highlighted by WHO (collaboration, consultation, accreditation). Many of these suggestions are based on the experience IAPO has had working with intergovernmental institutions. It is critical that all those affected by healthcare decision-making have a voice in the forum which sets policy, whether they are national, regional or

international. There is no voice more important than that of the patient, and patients' organizations are their legitimate representatives.

In assuring the legitimacy and credibility of all voices, criteria for consultation, collaboration and accreditation should take into consideration the broad range of stakeholders involved in healthcare and be directed toward bringing diverse voices to the table rather than exclusion. This goal can be achieved only with full disclosure and transparency. IAPO fully supports activities to improve transparency and accountability, and looks forward to working closely with WHO in achieving public health for all."

Website: [www.patientsorganizations.org](http://www.patientsorganizations.org)

#### **ICA HAS A NEW EXECUTIVE DIRECTOR**

The Interstitial Cystitis Association (ICA) recently had pleasure in announcing the appointment of a new Executive Director, Lee Claassen, to take over from outgoing Executive Director Barbara Gordon. The ICA writes that Lee Claassen has held a variety of leadership positions in health and science-based organizations, as well as serving as a member of nonprofit association boards. Most recently, she served as Director for the Spinal Research Foundation, a patient advocacy organization. The IPBF wishes her every success in her new position with the ICA.

#### **IASP SPECIAL INTEREST GROUP PUGO (PAIN OF UROGENITAL ORIGIN) TO BE CHANGED TO SPECIAL INTEREST GROUP ON ABDOMINAL AND PELVIC PAIN.**

Many of you will have heard of PUGO, one of the Special Interest Groups (SIGs) of the International Association for the Study of Pain (IASP). PUGO stands for Pain of Urogenital Origin. In recent years it was felt that this name is a little outdated and does not really cover the full scope. It is now known that pain perceived to be in an organ may actually originate elsewhere, especially in the central nervous system. Furthermore, the term urogenital is considered to be too restricted. Abdominal and pelvic pain have so much in common that they needed to be merged into one special interest group. It has therefore been decided to change the name into: IASP special interest group on abdominal and pelvic pain. This change will be officially announced at the 1st World Congress on Abdominal and Pelvic Pain in May 2013 in Amsterdam. This will be welcome news to the IC world since IC patients often have comorbidities such as gastrointestinal disorders/IBS which extend beyond the pelvic floor.

#### **BOOKS, VIDEOS & WEBSITES**

##### **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*

This new book 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](#).

#### EAU GUIDELINE ON CHRONIC PELVIC PAIN

Clicking on this link <http://www.uroweb.org/guidelines/online-guidelines/> will take you to the complete list of EAU Guidelines. If you then click on Chronic Pelvic Pain, you will find that this guideline is not only available in English but also in a number of other languages such as Portuguese, Serbian, Greek, Russian, Turkish, Spanish and Czech.

#### PAIN CLINICAL UPDATES FROM THE IASP

The International Association for the Study of Pain (IASP) regularly produces clinical updates on different aspects of pain. Two recent additions are:

- Interdisciplinary Chronic Pain Management: International Perspectives, December 2012 Volume XX, Issue 7. Author: Michael E. Schatman.
- Chronic Pain Management: Measurement-Based Step Care Solutions, December 2012 Volume XX, Issue 8. Author: David Tauben.

All clinical updates are available to the public and many are available in Spanish as well as English. Go to the website: [www.iasp-pain.org](http://www.iasp-pain.org) and click on Publications and then Pain: Clinical Updates.

#### REMINDER: INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN (IASP) UPDATED CLASSIFICATION OF CHRONIC PAIN ONLINE ([www.iasp-pain.org](http://www.iasp-pain.org))

An updated, free version of what was formerly published in book form, *Classification of Chronic Pain*, is now exclusively available in downloadable PDFs on the IASP website. This popular publication provides researchers and clinicians dealing with pain an approved vocabulary, definitions, and codes for their field. Originally published in 1986 and updated in 1994, the book includes pain definitions (taxonomy) which were revised in 2011 and two areas – one section on Complex Regional Pain Syndromes (CRPS) and six sections on abdominal, pelvic, and urogenital pain – which were revised in 2012.

In order to find the section on chronic pelvic pain syndromes, go to:

[http://www.iasp-pain.org/AM/Template.cfm?Section=Classification\\_of\\_Chronic\\_Pain&Template=/CM/ContentDisplay.cfm&ContentID=16280](http://www.iasp-pain.org/AM/Template.cfm?Section=Classification_of_Chronic_Pain&Template=/CM/ContentDisplay.cfm&ContentID=16280)

And then look for: [GROUP XXIII: CHRONIC PELVIC PAIN SYNDROMES](#)

### 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 syndrome, chronic pelvic pain (syndrome) or combinations of these. When reviewing the article, we generally use the terminology used by the authors.

#### INTERSTITIAL CYSTITIS PATIENTS' USE AND RATING OF COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES.

*O'Hare PG 3rd, Hoffmann AR, Allen P, Gordon B, Salin L, Whitmore K. Int Urogynecol J. 2012 Nov 14. [Epub ahead of print] PMID: 23149598*

The purpose of this study from Drexel University College of Medicine was to describe the use of complementary and alternative medicine (CAM) therapies among interstitial cystitis (IC) patients, patients' perception of CAM therapies' effectiveness, and the association of time since diagnosis with perceived effectiveness of these therapies. In April 2009, the Interstitial Cystitis Association (ICA) initiated an Internet-based survey on CAM. Respondents indicated whether they received an IC diagnosis and how long ago, whether they had tried CAM, and who had recommended it. On a 5-point scale, respondents rated 49 therapies. A total of 2,101 subjects responded to the survey; 1,982 confirmed an IC diagnosis. Most (84.2 %) had tried CAM, and 55 % said physicians had recommended CAM. Of those trying CAM, 82.8 % had tried diet or physical therapy and 69.2 % other therapies. Of the therapies, 22 were rated positively and 20 negatively; 7 were inconclusive. Therapies patients perceived to be helpful included dietary management and pain management adjuncts such as physical therapy, heat and cold, meditation and relaxation, acupuncture, stress reduction, exercise, and sleep hygiene. Many therapies worked better for those diagnosed recently than for those diagnosed long before. The authors concluded that randomized, placebo-controlled studies are needed to demonstrate which therapies may indeed control IC symptoms and help send research in new and productive directions.

#### **THE PREVALENCE AND OVERLAP OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME IN MEN: RESULTS OF THE RAND INTERSTITIAL CYSTITIS EPIDEMIOLOGY MALE STUDY.**

*Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttrop MJ, Clemens JQ. J Urol. 2012 Nov 16. pii: S0022-5347(12)04707-6. doi: 10.1016/j.juro.2012.08.088. [Epub ahead of print] PMID: 23164386*

As part of the RICE (RAND Interstitial Cystitis Epidemiology) study, the authors developed validated case definitions to identify interstitial cystitis/bladder pain syndrome in women and chronic prostatitis/chronic pelvic pain syndrome in men. Using population based screening methods, they applied these case definitions to determine the prevalence of these conditions in men. A total of 6,072 households were contacted by telephone to screen for men who had symptoms of interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome. An initial 296 men screened positive, of whom 149 met the inclusionary criteria and completed the telephone interview. For interstitial cystitis/bladder pain syndrome 2 case definitions were applied (1 with high sensitivity and 1 with high specificity), while for chronic prostatitis/chronic pelvic pain syndrome a single case definition (with high sensitivity and specificity) was used. These case definitions were used to classify subjects into groups based on diagnosis. They found that symptoms of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome are widespread among men in the United States. The prevalence of interstitial cystitis/bladder pain syndrome symptoms in men approaches that in women, suggesting that this condition may be underdiagnosed in the male population.

#### **INTRAVESICAL TREATMENTS OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.**

*Neuhaus J, Schwalenberg T. Nat Rev Urol. 2012 Nov 27. doi: 10.1038/nrurol.2012.217. [Epub ahead of print] PMID: 23183946*

Neuhaus and colleagues from Leipzig note that bladder pain syndrome/interstitial cystitis (BPS/IC) is a disabling chronic condition that affects up to 7% of women in the USA. In men, BPS/IC seems to be less common, but might be underestimated because it can be confused with chronic prostatitis. The aetiology and pathophysiology of BPS/IC are not well understood. Consequently, diagnosis and treatment is challenging and most therapies used to date are off-label. These therapies include bladder instillation with dimethyl sulfoxide (DMSO) and BCG, as well as hyperbaric oxygen therapy. Overall, botulinum neurotoxin A injection, intravesical sodium hyaluronate instillation and DMSO

instillation seem to be the best-performing treatments, with response rates of 79%, 76% and 75%, respectively, and can be used effectively as second-line or third-line therapies for BPS/IC. However, additional high-quality randomized controlled trials are necessary to improve the available data.

**THE DISTRIBUTION AND FUNCTION OF CHONDROITIN SULFATE AND OTHER SULFATED GLYCOSAMINOGLYCANS IN THE HUMAN BLADDER AND THEIR CONTRIBUTION TO THE PROTECTIVE BLADDER BARRIER.**

*Janssen DA, van Wijk XM, Jansen KC, van Kuppevelt TH, Heesakkers JP, Schalken JA. J Urol. 2013 Jan;189(1):336-42. doi: 10.1016/j.juro.2012.09.022. Epub 2012 Nov 20. PMID: 23174248*

Glycosaminoglycan replenishment therapies are commonly applied to treat bladder inflammatory conditions such as bladder pain syndrome/interstitial cystitis. Although there is evidence that these therapies are clinically effective, much is still unknown about the location and function of different types of glycosaminoglycans in the bladder. Janssen and colleagues from Nijmegen, Netherlands investigated the location of sulfated glycosaminoglycans in the bladder and evaluated their contribution to the urothelial barrier. High glycosaminoglycan concentrations are located around the urothelial basal membrane and at the urothelial luminal surface. After removing the glycosaminoglycan layer, urothelial permeability increased. Natural recovery of the glycosaminoglycan layer takes less than 24 hours. Chondroitin sulfate was the only sulfated glycosaminoglycan that was located on the urothelial luminal surface and that contributed to urothelial barrier function. According to the authors, this study reveals an important role for chondroitin sulfate in bladder barrier function. Therapies aiming at restoring the luminal glycosaminoglycan layer in pathological conditions such as bladder pain syndrome/interstitial cystitis are based on a sound principle.

**PAIN IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: DO CHARACTERISTICS DIFFER IN ULCERATIVE AND NON-ULCERATIVE SUBTYPES?**

*Killinger KA, Boura JA, Peters KM. Int Urogynecol J. 2012 Dec 4. [Epub ahead of print] PMID: 23208005*

Key differences between interstitial cystitis/bladder pain syndrome (IC/BPS) subtypes (with and without Hunner's ulcer) have been noted. Killinger and colleagues from the William Beaumont Hospital hypothesized that pain characteristics in women grouped by IC/BPS subtype would differ. A survey was mailed to 749 women to assess IC/BPS pain and other characteristics. Cystoscopy/hydrodistention reports were reviewed for presence/absence of Hunner's ulcer. The McGill Pain Questionnaire Short Form© (MPQ-SF), Brief Pain Inventory (BPI), and Interstitial Cystitis Symptom and Problem Indices (ICSI-PI) assessed symptoms. Data were analyzed with Pearson's chi-square, Fisher's exact, t tests, and Wilcoxon rank tests. Of the 214 women that returned a survey (36 ulcerative and 178 non-ulcerative IC/BPS), similar proportions in each group reported that certain foods, exercise, and/or stress triggered symptoms. Fewer ulcerative patients reported pain with vaginal penetration than non-ulcerative. On the BPI, the ulcerative and non-ulcerative groups reported similar numbers of painful areas while lower abdominal/pelvic pain was reported most followed by lower back pain. Even though ICSI-PI, MPQ-SF, and BPI scores/responses did not differ, on the MPQ-SF the three words most frequently used by ulcerative patients to describe their pain were sharp, stabbing, and hot burning, and in non-ulcerative were aching, cramping, and tender. The authors concluded that these measures did not reveal any significant differences in pain between subtypes and that more research is needed in larger samples to determine whether differences exist.

**ESTIMATING THE EFFICACY OF AN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME MEDICATION IN A RANDOMIZED TRIAL WITH BOTH NON-ADHERENCE AND LOSS TO FOLLOW-UP.**

*Yang W, Probert KJ, Richard Landis J. Stat Med. 2012 Dec 10. doi: 10.1002/sim.5702. [Epub ahead of print]. PMID: 23225539*



This was a randomized clinical trial evaluating the efficacy of amitriptyline for the treatment of interstitial cystitis and painful bladder syndrome in patients who had received no previous treatment. In the trial, both the non-adherence rate and the rate of loss to follow-up are fairly high. Yang and colleagues re-analyzed the data from the trial and found a possible benefit of amitriptyline when administered at a high-dose level.

#### **EFFICACY OF SACRAL NEUROMODULATION IN TREATING CHRONIC PAIN RELATED TO PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS IN ADULTS.**

*Srivastava D. J Anaesthesiol Clin Pharmacol. 2012 Oct;28(4):428-35. doi: 10.4103/0970-9185.101890. PMID: 23225919*

The objective of this review from the United Kingdom was to evaluate the efficacy and safety of sacral neuromodulation in treating chronic pelvic pain related to painful bladder syndrome/interstitial cystitis. Overall 70.8% or 170/244 patients were successful at the trial stage. The only randomized controlled trial reported a decrease in Visual analogue pain scores of 49% (7.9 to 4.0) for sacral nerve stimulation [SNS] and 29%(4.5 to 3.2) for pudendal nerve stimulation [PNS] at 6 months follow up. Nine observational studies reported a decrease in pain scores/decrease in pain medications at long term follow up following permanent sacral neuromodulation. One study showed an 80% improvement in Global response assessment score. The author concluded that the results from the randomised controlled trial and case series/case reports demonstrate a reduction in pain symptoms of painful bladder syndrome following sacral neuromodulation.

#### **A SYNTHETIC FORM OF FRIZZLED 8-ASSOCIATED ANTIPROLIFERATIVE FACTOR ENHANCES P53 STABILITY THROUGH USP2A AND MDM2.**

*Kim J, Keay SK, You S, Loda M, Freeman MR. PLoS One. 2012;7(12):e50392. doi: 10.1371/journal.pone.0050392. Epub 2012 Dec 6. PMID: 23236372*

**Free full text. [Click on title.](#)**

Frizzled 8-associated Antiproliferative Factor (APF) is a sialoglycopeptide urinary biomarker of interstitial cystitis/painful bladder syndrome (IC/PBS), a chronic condition of unknown etiology with variable symptoms that generally include pelvic and/or perineal pain, urinary frequency, and urgency. Kim and colleagues from Los Angeles previously reported that native human APF suppresses the proliferation of normal bladder epithelial cells through a mechanism that involves increased levels of p53. The goal of this study was to delineate the regulatory mechanism whereby p53 expression is regulated by APF. Two APF-responsive cell lines (T24 bladder carcinoma cells and the immortalized human bladder epithelial cell line, TRT-HU1) were treated with asialo-APF (as-APF), a chemically synthesized form of APF. Biochemical analysis revealed that as-APF increased p53 levels in two ways: by decreasing ubiquitin specific protease 2a (USP2a) expression leading to enhanced ubiquitination of murine double minute 2 E3 ubiquitin ligase (MDM2), and by suppressing association of p53 with MDM2, thus impairing p53 ubiquitination. Biological responses to as-APF were suppressed by increased expression of wild type, but not mutant USP2a, which enhanced cell growth via upregulation of a cell cycle mediator, cyclin D1, at both transcription and protein levels. Consistent with this, gene silencing of USP2a with siRNA arrested cell proliferation. Their findings suggest that APF upregulates cellular p53 levels via functional attenuation of the USP2a-MDM2 pathway, resulting in p53 accumulation and growth arrest. These data also imply that targeting USP2a, MDM2, p53 and/or complex formation by these molecules may be relevant in the development of novel therapeutic approaches to IC/PBS.

#### **INTRAVESICAL DRUG DELIVERY FOR DYSFUNCTIONAL BLADDER.**

*Hsu CC, Chuang YC, Chancellor MB. Int J Urol. 2013 Jan 22. doi: 10.1111/iju.12085. [Epub ahead of print]. PMID: 23336527*

Hsu and colleagues from Taiwan note that with advancing technology, local organ-specific therapy and drug delivery is of increasing interest for treating dysfunctional bladder, including interstitial cystitis/bladder pain syndrome, overactive bladder and sterile hemorrhagic cystitis after chemotherapy or pelvic radiation. Intravesical therapy has shown varying degrees of efficacy and safety in treating interstitial cystitis/bladder pain syndrome, overactive bladder and hemorrhagic cystitis with new modalities being developed. Intravesical therapy has several advantages over oral therapy, including high local concentration and less systemic toxicity. In recent years, intravesical delivery of biotechnological products including neurotoxins and immunosuppressive agents, and delivery platform including liposomes has shown promise for lower urinary tract symptoms. This review considers the current status of intravesical therapy in dysfunctional bladder including interstitial cystitis/bladder pain syndrome, overactive bladder and hemorrhagic cystitis with special attention to lipid based novel drug-delivery.

#### **MAPPING THE CYTOKINE PROFILE OF PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS IN HUMAN BLADDER AND URINE SPECIMENS.**

*Corcoran AT, Yoshimura N, Tyagi V, Jacobs B, Leng W, Tyagi P. World J Urol. 2013 Feb;31(1):241-6. doi: 10.1007/s00345-012-0852-y. Epub 2012 Mar 24. PMID: 22441309*

This study from Pittsburgh investigated the cytokine profile in bladder tissue and urine of painful bladder syndrome/interstitial cystitis (PBS/IC) patients. Multiplex analysis of 23 cytokines was performed with a multiple antigen bead assay (Luminex 100 IS) on cold cup bladder biopsy and urine specimens collected during cystoscopy with hydrodistention (HD) under general anesthesia from 10 PBS/IC patients (ICS definition). Collected tissue specimens and urine from pre-HD and post-HD (mean 27 days) were compared to banked urine and tissue specimens collected from control subjects without PBS/IC symptoms. Univariate comparison of bladder tissue levels found significant elevation of IL-16, IL-18, CTACK, ICAM-1, MCP-3, SCGF $\beta$ , TRAIL, and VCAM-1 in PBS/IC relative to controls. Multivariate analysis revealed VCAM-1 and ICAM-1 were responsible for the discrimination of both tissue and urine of PBS/IC from controls. Urine levels of MCP-3 and TRAIL were significantly reduced a month after HD in concert with improvement in standardized measures of clinical symptoms (pain, urgency, and frequency (PUF) overall score and symptom score). Post-HD urine levels of MCSF, MCP-3, SDF1 $\alpha$ , and IL-18 positively correlated with improved symptom scores. The authors concluded that these results indicate significant elevation of cytokines in PBS/IC bladder tissue relative to controls. Significant reduction in post-HD urine levels of MCP-3 and TRAIL relative to pre-HD in PBS/IC was associated with clinical improvement (as measured by PBS/IC symptom scores) to qualify them as biomarker candidates.

#### **EFFECT OF SUPPLEMENTATION WITH HYDROGEN-RICH WATER IN PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.**

*Matsumoto S, Ueda T, Kakizaki H. Urology. 2013 Feb;81(2):226-30. doi: 10.1016/j.urology.2012.10.026. PMID: 23374763*

The aim of this study from Japan was to investigate the efficacy of hydrogen-rich water for the treatment of patients with interstitial cystitis/painful bladder syndrome (IC/PBS) by conducting a prospective, randomized, double-blind, placebo-controlled clinical trial of hydrogen-rich water in patients with IC/PBS. Inclusion criteria were stable symptoms of IC/PBS for  $\geq 12$  weeks after bladder hydrodistension, Interstitial Cystitis Symptom Index score of  $\geq 7$  and bladder pain (question 4 on Interstitial Cystitis Symptom Index) of  $\geq 4$ . They were randomized by a 2:1 ratio to receive hydrogen-rich water or placebo water for 8 weeks. The symptoms were assessed using the Interstitial Cystitis Symptom Index, Interstitial Cystitis Problem Index, Parsons' Pelvic Pain and Urgency/Frequency Patient Symptom Scale, visual analog scale bladder pain scores, and a standard 3-day voiding diary. The primary outcome was improvement of patient-reported symptoms evaluated after treatment. A total of 30 participants (29 women and 1 man, age  $64.0 \pm 14.8$  years) were enrolled in the present

study, and 2 patients (both women) were withdrawn from the study. The score of bladder pain was significantly reduced in both groups. However, the effect of hydrogen-rich water on symptoms was not significantly different from that of placebo, although supplementation with hydrogen-rich water was extremely effective in improving the bladder pain score in 11% of the patients. The authors concluded that the results of the present study do not support the use of supplementation with hydrogen-rich water for treating patients with IC/PBS.

#### **'OMICS' APPROACHES TO UNDERSTANDING INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME/BLADDER PAIN SYNDROME.**

*You S, Yang W, Anger JT, Freeman MR, Kim J. Int Neurourol J. 2012 Dec;16(4):159-68. doi: 10.5213/inj.2012.16.4.159. Epub 2012 Dec 31. PMID: 23346481*

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Recent efforts in the generation of large genomics, transcriptomics, proteomics, metabolomics and other types of 'omics' data sets have provided an unprecedentedly detailed view of certain diseases, however to date most of this literature has been focused on malignancy and other lethal pathological conditions. Very little intensive work on global profiles has been performed to understand the molecular mechanism of interstitial cystitis/painful bladder syndrome/bladder pain syndrome (IC/PBS/BPS), a chronic lower urinary tract disorder characterized by pelvic pain, urinary urgency and frequency, which can lead to long lasting adverse effects on quality of life. A lack of understanding of molecular mechanism has been a challenge and dilemma for diagnosis and treatment, and has also led to a delay in basic and translational research focused on biomarker and drug discovery, clinical therapy, and preventive strategies against IC/PBS/BPS. This review describes the current state of 'omics' studies and available data sets relevant to IC/PBS/BPS, and presents opportunities for new research directed at understanding the pathogenesis of this complex condition.

#### **BOTULINUM TOXIN FOR CONDITIONS OF THE FEMALE PELVIS.**

*El-Khawand D, Wehbe S, Whitmore K. Int Urogynecol J. 2013 Jan 24. [Epub ahead of print]. PMID: 23344218*

Botulinum toxin has recently been approved by the Food and Drug Administration (FDA) for the treatment of urinary incontinence associated with neurogenic detrusor overactivity. However, it has also been used off-label for a multitude of other conditions in the female pelvis, including urological, gynecological, and colorectal. This article from Drexel University College of Medicine, Philadelphia reviews the most recent data regarding its efficacy and safety, and administration techniques for those conditions. This comprised a literature review of the most relevant reports published between 1985 and 2012. It was found that urinary incontinence related to neurogenic detrusor overactivity is currently the only approved indication in the female pelvis. Other supported off-label uses include: idiopathic detrusor overactivity, interstitial cystitis/bladder pain syndrome, detrusor sphincter dyssynergia, high-tone pelvic floor dysfunction, anal fissure, anismus, and functional anal pain. The authors concluded that botulinum toxin may effectively and safely be used in many conditions of the female pelvis. More high quality research is needed to better clarify its role in the therapeutic algorithm for those indications.

#### **REPEATED ONABOTULINUMTOXIN-A INJECTIONS PROVIDE BETTER RESULTS THAN SINGLE INJECTION IN TREATMENT OF PAINFUL BLADDER SYNDROME.**

*Kuo HC. Pain Physician. 2013 Jan;16(1):E15-23. PMID: 23340540*

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Onabotulinumtoxin-A (BoNT-A) is effective for the treatment of interstitial cystitis/painful bladder syndrome (IC/PBS). However, long-term follow-up does not show successful outcome after a single injection. The purpose of this prospective interventional study from a tertiary medical centre in Taiwan was to evaluate the efficacy and safety of repeated intravesical BoNT-A injections for

treatment of IC/PBS and compare the success rates among patient groups receiving different injection numbers. Intravesical injection of 100 U of BoNT-A was performed in 81 patients every 6 months for up to 4 times or until patients' symptoms significantly improved. Patients who received a single injection served as active controls. Measured parameters included O'Leary-Sant symptom indexes (ICSI) and problem indexes (ICPI), visual analogue score (VAS) for pain, voiding diary variables, urodynamic parameters, maximal bladder capacity under anaesthesia, glomerulation grade, and global response assessment. Multiple measurements and Kaplan-Meier analysis were used for comparison of consecutive data and success rates among groups. They found that repeated intravesical BoNT-A injections were safe and effective for pain relief and they increased bladder capacity and provided a better long-term success rate than a single injection did for treatment of IC/PBS. However, the lack of a placebo control group was the main limitation.

**EFFECTS OF A SHORT COURSE OF ORAL PREDNISOLONE IN PATIENTS WITH BLADDER PAIN SYNDROME WITH FLUCTUATING, WORSENING PAIN DESPITE LOW-DOSE TRIPLE THERAPY.**

*Jeong HJ. Int Neurourol J. 2012 Dec;16(4):175-80. doi: 10.5213/inj.2012.16.4.175. Epub 2012 Dec 31. PMID: 23346483*

[Free full text. Click on title.](#)

Triple therapy with gabapentin, amitriptyline, and nonsteroidal antiinflammatory drugs is efficacious for chronic bladder pain syndrome/interstitial cystitis (BPS/IC). However, transient, fluctuating, worsening pain or flare-up symptoms may develop during treatment for a variety of reasons. Here, Jeong and colleagues from Korea assessed the validity of their observational experience regarding a short course of oral prednisolone therapy, which might be of value in the management of flare-up symptoms of BPS/IC. Between May 2007 and May 2012, 7 women (mean age, 61.5 years; range, 44.8 to 75.4 years) with BPS/IC presenting with transient, fluctuating, worsening pain as a flare-up symptom despite low-dose triple therapy received a 1- to 3-month course of oral prednisolone 10 mg. The outcome measures used were the IC symptom scale (ICSS, O'Leary-Sant Interstitial Cystitis Symptom Index) and a visual analogue scale (VAS), which were completed at baseline and after treatment. There were statistically significant differences in the ICSS and VAS score before and after prednisolone treatment. Low-dose triple therapy with prednisolone caused no significant adverse effects. It was concluded that in patients with BPS/IC who show transient, fluctuating, worsening pain as flare-up symptoms despite undergoing low-dose triple therapy, a short course of oral prednisolone therapy was sufficiently effective. However, the authors are of the opinion that large-scale studies should be performed to verify their findings.

**PERSISTENT THERAPEUTIC EFFECT OF REPEATED INJECTIONS OF ONABOTULINUM TOXIN A IN REFRACTORY BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.**

*Pinto R, Lopes T, Silva J, Silva C, Dinis P, Cruz F. J Urol. 2013 Feb;189(2):548-53. doi: 10.1016/j.juro.2012.09.027. Epub 2012 Dec 14. PMID: 23253961*

Pinto and colleagues from Porto, Portugal evaluated the efficacy and safety of repeated intratrigoal injections of onabotulinum toxin A in patients with bladder pain syndrome/interstitial cystitis. This is a single centre, long-term, prospective study in which 16 women with bladder pain syndrome/interstitial cystitis refractory to standard treatment received 4 consecutive intratrigoal injections of onabotulinum toxin A. Onabotulinum toxin A (100 U) was injected under cystoscopic control in 10 trigonal sites, each receiving 10 U in 1 ml saline. General anaesthesia was used in all treatments. Re-treatment was allowed 3 months after injection. Outcome measures included pain visual analog scale (0-10), O'Leary-Sant score, a 3-day voiding chart and a quality of life questionnaire at the first month and every 3 months after each injection. Voiding dysfunction and urinary tract infections were

assessed at 2 weeks and every 3 months afterward. Treatment duration was determined when patients requested another injection. Individual symptom relief lasted 6 to 12 months with an average duration of  $9.9 \pm 2.4$  months. There were no cases of voiding dysfunction. Five patients had noncomplicated urinary tract infections. The authors found that symptomatic improvement of bladder pain syndrome/interstitial cystitis persists in a repeated intratrigenal injection program of 100 U onabotulinum toxin A. Time to request re-treatment remained stable. Adverse events were mild, without voiding dysfunction requiring intermittent catheterization.

#### **TEMPORAL ORDERING OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND NON-BLADDER CONDITIONS.**

*Clemens JQ, Elliott MN, Suttorp M, Berry SH. Urology. 2012 Dec;80(6):1227-32. doi: 10.1016/j.urology.2012.06.059. PMID: 23206765*

The purpose of this study from Michigan was to examine the prevalence and timing of nonbladder conditions in a community cohort of women with symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). As part of the Rand Interstitial Cystitis Epidemiology (RICE) study, we identified 3397 community women who met a validated case definition for IC/BPS symptoms. Each completed a survey asking if they had a physician diagnose them as having irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, migraines, panic attacks, or depression. If a positive response was received, subjects were asked to provide the age of symptom onset. All subjects were also asked to provide the date of IC/BPS symptom onset. A total of 2185 women reported a diagnosis of at least one of the nonbladder conditions. Onset of bladder symptoms was not consistently earlier or later than the onset of nonbladder symptoms. Depression tended to occur earlier, whereas fibromyalgia generally occurred later. Mean age of onset was lowest for migraine symptoms, depression symptoms, and panic attacks symptoms, and greatest for fibromyalgia and chronic fatigue syndrome symptoms. Mean age of irritable bowel syndrome and IC/BPS symptom onset was between these other conditions. These findings confirm the common co-occurrence of IC/BPS with chronic nonbladder conditions. In women with IC/BPS symptoms and coexistent nonbladder conditions, bladder symptoms do not uniformly predate the nonbladder symptoms. These observations suggest that phenotypic progression from isolated bladder symptoms to regional/systemic symptoms is not a predominant pattern in IC/BPS, although such a pattern may occur in a subset of individuals.

#### **KETAMINE-ASSOCIATED CYSTITIS**

##### **ILLICIT KETAMINE AND ITS BLADDER CONSEQUENCES: IS IT IRREVERSIBLE?**

*Jalil R, Gupta S. BMJ Case Rep. 2012 Oct 30;2012. pii: bcr2012007244. doi: 10.1136/bcr-2012-007244. BMJ Case Rep. 2012 Oct 30;2012. pii: bcr2012007244. doi: 10.1136/bcr-2012-007244. PMID: 23112264*

Jalil and Gupta from London write that the ketamine bladder is a new clinical entity that may lead to irreversible damage to the urinary system. They report here on the severe lower urinary tract symptoms of four young patients referred to their urology unit who were found to have ulcerative cystitis secondary to ketamine abuse. The pathophysiology remains unclear and the treatment is symptomatic.

##### **KETAMINE CYSTITIS: AN EMERGING DIAGNOSTIC AND THERAPEUTIC CHALLENGE.**

*Gray T, Dass M. Br J Hosp Med (Lond). 2012 Oct;73(10):576-9. PMID: 23124288*

Ketamine abuse is increasingly common in the UK. Ketamine-induced cystitis can cause serious damage to the urinary tract. This emerging problem presents a new diagnostic challenge and is very likely to increase in incidence over the coming years.

#### **DUAL INVOLVEMENTS OF CYCLOOXYGENASE AND NITRIC OXIDE SYNTHASE EXPRESSIONS IN KETAMINE-INDUCED ULCERATIVE CYSTITIS IN RAT BLADDER**

*Chuang SM, Liu KM, Li YL, Jang MY, Lee HH, Wu WJ, Chang WC, Levin RM, Juan YS. NeuroUrol Urodyn. 2013 Jan 28. doi: 10.1002/nau.22367. [Epub ahead of print]. PMID: 23359243*

The aims of this rat study from Taiwan were to investigate voiding patterns, tissue constituents and the expressions of cyclooxygenase-2 (COX-2) and nitric oxide synthase (NOS) involved in ketamine-induced ulcerative cystitis in rat urinary bladder. Thirty Sprague-Dawley rats were distributed into three groups which received saline or ketamine for a period of 14 and 28 days. Ketamine treatment resulted in bladder hyperactivity and the non-voiding contractions were significantly increased. The urine concentrations of ketamine and norketamine were much higher in the ketamine-treated group. Moreover, ulcerated urothelium and mononuclear cell infiltration were noted in the ketamine-treated group. These alterations in urodynamic functions and tissue constituents were accompanied by increases in the expression of COX-2. Two NOS isoforms (iNOS and eNOS) were also overexpressed, but no significant change was observed for nNOS. COX-2 positive stained cells were significantly increased. Meanwhile, increased amounts of ED-1 positive stained macrophages were present and most of COX-2 expressed cells were co-stained with ED-1 in the early stage of ketamine treatment. The authors concluded that ketamine treatment affected bladder tissues by enhancing interstitial fibrosis and accelerating macrophages infiltration. Ketamine also initiated the up-regulations of COX-2 and iNOS and eNOS expressions. These up-regulated enzymes might play an important role in contributing to ketamine-induced alterations in micturition patterns and ulcerative cystitis.

#### **EFFECTS OF LONG-TERM KETAMINE ADMINISTRATION ON RAT BLADDER PROTEIN LEVELS: A PROTEOMIC INVESTIGATION USING TWO-DIMENSIONAL DIFFERENCE GEL ELECTROPHORESIS SYSTEM.**

*Gu D, Huang J, Shan Z, Yin Y, Zheng S, Wu P. Int J Urol. 2013 Feb 5. doi: 10.1111/iju.12100. [Epub ahead of print]. PMID: 23379290*

Gu and colleagues from China report that while long-term ketamine abuse can affect the urinary system, resulting in interstitial cystitis-like syndrome, its pathogenesis remains unclear. In this study, a proteomic approach of two-dimensional difference gel electrophoresis followed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry was carried out to investigate the potential disease-associated proteins in a rat model of ketamine-associated cystitis. Rats were randomly assigned to control, normal saline, low dose of ketamine (10 mg/kg) and high-dose of ketamine (50 mg/kg) groups with six rats in each group. The two experimental groups were given ketamine hydrochloride i.p. daily, whereas the normal saline group rats were treated with saline. A histological study showed hyperplastic epithelium and inflammatory cells infiltration in the high dose of ketamine-treated rat bladders. Two-dimensional difference gel electrophoresis revealed 30 altered expressions between the normal saline and high dose of ketamine-treated group. Among these proteins, two upregulated and two downregulated protein spots were all identified as smooth muscle protein-22/transgelin. Immunohistochemical staining and western blot analysis showed that the expression of total transgelin had no significant difference between groups. However, the expression of phosphorylated transgelin in the low-dose and high dose of ketamine groups was increased, whereas the non-phosphorylated transgelin was decreased when compared with the normal saline group. The authors concluded that long-term ketamine abuse induces phosphorylation of transgelin in the bladder wall, and this might play an important role in the pathogenesis of ketamine-associated cystitis.

#### **EVIDENCE FOR OVERLAP BETWEEN UROLOGICAL AND NONUROLOGICAL UNEXPLAINED CLINICAL CONDITIONS.**

*Bullones Rodríguez MÁ, Afari N, Buchwald DS; NIDDK Working Group on Urological Chronic Pelvic Pain. Collaborators (14): Afari N, Buchwald DS, Clauw D, Dimitrakov J, Kusek J, Mullins C, Nyberg L, Payne C, Peñacoba C, Pezzone M, Pontari M, Potts J, Bullones Rodríguez MÁ, Warren J. J Urol. 2013 Jan;189(1 Suppl):S66-74. doi: 10.1016/j.juro.2012.11.019. PMID: 23234637*

Unexplained clinical conditions share common features such as pain, fatigue, disability out of proportion to physical examination findings, inconsistent laboratory abnormalities, and an association with stress and psychosocial factors. This team examined the extent of the overlap among urological and nonurological unexplained clinical conditions characterized by pain. They describe the limitations of previous research and suggest several possible explanatory models. Using hallmark symptoms and syndromes as search terms, a search of 12 databases identified a total of 1,037 full-length published articles in 8 languages from 1966 to April 2008. The search focused on the overlap of chronic pelvic pain, interstitial cystitis, painful bladder syndrome, chronic prostatitis/chronic pelvic pain syndrome or vulvodynia with fibromyalgia, chronic fatigue syndrome, temporomandibular joint and muscle disorders or irritable bowel syndrome. They abstracted information on authorship, type of case and control groups, eligibility criteria, case definitions, study methods and major findings. They found that the literature suggests considerable comorbidity between urological and nonurological unexplained clinical conditions. The most robust evidence for overlap was for irritable bowel syndrome and urological unexplained syndromes with some estimates of up to 79% comorbidity between chronic pelvic pain and symptoms of irritable bowel syndrome. However, most studies were limited by methodological problems, such as varying case definitions and selection of controls. The authors concluded that the overlap between urological and selected nonurological unexplained clinical conditions is substantial. Future research should focus on using standardized definitions, and rigorously designed, well controlled studies to further assess comorbidity, clarify the magnitude of the association and examine common pathophysiological mechanisms.

## **PELVIC PAIN**

### **COMPARISON OF QUESTIONNAIRES USED FOR THE EVALUATION OF PATIENTS WITH CHRONIC PELVIC PAIN**

*Quaghebeur J, Wyndaele JJ. NeuroUrol Urodyn. 2013 Jan 28. doi: 10.1002/nau.22364. [Epub ahead of print]. PMID: 23359143*

The purpose of this study from Belgium was to compare questionnaires for the evaluation of symptoms and QoL in patients with CPPS. The MPQ-DLV, PDI, NIH-CPSI, ICSI, and PUF, were compared for: pain, bladder complaints, and for QoL. The studied group N = 26 (male: 16; female: 10) showed a good distribution in gender for the age (MW-U: P = 0.6) and BMI (MW-U: P = 0.5). The intraclass correlation (ICC) for pain intensity of MPQ-NWC and MPQ-PRIT was 0.55. The ICC's, for other different pain intensity scores were mostly <0.25 (global = 0.23). For bladder complaints a positive global score (ICC = 0.64) was shown, with the score for NIH-CPSI and ICSI > 0.77. The ICC for NIH-CPSI and PUF-SS was the lowest (=0.48). The QoL showed a global bad correlation (ICC ≤ 0.27) with MPQ-DLV-QoL/PDI, PDI/ICPI, PDI/PUF-BS and ICPI/PUF-BS scoring >0.5. The authors concluded that when the most used questionnaires for QoL assessment in patients with CPPS are compared, very different results can be found. This indicates that results from one questionnaire cannot be used for overall conclusions concerning pain intensity and QoL. For bladder symptoms the results seem to correspond better. To develop one generally accepted questionnaire would facilitate the interpretation and comparison of data in this condition.

### **RANDOMIZED MULTICENTER FEASIBILITY TRIAL OF MYOFASCIAL PHYSICAL THERAPY FOR THE TREATMENT OF UROLOGICAL CHRONIC PELVIC PAIN SYNDROMES.**

Fitzgerald MP, Anderson RU, Potts J, Payne CK, Peters KM, Clemens JQ, Kotarinos R, Fraser L, Cosby A, Fortman C, Neville C, Badillo S, Odabachian L, Sanfield A, O'Dougherty B, Halle-Podell R, Cen L, Chuai S, Landis JR, Mickelberg K, Barrell T, Kusek JW, Nyberg LM; Urological Pelvic Pain Collaborative Research Network. *J Urol.* 2013 Jan;189(1 Suppl):S75-85. doi: 10.1016/j.juro.2012.11.018. PMID: 23234638

The aim of this study was to determine the feasibility of conducting a randomized clinical trial designed to compare 2 methods of manual therapy (myofascial physical therapy and global therapeutic massage) in patients with urological chronic pelvic pain syndromes. 48 subjects (23 men and 24 women) with chronic prostatitis/chronic pelvic pain syndrome or interstitial cystitis/painful bladder syndrome were recruited at 6 clinical centres. Of the patients 24 were randomized to global therapeutic massage, 23 to myofascial physical therapy and 44 completed the study. Therapist adherence to the treatment protocols was excellent. The global response assessment response rate of 57% in the myofascial physical therapy group was significantly higher than the rate of 21% in the global therapeutic massage treatment group. The authors considered it feasible to conduct a full-scale trial of physical therapy methods and felt that the preliminary findings of a beneficial effect of myofascial physical therapy warrants further study.

#### **MOTOR CORTEX STIMULATION IN REFRACTORY PELVIC AND PERINEAL PAIN: REPORT OF TWO SUCCESSFUL CASES**

Louppe JM, Nguyen JP, Robert R, Buffenoir K, de Chauvigny E, Riant T, Péréon Y, Labat JJ, Nizard J. *NeuroUrol Urodyn.* 2013 Jan;32(1):53-7. doi: 10.1002/nau.22269. Epub 2012 Jun 5. PMID: 22674567

Louppe and colleagues from Nantes, France note that in some patients, with refractory chronic pelvic and perineal pain, pain and quality of life are barely alleviated despite optimal medical treatment, infiltrations and surgical release of the pudendal nerve. The management of these patients is complex, especially after failure of neuromodulation techniques (spinal cord stimulation, S3 nerve root stimulation and direct stimulation of the pudendal nerve). The authors report the first two cases illustrating the value of motor cortex stimulation (MCS), in this new indication. The history, decision-making process, intraoperative findings and results of this technique are presented. The perineal cortical area was identified by intraoperative motor evoked potentials in the external anal sphincter, confirming its location in the primary motor cortex between the inferior and superior limb positions. As predictive value of repetitive transcranial magnetic stimulation (rTMS) in the identification of responders to MCS for pain is now established, they performed pre-operative rTMS sessions for both patients. The first patient was a 74-years-old woman who reported an 11-year history of left lateral perineal pain. The second patient was a 45-year-old woman who reported a 4-year history of perineal pain following hysterectomy with ovariectomy. After respectively 40 months and 19 months of follow up, both patients reported an improvement of pain ranging from 40 to 50%. Time to onset of pain on sitting was markedly improved from a few minutes to 90 minutes, and largely contributing to improvement of activities of daily living and of quality of life. These two first cases suggest that motor cortex stimulation constitutes a new treatment for refractory pelvic and perineal pain, and should be considered after failure of conventional neuromodulation techniques, especially spinal cord stimulation.

#### **PELVIC PAIN: MECHANISTICALLY ENIGMATIC, THERAPEUTICALLY CHALLENGING.**

Puylaert M. *Pain Pract.* 2013 Jan;13(1):1-2. doi: 10.1111/papr.12019. Epub 2012 Dec 13. PMID: 23241211

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An editorial. Comment on [Neuromodulation of Pelvic Visceral Pain: Review of the Literature and Case Series of Potential Novel Targets for Treatment](#) (also [free full text](#)).



### **ASSESSING CHRONIC PELVIC PAIN SYNDROME PATIENTS: BLOOD PLASMA FACTORS AND CORTISOL SALIVA.**

*Lundh D, Hedelin H, Jonsson K, Gifford M, Larsson D. Scand J Urol. 2013 Feb 11. [Epub ahead of print] PMID: 23394140*

The aim of this study from Sweden was to identify changes in inflammatory molecules in the blood (plasma) of patients with chronic prostatitis/chronic pelvic syndrome (CP/CPPS) compared with controls. Altered levels indicate a systemic component by possible involvement of the prostate and/or the inner pelvic floor musculature. In 32 patients with CP/CPPS and 37 controls, blood plasma levels of testosterone, macrophage migration inhibitory factor (MIF), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), TNF- $\beta$ , interleukin-2 (IL-2) and IL-1 $\beta$  were measured by enzyme-linked immunosorbent assay. Cortisol in saliva samples was measured in the morning and late evening. All participants answered a questionnaire regarding their health profile. Significantly higher levels of MIF were detected in patients. The testosterone level was, contrary to other studies, little lower in patients. When controls with health issues and patients with a parallel disease were excluded, the MIF and TNF- $\alpha$  levels were higher in the patients than in controls, and the testosterone was slightly lower in patients. The authors believe that the findings show an immune response extending to the circulatory system, in which MIF makes a significant contribution to CP/CPPS. This study also indicates TNF- $\alpha$  as a circulatory component when excluding subjects with concomitant diseases. Both MIF and TNF- $\alpha$  have previously been highlighted for other diseases related to chronic pain and here also for CP/CPPS. These results provide further insights into the immunological basis of CP/CPPS.

### **MYOFASCIAL PHYSICAL THERAPY**

#### **RANDOMIZED MULTICENTER FEASIBILITY TRIAL OF MYOFASCIAL PHYSICAL THERAPY FOR THE TREATMENT OF UROLOGICAL CHRONIC PELVIC PAIN SYNDROMES.**

*Fitzgerald MP, Anderson RU, Potts J, Payne CK, Peters KM, Clemens JQ, Kotarinos R, Fraser L, Cosby A, Fortman C, Neville C, Badillo S, Odabachian L, Sanfield A, O'Dougherty B, Halle-Podell R, Cen L, Chuai S, Landis JR, Mickelberg K, Barrell T, Kusek JW, Nyberg LM; Urological Pelvic Pain Collaborative Research Network. J Urol. 2013 Jan;189(1 Suppl):S75-85. doi: 10.1016/j.juro.2012.11.018. PMID: 23234638*

The authors determined the feasibility of conducting a randomized clinical trial designed to compare 2 methods of manual therapy (myofascial physical therapy and global therapeutic massage) in patients with urological chronic pelvic pain syndromes. They recruited 48 subjects with chronic prostatitis/chronic pelvic pain syndrome or interstitial cystitis/painful bladder syndrome at 6 clinical centers. Eligible patients were randomized to myofascial physical therapy or global therapeutic massage and were scheduled to receive up to 10 weekly treatments of 1 hour each. Criteria to assess feasibility included adherence of therapists to prescribed therapeutic protocol as determined by records of treatment, adverse events during study treatment and rate of response to therapy as assessed by the patient global response assessment. Primary outcome analysis compared response rates between treatment arms using Mantel-Haenszel methods. There were 23 (49%) men and 24 (51%) women randomized during a 6-month period. Of the patients 24 (51%) were randomized to global therapeutic massage, 23 (49%) to myofascial physical therapy and 44 (94%) completed the study. Therapist adherence to the treatment protocols was excellent. The global response assessment response rate of 57% in the myofascial physical therapy group was significantly higher than the rate of 21% in the global therapeutic massage treatment group. The authors judged the feasibility of conducting a full-scale trial of physical therapy methods and the preliminary findings of a beneficial effect of myofascial physical therapy warrants further study.

### **ACUPUNCTURE**

#### **TRADITIONAL ACUPUNCTURE TRIGGERS A LOCAL INCREASE IN ADENOSINE IN HUMAN SUBJECTS**

*Takano T, Chen X, Luo F, Fujita T, Ren Z, Goldman N, Zhao Y, Markman JD, Nedergaard M. J Pain 2012 Dec;13(12):1215-23. doi: 10.1016/j.jpain.2012.09.012. PMID: 23182227*

Despite its long history and worldwide application, the biological mechanisms of acupuncture in relieving pain have been poorly defined. Recent studies in mice, however, demonstrate that acupuncture triggers increases in interstitial adenosine, which reduces the severity of chronic pain through adenosine A1 receptors, suggesting that adenosine-mediated antinociception contributes to the clinical benefits of acupuncture. In this study, the authors investigated whether acupuncture in human subjects is also linked to a local increase in interstitial adenosine concentration. They collected microdialysis samples of interstitial fluid before, during, and after delivering 30 minutes of conventional acupuncture in the Zusanli point in human subjects. They found that the interstitial adenosine concentration increased significantly during acupuncture and remained elevated for 30 minutes after the acupuncture. Acupuncture-mediated adenosine release was not observed if acupuncture was not delivered in the Zusanli point or if the acupuncture needle was inserted, but not rotated. This study strengthens the role of adenosine in acupuncture-mediated antinociception by directly providing such evidence in humans. The authors suggest that these results present further evidence of the role of adenosine in acupuncture-mediated antinociception by demonstrating that local adenosine concentrations increase in the acupoint in human subjects receiving traditional acupuncture.

#### **IRRITABLE BOWEL SYNDROME**

#### **BREAKS IN THE WALL: INCREASED GAPS IN THE INTESTINAL EPITHELIUM OF IRRITABLE BOWEL SYNDROME PATIENTS IDENTIFIED BY CONFOCAL LASER ENDOMICROSCOPY (WITH VIDEOS).**

*Turcotte JF, Kao D, Mah SJ, Claggett B, Saltzman JR, Fedorak RN, Liu JJ. Gastrointest Endosc. 2013 Jan 25. pii: S0016-5107(12)02875-1. doi: 10.1016/j.gie.2012.11.006. [Epub ahead of print]. PMID: 23357497*

Altered intestinal permeability and mucosal inflammation have been reported in irritable bowel syndrome (IBS) patients. Increased cell extrusion in the epithelium as measured by epithelial gaps may be associated with barrier dysfunction and may lead to mucosal inflammation. Confocal laser endomicroscopy can be used to identify and quantitate epithelial gaps in the small intestine. The purpose of this prospective, controlled cohort study from a tertiary referral centre in Canada was to determine the epithelial gap density in IBS and healthy control patients. In IBS and control patients undergoing routine colonoscopy, probe-based confocal laser endomicroscopy was used to image the terminal ileum. The primary outcome was the density of epithelial gaps (gaps/cells counted) in adequately imaged villi using pCLE. Images were reviewed by 2 blinded reviewers. The authors recruited 18 healthy controls and 16 IBS patients. The median epithelial gap densities for control and IBS patients were 6 and 32 gaps per 1000 cells, respectively. There was a trend toward higher gap density in female and younger patients. Using 3% (90% of the control population) as the cutoff for abnormal gap density, they found the diagnostic accuracy for IBS to be as follows: 62% sensitivity, 89% specificity, 83% positive predictive value, and 73% negative predictive value. The authors concluded that IBS patients have significantly more epithelial gaps in their small intestine compared with healthy controls, which suggests that increased epithelial cell extrusion may be a cause of altered intestinal permeability observed in IBS. This study had limitations being a single-center study with a small number of patients.

#### **TEMPOROMANDIBULAR JOINT PAIN**

#### **DEPRESSIVE AND ANXIETY SYMPTOMS AS RISK FACTORS FOR TEMPOROMANDIBULAR JOINT PAIN: A PROSPECTIVE COHORT STUDY IN THE GENERAL POPULATION.**

Kindler S, Samietz S, Houshmand M, Grabe HJ, Bernhardt O, Biffar R, Kocher T, Meyer G, Völzke H, Metelmann HR, Schwahn C. *J Pain*. 2012 Dec;13(12):1188-97. doi: 10.1016/j.jpain.2012.09.004. Epub 2012 Nov 8. PMID: 23141187.

In this study from Germany, the 5-year follow-up data of the population-based Study of Health in Pomerania (SHIP) were analyzed. To estimate the effect of symptoms of depression and those of anxiety on the risk of TMD pain, the Composite International Diagnostic-Screener (CID-S) and a clinical functional examination with palpation of the temporomandibular joint and the masticatory muscles were used. After exclusion of subjects having joint pain at baseline, a sample of 3,006 Caucasian participants with a mean age of 49 years resulted. Of those, 122 participants had signs of TMD joint pain upon palpation. Subjects with symptoms of depression had an increased risk of TMD joint pain upon palpation. Anxiety symptoms were associated with joint and with muscle pain. The diagnosis, prevention, and therapy of TMD pain should also consider symptoms of depression and those of anxiety, and appropriate therapies if necessary. The authors conclude that depressive and anxiety symptoms should be considered as risk factors for TMD pain. Depressive symptoms are specific for joint pain whereas anxiety symptoms are specific for muscle pain, findings that deserve detailed examination. These findings may support decision-making in treating TMD.

### THE COST OF CHRONIC PAIN

#### CHRONIC DISEASES IN THE EUROPEAN UNION: THE PREVALENCE AND HEALTH COST IMPLICATIONS OF CHRONIC PAIN.

Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. *J Pain Palliat Care Pharmacother*. 2012 Dec;26(4):310-25. doi: 10.3109/15360288.2012.736933. PMID: 23216170

The objective of this study was to assess recent data on the prevalence of chronic pain as part of chronic diseases; the prevalence of chronic pain as a chronic condition in its own right; the costs attributed to chronic pain; and the European Union (EU) policies to addressing chronic pain. Recent literature was reviewed for data on the prevalence and cost implications of chronic pain in the EU. Following on from an earlier systematic review, 8 databases were searched for prevalence and 10 for cost information from 2009 to 2011 and relevant EU organizations were contacted. Ten cost and 29 prevalence studies were included from the 142 full papers screened. The general adult population reported an average chronic pain prevalence of 27%, which was similar to those for common chronic conditions. Fibromyalgia had the highest unemployment rate (6%; Rivera et al., *Clin Exp Rheumatol*. 2009;27[Suppl 56]:S39-S45) claims for incapacity benefit (up to 29.9%; Sicras-Mainar et al., *Arthritis Res Ther*. 2009;11:R54), and greatest number of days of absence from work (Rivera et al., *Clin Exp Rheumatol*. 2009;27[Suppl 56]:S39-S45). Chronic pain is common and the total population cost is high. Despite its high impact, chronic pain as a condition seems to have had little specific policy response. However, there does appear to be sufficient evidence to at least make addressing chronic pain a high priority alongside other chronic diseases as well as to conduct more research, particularly regarding cost.

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