

# 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 36, May 2014

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

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

- **Editorial Overview**
- **Meeting Reviews**
- **Upcoming Events**
- **Health politics**
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### EDITORIAL OVERVIEW

The IPBF is once again pleased to present you with an overview of recent scientific publications, providing a wide overview of interstitial cystitis/bladder pain syndrome and related topics, with some interesting feedback papers from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network project. We have again included an update on ketamine cystitis research as it seems useful to keep a close eye on developments in this field, as well as raising awareness of the fact that IC-like symptoms particularly among young people can also be caused by ketamine abuse. Articles on comorbidities include updates for example on fibromyalgia, vulvodynia, chronic pelvic pain, irritable bowel syndrome and Sjögren's syndrome with a review article from the Netherlands on distal renal tubular acidosis which, in its hypokalemic form, can cause particularly painful bladder flares in patients with IC/BPS combined with SS. And finally one paper explains how the use of cartoons in patient information can be used to address health literacy issues. This method is already being used in some developing countries and in rural areas. The Continence Foundation of Australia uses it with great success.

**Access to scientific publications:** Continuing on the topic of research, it should once again be mentioned that better (= affordable) access to scientific publications would be helpful for patient advocates/organisations. Some publishers have already set up a special low rate for patient access to certain journals, but most not yet. In today's world, in which patients are being told by authorities that they have to play an increasing role in the management of their healthcare, it is essential for patients and their advocates to have the opportunity to gain insight into the latest developments. If they don't have this knowledge, they cannot play a full role and the patient organisations cannot then help the less able patients to find their way around the maze of modern healthcare. It would be much appreciated if more journal publishers could find some way of taking this into consideration.

**Conferences:** There are many conferences in the coming 12 months, both patient and professional, including special interest conferences such as ESSIC in June this year, entirely devoted to IC/BPS, at which special attention will be paid to Hunner's lesion this year. Please note that the 2<sup>nd</sup> World Congress on Abdominal and Pelvic Pain (WCAPP) is now scheduled for June 2015 in France. See below under [Upcoming Events](#) for details.

## MEETING REVIEWS

### IAPO 6TH GLOBAL PATIENTS CONGRESS: 'IT IS TIME TO STAND UP AND BE COUNTED'

The International Alliance of Patients' Organization's (IAPO) 6th Global Patients Congress, held in Ascot, United Kingdom 29-31 March 2014, was attended by some 178 delegates from no fewer than 48 countries worldwide! These included many patient advocates from all parts of the world attending this congress for the first time who were welcomed at a special breakfast briefing on the Saturday when it was emphasised that a strong point of IAPO is that it has always welcomed patient organisations on all scales, large and small, and everyone's voice counts. Furthermore, one organisation faced with a problem can learn from others who may have found a solution.

'It is time to stand up and be counted' was the call from Stephen Murby Wright, Consumers Health Forum of Australia, during a multi-stakeholder panel discussion. This was supported in her keynote address by Dame Sally Davies, Chief Medical Officer (CMO), UK Government who emphasised the importance of patient and public involvement: 'Healthcare research should be carried out by and with members of the public, not just done for or to the public.'

The theme of the Congress explored: 'Better access, better health: A patient-centred approach to universal health coverage'. Delegates explored the role of the patient in defining and implementing universal health coverage globally. A wide range of stakeholders, including patients, policy-makers, healthcare professionals, academics and industry representatives discussed the challenges in achieving healthcare for all. Dr Hernan Montenegro, Health Systems Advisor at the World Health Organization declared that: 'Universal health coverage is a vision which can identify all the different actors' but that in its implementation, 'there is no single magic solution, everything has to be context specific, tailored to the local reality.' Dr Otmar Kloiber, Secretary General of the World Medical Association stated that: 'It is complete nonsense to talk about healthcare as a cost item, let's talk about the value of healthcare for the people and for the economy.' This sentiment was echoed by patient representatives on the previous day who worked together to develop global principles of universal health coverage. Patient representatives emphasised that no system is truly universal if it is not providing equitable, high quality, affordable access to healthcare. These are the three pillars of universal health coverage. To improve access to healthcare for all, patients need to be involved in the design and delivery of healthcare. For this, patients need a strong, unified voice, as Margaret Murphy, External Lead Advisor, WHO Patients for Patient Safety stated: 'I like to look on us rather like the piece of grit in the oyster causing sufficient irritation to bring about the pearl – the pearl of healthcare improvement.' Delegates agreed that patients are increasingly working together, and with other stakeholders, to achieve access to healthcare for all. However, there was a plea heard from speaker and patient advocate Robert Johnstone for training of patient leaders in all aspects of healthcare so as to ensure that they can effectively participate in the system on behalf of their members, a plea strongly endorsed by all of us.

The congress was an ideal opportunity for networking and for meetings of same interest groups, including the **International Pelvic Pain Partnership** (<https://www.facebook.com/pages/International-Pelvic-Pain-Partnership/229848217207564>), organised by Judy Birch from the UK and attended by several patient representatives from the IC/BPS world, and a first meeting of those interested in the proposed setting up of a new **International Network of Pain Organizations**, organised by Penney Cowan from the USA, which likewise proved to be of great interest to IC/BPS representatives.

More information about the IAPO congress can be found at [www.globalpatientscongress.org](http://www.globalpatientscongress.org). For information on IAPO and how to join, [click here](#).

### **PAIN ALLIANCE EUROPE (PAE) ANNUAL GENERAL ASSEMBLY MEETING.**

At the PAE meeting in Brussels 8-9 April, the exhibition at the European Parliament featuring the “My pain feels like...” campaign attracted considerable interest. The link [http://www.mypainfeelslike.com/?pk\\_campaign=PAE\\_2014&pk\\_kwd=home](http://www.mypainfeelslike.com/?pk_campaign=PAE_2014&pk_kwd=home) offers further education and tools for pain patients, including a pain questionnaire. The next PAE General Assembly will be held in November this year, and will be combined with a training session/workshops on topics of common interest for advocacy (what you need to know about the EU institutions and how they work, best practices, health access etc). For further information about the PAE and membership, [click here](#). Pain Alliance Europe is an NGO umbrella organization of national associations which are all committed to improving the quality of life of people with chronic pain.

### **UPCOMING EVENTS**

#### **ECRD 2014 -EUROPEAN CONFERENCE ON RARE DISEASES & ORPHAN PRODUCTS – 8-10 MAY, BERLIN**

ECRD is the foremost meeting of the rare disease community and a unique platform across all rare diseases, across all European countries, bringing together all stakeholders – patients, caregivers and patients’ representatives; academics, scientists and researchers; payers and regulators; health care professionals, industry, policy makers and representatives of the Member States. ECRD covers research, development of new treatments, healthcare, social care, information, public health and support at European, national and regional levels and provides the state of the art of the rare disease environment, monitoring and benchmarking initiatives. This 7th European Conference on Rare Diseases & Orphan Products will be co-organised by the European Organisation for Rare Diseases (EURORDIS) and DIA Europe and all stakeholders involved in the rare disease environment are invited to attend and participate. Some 700 participants are expected to attend from over 40 countries. [Click here](#) for more information.

#### **EURORDIS MEMBERSHIP MEETING 8 MAY 2014**

Prior to the ECRD conference, the European Organisation for Rare Diseases (EURORDIS) General Assembly will be held on Thursday, 8 May at the Andels Hotel, Berlin. The General Assembly will take place from 9 to 11 am and is a Member only event. A selection of forums and capacity-building workshops will follow the EURORDIS General Assembly. These sessions are designed to empower patients and patients’ advocates and encourage learning from each other’s experience. No additional registration fees are charged to patients and patients’ advocates to attend these sessions. For further information, [click here](#).

#### **AMERICAN UROLOGICAL ASSOCIATION (AUA) ANNUAL MEETING, 16-21 MAY, ORLANDO**

The AUA annual meeting is offering a number of courses on IC/BPS, urogenital pain, female pelvic health, urologic pelvic pain as well as poster sessions. There will be a presentation on the MAPP Study at the Society for Infection and Inflammation in Urology meeting. For further information, go to [www.aua2014.org](http://www.aua2014.org).

#### **RSM PAIN ABROAD - FRIDAY 30 MAY 2014**

The Royal Society of Medicine (RSM) will be holding a meeting entitled Pain Abroad which will address problems to help facilitate better pain management in diverse settings. This meeting examines the need for pain management and how a multidisciplinary approach in different countries works. Venue: Royal Society Of Medicine, 1 Wimpole Street, LONDON, W1G 0AE. For further information, [click here](#).

#### **1<sup>ST</sup> GLOBAL CONGRESS ON LOWER URINARY TRACT DYSFUNCTION (LUTD) 11-13 JUNE 2014 - BRUSSELS, BELGIUM**

The 1st Global Congress on Lower Urinary Tract Dysfunction (LUTD) marks the kick off for a multidisciplinary global community of (neuro)urologists, (uro)gynaecologists, physiotherapists and all other associated specialties. From 11 to 13 June 2014, a truly worldwide selection of experts will meet in Brussels to discuss

LUTD in depth. The programme will be divided into three main topics: non-neurogenic male LUTD, non-neurogenic female LUTD, neurogenic LUTD, with a focus on difficulties and dilemmas in clinical decision making. For further information, [click here](#).

#### **ESSIC (INTERNATIONAL SOCIETY FOR THE STUDY OF BPS) ANNUAL MEETING, 14-15 JUNE 2014, PHILADELPHIA, USA**

This year, the ESSIC annual meeting will be held for the first time in the USA. The venue is Geary Hall, Hahnemann Hospital, Drexel University, 230 North Broad Street, Philadelphia. Information and registration details can be found on the ESSIC website: [www.essic.eu](http://www.essic.eu). For the tentative programme, please [click here](#). Following a presentation by the NIDDK on the current situation regarding the MAPP project, the first day will be largely devoted to presentations and discussions on "Hunner Disease". The programme on the second day will include presentations by patient advocates in a dedicated session.

**Please note:** In preparation for this meeting, there is an **ESSIC Survey on the Detection of Hunner lesions** (see link on the ESSIC [website home page](#)) which is open to non-members as well as members.

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

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

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

The ICS Annual Scientific Meeting is to be held in Rio de Janeiro, Brazil this year. The scientific programme will include posters and abstract presentation on IC/BPS and related topics as well as a number of workshops:  
**W6 Bladder Pain Syndrome and Interstitial Cystitis. A syndrome and a disease.** Monday 20 October 2014, 09:00-12:00

**W19 Final Frontier in LUTS; Targeting the Urothelium to Treat OAB, IC/BPS, Hypersensitive Bladder and Ketamine Cystitis** Tuesday 21 October 2014, 09:00-12:00

For those interested in standardisation, including the impact of terminology and definitions on the patient, there is the following workshop organised by the ICS Standardisation Steering Committee:

**W22 Setting the Standards; developing new ICS Standards in the era of evidence-based medicine. Standardisation Steering Committee activity.** Tuesday 21 October 2014, 09:00-12:00

The Public Forum, organised by the Continence Promotion Committee (CPC), is to return this year and will be held on Wednesday 22 October, 19.00-21.00. The CPC is inviting health care providers from all fields as well as patient advocacy groups and the general public. Various national patient advocacy groups will exchange and share their knowledge and expertise, and along with ICS opinion leaders will be discussing important news and changes.

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

#### **SOCIETAL IMPACT OF PAIN (SIP) 2014: SAVE THE DATE – 17-18 NOVEMBER, 2014**

Taking into account the fact the [announcement of the Italian Government in the media](#) that they intend to list Chronic Pain and Palliative Care as Healthcare Priorities during their Presidency of the EU Council in 2014, the SIP programme committee has decided to host SIP 2014 in the second half of the year in Brussels. To celebrate the 5th SIP symposium, the programme committee has invited one of the top European journalists and scientific moderators to lead four interactive panel discussions. Key stakeholders representing all the interest groups will be invited to debate what needs to be done to ensure that chronic pain becomes an EU and National Health Policy priority. Further information will follow. [www.sip-platform.eu](http://www.sip-platform.eu)

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

The second annual meeting of MIPS will be held in Nimes, France at the Novotel Atria Hotel. The theme will be: Pelvic Floor Dysfunctions in the Mediterranean: climbing a long hill? There will be simultaneous translation English/French. Following its first meeting in November last year, MIPS is now officially a legal entity.

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

Following the great success of the 1<sup>st</sup> WCAPP held in Amsterdam, this 2<sup>nd</sup> WCAPP will be organised in June 2015 in Nice, France by Convergences PP in collaboration with IPPS and APP-IASP and is expected to include patient advocacy participation. Further information will follow in due course.

## **HEALTH POLITICS**

### **CLINICAL TRIALS: CLEARER RULES, BETTER PROTECTION FOR PATIENTS IN THE EU**

Pharmaceutical companies and academic researchers will have to post the results of all their European clinical trials in a publicly-accessible database, under a draft law already informally agreed with EU ministers and passed by Parliament on Wednesday 2 April 2014. The law also facilitates cross-border cooperation to make clinical trials larger, more viable and more reliable, which should in turn boost efforts to develop special treatments, e.g. for rare diseases.

The Commission proposal aims to remedy the shortcomings of the existing Clinical Trials Directive by setting up a uniform framework for the authorisation of clinical trials by all the member states concerned with a given single assessment outcome. Simplified reporting procedures, and the possibility for the Commission to do checks, are among the law's key innovations. According to Glenis Willmott (UK), who steered the legislation through the European Parliament: "The new law will also offer hope to the millions of people in Europe suffering from rare diseases, by making cross-border trials much easier to conduct. There are simply not enough patients in one country alone to develop new or improved treatments for rare diseases. By working at EU level we can reduce the huge cost and burden of conducting trials across borders". For more information, [click here](#).

## **WEBSITES**

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

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

<http://www.digestive.niddk.nih.gov/ddiseases/pubs/yrdd/index.aspx>. Many IC/BPS patients suffer from irritable bowel syndrome with chronic abdominal pain, cramps, bloating, gas, constipation, and diarrhoea.

The NIDDK has free resources about IBS and related digestive disorders available to the public, including:

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

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

A useful list of health topics in the field of kidney and urologic diseases can be found at: <http://kidney.niddk.nih.gov/KUDiseases/a-z.aspx>. <http://kidney.niddk.nih.gov/KUDiseases/a-z.aspx>.

This is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) in the USA.

## **SURVEY**

### **PATIENT GROUP SURVEY BY PATIENTVIEW**

International Painful Bladder Foundation

This short study is being conducted independently by PatientView, and explores patient groups' opinions on the power of the patient movement in 2014. All respondents to any PatientView study get a final copy of the resulting report. Aims of the study : to quantify the impact of the patient movement, and identify areas in which progress could be made; to map the typical (and non-typical) activities of patient groups in various countries, and across a number of disease specialties; countries and disease specialties will be compared in the study results; the results will also be compared with those obtained in their first iteration of this survey, two years ago in 2012. The survey is open to any health advocacy organisation worldwide. The survey has only 8 very simple questions and is anonymous. The survey's closing date is 31 May 2014. Link to the study:

**[PatientView study: the power of the patient movement 2014](https://www.surveymonkey.com/s/Benchmarking-Patient-Movement-2014)**

**[\[https://www.surveymonkey.com/s/Benchmarking-Patient-Movement-2014\]](https://www.surveymonkey.com/s/Benchmarking-Patient-Movement-2014)**

For further information, please contact: Dr Alexandra Wyke, CEO, PatientView, email: [alexwyke@patient-view.com](mailto:alexwyke@patient-view.com); PatientView website: <http://www.patient-view.com>

## RESEARCH HIGHLIGHTS

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

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

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

### **HOW ARE WE GOING TO MAKE PROGRESS TREATING BLADDER PAIN SYNDROME? ICI-RS 2013.**

*Malykhina A, Hanno P. NeuroUrol Urodyn. 2014 Feb 24. doi: 10.1002/nau.22575. [Epub ahead of print] PMID: 24615847*

The purpose of this ICI-RS 2013 paper was to look at the current state of knowledge in bladder pain syndrome and ascertain how we can make advances in the near term. It formed a compendium of the ideas presented at the International Consultation on Incontinence Research Society 2013 meeting of clinicians and basic scientists. The meeting included the following topics: potential connection between defined and undefined IC/BPS; association between psychiatric disorders and IC/BPS; rationale for multimodal therapy approach in IC/BPS; and issues of a placebo control in human studies. It was concluded that translational research studies are still in need of improved animal models to study IC/BPS mechanisms and development of novel methods to objectively measure bladder pain in rodents. The need to try and develop better clinical therapies will best be met by proper phenotyping of this heterogeneous population and avoiding premature publication of clinical trials that are anecdotal and do not include randomized placebo control populations. Patients with Hunner's lesions should be identified prior to or in the course of clinical trials so that results in this subgroup can be evaluated.

### **ALTERATIONS IN RESTING STATE OSCILLATIONS AND CONNECTIVITY WITHIN SENSORY AND MOTOR NETWORKS IN WOMEN WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.**

*Kilpatrick LA, Kutch JJ, Tillisch K, Naliboff B, Labus J, Jiang Z, Farmer M, Apkarian AV, Mackey S, Martucci KT, Clauw D, Harris RE, Deutsch G, Ness T, Yang CC, Maravilla K, Mullins C, Mayer EA. J Urol. 2014 Mar 25. pii: S0022-5347(14)03044-4. doi: 10.1016/j.juro.2014.03.093. [Epub ahead of print] PMID: 24681331*

The pathophysiology of interstitial cystitis/painful bladder syndrome (IC/PBS) remains incompletely understood, but is thought to involve a central disturbance in the processing of pain and viscerosensory signals. The authors from many different US centres participating in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network project aimed to identify differences in brain activity and



connectivity between female IC/PBS patients and healthy controls in order to advance clinical phenotyping and treatment efforts for IC/PBS. They examined oscillation dynamics of intrinsic brain activity in a large sample of well-phenotyped female IC/PBS patients and female healthy controls collected during a 10-minute resting fMRI scan as part of the MAPP Research Network project. The BOLD signal was transformed to the frequency domain and relative power was computed for multiple frequency bands. The results demonstrated altered frequency distributions in viscerosensory (post insula), somatosensory (postcentral gyrus) and motor regions (anterior paracentral lobule, medial and ventral supplementary motor area (SMA)) in IC/PBS patients. Additionally, anterior paracentral lobule, medial SMA and ventral SMA all demonstrated increased functional connectivity to the midbrain (red nucleus) and cerebellum. This increased functional connectivity was greatest in patients reporting pain during bladder filling. These findings suggest that women with IC/PBS have a sensorimotor component to their pathology involving an alteration in the intrinsic oscillations and connectivity within a cortico-cerebellar network previously associated with urinary bladder function.

#### [UROLOGIC CHRONIC PELVIC PAIN SYNDROME SYMPTOM FLARES: CHARACTERIZATION OF THE FULL SPECTRUM OF FLARES AT TWO SITES OF THE MAPP RESEARCH NETWORK.](#)

*Sutcliffe S, Colditz GA, Goodman MS, Pakpahan R, Vetter J, Ness TJ, Andriole GL, Lai HH. BJU Int. 2014 Apr 15. doi: 10.1111/bju.12778. [Epub ahead of print] PMID: 24730356*

The purpose of this study from the Washington University School of Medicine was to describe the full spectrum of symptom exacerbations defined by interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome patients as flares, and to investigate their associated health-care utilization and bother at two sites of the Trans-Multidisciplinary Approaches to the Study of Chronic Pelvic Pain (Trans-MAPP) Epidemiology and Phenotyping study. Participants completed a flare survey that asked them: 1) whether they had ever had flares ("symptoms that are much worse than usual") that lasted <1 hr, >1 hr and <1 day, and >1 day; and 2) for each duration of flare, to report their: a) average length and frequency; b) typical levels of urologic and pelvic pain symptoms; and c) levels of health-care utilization and bother. The authors compared participants' responses to their non-flare Trans-MAPP values and across flares using generalized linear mixed models. 76 of 85 participants (89.4%) completed the flare survey, 72 of whom reported having flares (94.7%). Flares varied widely in terms of their duration (seconds to months), frequency (several times per day to once per year or less), and intensity and type of symptoms (e.g. pelvic pain versus urologic symptoms). Flares of all duration were associated with greater pelvic pain, urologic symptoms, disruption to participants' activities, and bother, with increasing severity of each of these factors as the duration of flares increased. Days-long flares were also associated with greater health-care utilization. In addition to duration, symptoms (pelvic pain, in particular) were also significant determinants of flare-related bother. The authors report that their findings suggest that flares are common and associated with greater symptoms, health-care utilization, disruption, and bother. Their findings also inform the characteristics of flares most bothersome to patients (i.e. increased pelvic pain and duration), and therefore of greatest importance to consider in future research on flare prevention and treatment.

#### [THE PAIN OF PAINFUL BLADDER.](#)

*Payne C. Can Urol Assoc J. 2013 Sep;7(9-10 Suppl 4):S203-S205. PMID: 24523848*

[Free full article, click on title.](#)

Bladder pain can have a number of different etiologies. This brief summary by Christopher Payne MD provides an overview of bladder pain syndrome, including current evidence-based recommendations for diagnosis and management. The author emphasises that it is essential to understand that Hunner's lesions appear to be an entirely different condition to bladder pain syndrome.

#### [URINARY BLADDER, CYSTITIS AND NERVE/UROTHELIAL INTERACTIONS.](#)

*Birder LA. Auton Neurosci. 2014 May;182:89-94. doi: 10.1016/j.autneu.2013.12.005. Epub 2013 Dec 25. PMID: 24412640*

A hallmark of functional pain syndromes, such as bladder pain syndrome/interstitial cystitis (BPS/IC) is pain in the absence of demonstrable infection or pathology of the viscera or associated nerves, writes expert in this field Dr Lori Birder from Pittsburgh. There are no clear definitions of this syndrome, no proven etiologies and no effective treatments able to eradicate the symptoms. This condition is characterized by suprapubic pain,

associated with bladder filling and can also be accompanied by a persistent strong desire to void, increased frequency of urination and nocturia. Severe cases of this disorder, which affects primarily women, can have considerable impact on the quality of life of patients due to extreme pain and urinary frequency, which are often difficult to treat. In addition, BPS/IC patients may also suffer co-morbid conditions where pain is a common symptom (such as irritable bowel syndrome, fibromyalgia). Theories explaining the pathology of bladder pain syndrome are many and include an altered bladder lining and possible contribution of a bacterial agent. The author concludes by suggesting that pharmacologic interventions aimed at targeting urothelial receptor/ion channel expression or transmitter release mechanisms may provide a new strategy for the clinical management of bladder disorders such as BPS/IC

#### **URINARY SYMPTOMS AS A PRODROME OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.**

Warren JW, Wesselmann U, Greenberg P, Clauw DJ. *Urology*. 2014 May;83(5):1035-40. doi: 10.1016/j.urology.2014.01.012. Epub 2014 Mar 25. PMID: 24674116

The purpose of this study was to test the hypothesis that more bladder pain syndrome/interstitial cystitis (BPS/IC) cases than controls report pre-onset urinary symptoms. In a risk factor study, the date of BPS/IC onset (index date) was systematically determined in 312 female incident cases; the mean age at onset was 42.3 years. Frequency-matched controls were compared on pre-index date medical history. Three pre-index date symptoms were more common in BPS/IC cases: pelvic pain with urinary features, frequency, and bladder pain; 178 cases (57%) vs 56 controls (18%) had at least 1 symptom. Several perspectives suggested that prodromal symptoms were different from BPS/IC symptoms. In prodromal women, the median age of the earliest urinary symptom "more than other people" was 20 years. Women with the prodrome were significantly more likely than those without to have pre-index date nonbladder syndromes (NBSs). The prodrome predicted not only BPS/IC but also a worse prognosis for it. Before the onset of BPS/IC, pelvic pain with urinary features, frequency, and/or bladder pain were reported by more than half the cases. Prodromal women recalled abnormal urinary symptoms decades before the onset of BPS/IC. The prodrome was associated with prior NBSs and predicted not only BPS/IC but also its poor prognosis. These data generated 2 hypotheses: that (1) prodromal symptoms are different from BPS/IC symptoms and (2) pain amplification links NBSs, the prodrome, the appearance of BPS/IC, and its poor prognosis. Recognition of the prodrome might provide opportunities for prevention of fully developed BPS/IC.

*Editor's note: [click here](#) if you are not too sure what a "prodrome" is.*

#### **ADVANCES IN THE METHODS FOR DISCOVERING NOVEL PAINFUL BLADDER SYNDROME THERAPIES.**

Tseng LH. *Expert Opin Drug Discov*. 2014 Apr;9(4):423-32. doi: 10.1517/17460441.2014.894975. Epub 2014 Mar 7. PMID: 24606198

Tseng from Taiwan notes that advances in the treatment of interstitial cystitis or bladder pain syndrome (IC/BPS) depend on a good understanding of its pathogenesis. Presently, oral medicine and intravesical drug instillations may be the most popular therapies in daily practice. To improve the efficacy of intravesical drug delivery, the system requires modulation through coupling them to novel carriers. Numerous investigators have attempted alternative reconstructive procedures for bladder replacement/repair using scaffolds. These scaffolds include acellular extracellular matrix grafts or tissue-derived cell-seeded extracellular matrix grafts as well as the transplantation of mesenchymal progenitor cells into the damaged bladder. This review focuses on currently available IC/BPS treatments and the different strategies employing nanotechnology or tissue engineering in the discovery of novel IC/BPS therapies. The author reports that current studies in the discovery of novel IC/BPS therapies are still imperfect, with novel approaches that use biocompatible nanomaterials or tissue engineering still ongoing. These nanoformulations give the benefit of protecting easily degradable molecules and enhance targeted delivery. Tissue engineering holds the promise of regenerating damaged tissues and organs by replacing damaged tissue and/or by stimulating the body's own repair mechanisms to heal previously irreparable tissues and organs. For these reasons, nanotechnology and tissue engineering could play key roles in the discovery of novel painful bladder syndrome therapies.

#### **PHARMACOKINETIC CONSIDERATIONS FOR THERAPIES USED TO TREAT INTERSTITIAL CYSTITIS.**



*Gardella B, Porru D, Allegri M, Bogliolo S, Iacobone AD, Minella C, Nappi RE, Ferrero S, Spinillo A. Expert Opin Drug Metab Toxicol. 2014 May;10(5):673-84. doi: 10.1517/17425255.2014.896338. Epub 2014 Mar 12. PMID: 24621003*

Introduction: Interstitial cystitis (IC) or bladder pain syndrome (BPS) is defined as supra-pubic pain related to bladder filling. IC is characterized by a particular symptom complex with no identifiable causes; as with bladder hypersensitivity it is usually associated with urinary frequency and urgency with bladder pain. No current treatments have a significant impact on symptoms over time. Areas covered: This systematic review from Pavia, Italy examines the pharmacokinetic aspects and adverse event of present IC therapy to highlight appropriate treatment to improve the symptoms of IC. This article reviews material obtained via Medline, PubMed, and EMBASE literature searches up to October 2013. Expert opinion: The correct approach to IC should consider a multidisciplinary team of specialists and a multimodal treatment package that include psychotherapy, behavior change, physical activation, and analgesic treatment. Unfortunately, a single therapeutic target for IC is not yet known. With regard to pathophysiology and therapy, there is more to discover. The first insult damages the bladder urothelium, hence vehicles that lead the drug to penetrate the wall of the bladder might be a novel strategic approach.

#### **INCREASED SEVERITY OF INFLAMMATION CORRELATES WITH ELEVATED EXPRESSION OF TRPV1 NERVE FIBERS AND NERVE GROWTH FACTOR ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.**

*Liu BL, Yang F, Zhan HL, Feng ZY, Zhang ZG, Li WB, Zhou XF. Urol Int. 2014;92(2):202-8. doi: 10.1159/000355175. Epub 2014 Jan 23. PMID:24458144*

Noting that the mechanism of IC/BPS remains unknown, Liu and colleagues from Guangzhou, China investigated whether inflammation causes an elevated expression of nerve growth factor (NGF) and transient receptor potential vanilloid receptor subtype 1 (TRPV1) and correlated them with the symptoms. Bladder biopsies were obtained from 53 IC/BPS patients and 27 controls, and hematoxylin and eosin staining, immunostaining and Western blotting were performed to detect inflammation, TRPV1-immunoreactive and PGP9.5-immunoreactive nerve fibers, and NGF, respectively. Symptoms were assessed using the Pelvic Pain/Urgency/Frequency (PUF) questionnaire and pain visual analogue scale scores. Suburothelial nerve fiber density was quantified and correlated with PUF scores. Increased severity of inflammation was correlated with a higher TRPV1-immunoreactive nerve fiber density and higher NGF levels. Suburothelial TRPV1-immunoreactive nerve fiber density was significantly correlated with pain scores and urgency scores. PGP9.5-immunoreactive nerve fibers were significantly increased in IC/BPS and had a positive relationship with inflammation severity. The authors concluded that their study revealed increased severity of inflammation correlated with a higher expression of TRPV1-immunoreactive nerve fibers and NGF in IC/BPS and correlated with clinical symptoms.

*Editor's Note: for information on TRPV and what this is, [click here](#).*

#### **TRPA1 MEDIATES BLADDER HYPERALGESIA IN A MOUSE MODEL OF CYSTITIS.**

*Deberry JJ, Schwartz ES, Davis BM. Pain. 2014 3 Apr 2. pii: S0304-3959(14)00152-3. doi: 10.1016/j.pain.2014.03.023. [Epub ahead of print] PMID: 24704367*

Urinary bladder pain is a primary symptom associated with interstitial cystitis/painful bladder syndrome. Deberry and colleagues from Pittsburgh employed systemic injections of cyclophosphamide (CYP), an alkylating anti-neoplastic agent, to induce cystitis and examine the roles of two channels previously shown to be required for inflammatory visceral hyperalgesia: transient receptor potential vanilloid-1 (TRPV1) and ankyrin-1 (TRPA1). Injection of CYP (100 mg/kg, i.p.) every other day for five days was accompanied by bladder edema and urothelial ulceration, but without significant plasma extravasation or infiltration of neutrophils. Toluidine blue staining showed a significant increase in the number of degranulated bladder mast cells following CYP treatment. Despite this mild pathology, CYP-treated mice exhibited bladder hyperalgesia one day following the final injection that persisted seven days later. Although many previous studies of visceral hyperalgesia have reported changes in dorsal root ganglion neuron TRPV1 expression and/or function, they found no change in bladder afferent TRPV1 expression or sensitivity, based on the percentage of bladder afferents responsive to capsaicin, including at sub-maximal concentrations. In contrast, the percentage of bladder afferents expressing functional TRPA1 protein (i.e., those responsive to mustard oil) increased ~2.5-fold one day after CYP

treatment, and remained significantly elevated seven days later. Moreover, bladder hyperalgesia was reversed by acute treatment with the TRPA1 antagonist, HC-030031 (300 mg/kg, i.p.). Their results indicate that CYP-induced bladder hyperalgesia can be induced without robust inflammation or changes in primary afferent TRPV1. However, significant changes were seen in TRPA1 expression, and blockade of TRPA1 alleviated CYP-induced bladder hyperalgesia.

#### **METALLOTHIONEIN OVEREXPRESSION OF BLADDER BIOPSIES ASSOCIATED WITH TISSUE HYPOXIA IN PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.**

*Lee JD, Lee MH. Int J Urol. 2014 Apr 2. doi: 10.1111/iju.12402. [Epub ahead of print]. PMID: 24698414*

The purpose of this study from Taiwan was to examine the relationship between hypoxia and metallothionein expression in bladder biopsies of 41 interstitial cystitis/painful bladder syndrome patients with a control group consisting of 12 volunteers without any interstitial cystitis/painful bladder syndrome symptoms. All biopsy specimens were analyzed for both proteins of hypoxia-inducible factor-1 $\alpha$  and metallothionein expression by immunoblotting, immunostaining and confocal laser scanning microscopy. Data were analyzed using the Mann-Whitney U-test. An increased expression of hypoxia-inducible factor-1 $\alpha$  and metallothionein was noted in the study group compared with the control group. Both proteins of hypoxia-inducible factor-1 $\alpha$  and metallothionein mainly distributed over bladder urothelium by immunohistochemical staining, and showed co-localization under confocal microscopy. High expression and co-localization of metallothionein and hypoxia-inducible factor-1 alpha in the bladder mucosa of patients with interstitial cystitis suggest that overexpression of metallothionein is associated with the bladder hypoxia related to this disease.

#### **CONDITIONED MEDIUM DERIVED FROM MESENCHYMAL STEM CELLS CULTURE AS A INTRAVESICAL THERAPY FOR CYSTITIS INTERSTITIALS.**

*Adamowicz J, Pokrywczyńska M, Drewa T. Med Hypotheses. 2014 Jun;82(6):670-3. doi: 10.1016/j.mehy.2014.02.027. Epub 2014 Mar 4. PMID: 24679668*

The treatment of Interstitial Cystitis (IC) is still a challenge for the urologist. Available therapies do not result in long-term control of symptoms and do not provide pain relief for patients. Unique abilities of mesenchymal stem cells (MSC) could be used to develop new treatment approaches for IC. Conditioned Medium (CM) derived from MSC culture is rich in growth factors, cytokines and trophic agents which were widely reported to enhance regeneration of urinary bladder in different conditions. Adamowicz and colleagues from Poland suggest that this ready mixture of growth factors could be used to develop intravesical therapy for patients with IC. MSC-CM has anti-apoptotic, anti-inflammatory, supportive, angiogenic, immunosuppressive and immunomodulative properties and seems to be an ideal substance to prevent IC recurrence and to create a favourable environment for the regeneration of damaged bladder wall.

#### **NERVE GROWTH FACTOR AND NOCICEPTION: FROM EXPERIMENTAL EMBRYOLOGY TO NEW ANALGESIC THERAPY.**

*Lewin GR, Lechner SG, Smith ES. Handb Exp Pharmacol. 2014;220:251-82. doi: 10.1007/978-3-642-45106-5\_10. PMID: 24668476*

Nerve growth factor (NGF) is central to the development and functional regulation of sensory neurons that signal the first events that lead to pain. These sensory neurons, called nociceptors, require NGF in the early embryo to survive and also for their functional maturation. The long road from the discovery of NGF and its roles during development to the realization that NGF plays a major role in the pathophysiology of inflammatory pain will be reviewed. In particular, the authors from Berlin discuss the various signalling events initiated by NGF that lead to long-lasting thermal and mechanical hyperalgesia in animals and in man. It has been realized relatively recently that humanized function blocking antibodies directed against NGF show remarkably analgesic potency in human clinical trials for painful conditions as varied as osteoarthritis, lower back pain, and interstitial cystitis. Thus, anti-NGF medication has the potential to make a major impact on day-to-day chronic pain treatment in the near future. It is therefore all the more important to understand the precise pathways and mechanisms that are controlled by NGF to both initiate and sustain mechanical and thermal hyperalgesia. Recent work suggests that NGF-dependent regulation of the mechanosensory properties of sensory neurons

that signal mechanical pain may open new mechanistic avenues to refine and exploit relevant molecular targets for novel analgesics.

*Editor's Note: for information on nerve growth factor, [click here](#).*

#### **URINARY NERVE GROWTH FACTOR LEVELS COULD BE A BIOMARKER FOR OVERACTIVE BLADDER SYMPTOM: A META-ANALYSIS.**

*Qu HC, Yan S, Zhang XL, Zhu XW, Liu YL, Wang P. Genet Mol Res. 2014 Apr 14;13(AOP). [Epub ahead of print] PMID: 24782215*

In this meta-analysis from Shenyang, China, Qu and colleagues examined whether urinary tract nerve growth factor (uNGF) could be a biomarker for overactive bladder (OAB) symptoms. They conducted a comprehensive meta-analysis of 8 case-control studies. In all the studies considered, patients with OAB symptoms had a higher uNGF level compared to healthy people. In addition, patients had a significantly lower uNGF level after successful treatment. In the subgroup analysis, they found that patients with OAB-wet symptoms had a higher uNGF level than patients with OAB-dry symptoms. However, no significant difference was found between patients with OAB symptoms and patients with interstitial cystitis/painful bladder syndrome (IC/PBS) symptoms in uNGF/Cr levels. The authors concluded that uNGF level could be a useful biomarker for the diagnosis of OAB, a possible biomarker for differentiation between OAB subtypes (wet or dry), and a predictive biomarker for a specific treatment, but that it cannot be used as the urinary biomarker for the differential diagnosis of IC/PBS and OAB.

#### **THE ROLE(S) OF CYTOKINES/CHEMOKINES IN URINARY BLADDER INFLAMMATION AND DYSFUNCTION.**

*Gonzalez EJ, Arms L, Vizzard MA. Biomed Res Int. 2014;2014:120525. Epub 2014 Mar 12. PMID: 24738044*

Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a chronic pain syndrome characterized by pain, pressure, or discomfort perceived to be bladder related and with at least one urinary symptom. It was recently concluded that 3.3-7.9 million women (>18 years old) in the United States exhibit BPS/IC symptoms. The impact of BPS/IC on quality of life is enormous and the economic burden is significant. Although the etiology and pathogenesis of BPS/IC are unknown, numerous theories including infection, inflammation, autoimmune disorder, toxic urinary agents, urothelial dysfunction, and neurogenic causes have been proposed. Altered visceral sensations from the urinary bladder (i.e., pain at low or moderate bladder filling) that accompany BPS/IC may be mediated by many factors including changes in the properties of peripheral bladder afferent pathways such that bladder afferent neurons respond in an exaggerated manner to normally innocuous stimuli (allodynia). The goals for this review from the Department of Neurological Sciences, University of Vermont College of Medicine were to describe chemokine/receptor (CXCL12/CXCR4; CCL2/CCR2) signalling and cytokine/receptor (transforming growth factor (TGF- $\beta$ )/TGF- $\beta$  type 1 receptor) signalling that may be valuable LUT targets for pharmacologic therapy to improve urinary bladder function and reduce somatic sensitivity associated with urinary bladder inflammation.

#### **IMMUNOMODULATORY ACTIVITY OF ORPHAN DRUG ELMIRON® IN FEMALE B6C3F1/N MICE.**

*Thakur SA, Nyska A, White KL Jr, Smith MJ, Auttachoat W, Germolec DR. Food Chem Toxicol. 2014 Mar 20;68C:196-203. doi: 10.1016/j.fct.2014.03.015. [Epub ahead of print] PMID: 24657363*

Interstitial cystitis (IC) is a chronic disorder characterized by bladder discomfort and urinary urgency in the absence of identifiable infection. Despite the expanding use in IC treatment and other chronic conditions, the effects of Elmiron® treatment on immune system remain unknown. Therefore, female B6C3F1/N mice were orally administered Elmiron® daily for 28-days at doses of 63, 125, 250, 500 or 1000mg/kg to evaluate its immunomodulatory effects. Mice treated with Elmiron® had a significant increase in absolute numbers of splenic macrophages (63, 500 and 1000mg/kg) and natural killer (NK) cells (250 and 1000mg/kg). Elmiron® treatment did not affect the humoral immune response or T cell proliferative response. However, innate immune responses such as phagocytosis by liver macrophages (1000mg/kg) and NK cell activity were enhanced (500 and 1000mg/kg). Further analysis using a disease resistance model showed that Elmiron®-treated mice demonstrated significantly increased anti-tumor activity against B16F10 melanoma cells at the 500 and 1000mg/kg doses. Collectively, the authors conclude that Elmiron® administration stimulates the immune system, increasing numbers of specific cell populations and enhancing macrophage phagocytosis and NK cell

activity in female B6C3F1/N mice. This augmentation may have largely contributed to the reduced number of B16F10 melanoma tumors.

#### **EVALUATION OF THE METABOLISM OF GLYCOSAMINOGLYCANS IN PATIENTS WITH INTERSTITIAL CYSTITIS.**

*Lucon M, Martins JR, Leite KR, Soler R, Nader HB, Srougi M, Bruschini H. Int Braz J Urol. 2014 Jan-Feb;40(1):72-9. doi: 10.1590/S1677-5538.IBJU.2014.01.11. PMID: 24642152*

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Painful bladder syndrome/interstitial cystitis (PBS/IC) pathogenesis is not fully known, but evidence shows that glycosaminoglycans (GAG) of bladder urothelium can participate in its genesis. The loss of these compounds facilitates the contact of urine compounds with deeper portions of bladder wall triggering an inflammatory process. Lucon and colleagues from Sao Paulo, Brazil investigated GAG in urine and tissue of PBS/IC and pure stress urinary incontinence (SUI) patients to better understand its metabolism. Tissue and urine of 11 patients with PBS/IC according to NIDDK criteria were compared to 11 SUI patients. Tissue samples were analyzed by histological, immunohistochemistry and immunofluorescence methods. Statistical analyses were performed using the Student test and Anova, considered significant when  $p < 0.05$ . Results showed that PBS/IC patients had lower concentration of GAG in urine when compared to SUI. However, there was no reduction in the content of GAG in the urothelium of both groups. Immunofluorescence showed that PBS/IC patients had a stronger staining of TGF-beta, decorin (a proteoglycan of chondroitin/dermatan sulfate), fibronectin and hyaluronic acid. The results suggest that GAG may be related to the ongoing process of inflammation and remodelling of the dysfunctional urothelium that is present in PBS/IC.

#### **GAGS AND GAGS DISEASES: WHEN PATHOPHYSIOLOGY SUPPORTS THE CLINIC.**

*Costantini E, Lazzeri M, Porena M. Urologia. 2013 Oct 18;80(3):173-8. doi: 10.5301/RU.2013.11500. Epub 2013 Sep 30. PMID: 24526593*

The urinary epithelium has been the subject of considerable interest and much research in recent years. According to Costantini and colleagues from Italy, what has radically changed in the last decade is the concept of what the bladder epithelium really is. It is currently no longer considered just a simple barrier and a non-specific defence against infections, and it has been recognized as a specialized tissue regulating complex bladder functions and playing a fundamental and active role in the pathogenesis of cystitis. Researchers have been focusing on the receptors and mediators that are active in the sub-epithelial layer, in the hope that understanding the role of the urothelium defect will offer opportunities for new therapeutic strategies. On the surface of the urothelial umbrella-cells, there is a thick layer of glycoproteins and proteoglycans, which together are called Glycosaminoglycans (GAGs). They constitute a hydrophilic mucosal coating and act as a barrier against solutes found in urine. In recent years they have received special attention because injury to Gags, due to different noxae, has been identified as the first step in the genesis of chronic inflammatory bladder diseases, such as recurrent urinary tract infections, chemical or radiation cystitis, interstitial cystitis and/or Bladder Pain Syndrome. The aim of this study was to define the importance of the urothelium starting from the anatomy and physiology of the bladder wall. Furthermore, they underline the role of glycosaminoglycans, focusing both on their pathophysiological role in the principal bladder diseases and on the therapeutic aspects from the clinical point of view.

#### **CHANGES IN SEXUAL FUNCTION OF WOMEN WITH REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AFTER INTRAVESICAL THERAPY WITH A HYALURONIC ACID SOLUTION.**

*Hung MJ, Su TH, Lin YH, Huang WC, Lin TY, Hsu CS, Chuang FC, Tsai CP, Shen PS, Chen GD. J Sex Med. 2014 Mar 17. doi: 10.1111/jsm.12507. [Epub ahead of print] PMID: 24636240*

Intravesical instillation with a hyaluronic acid (HA) solution is an effective treatment for interstitial cystitis/bladder pain syndrome (IC/BPS), but its impact on sexual functioning of patients is not known. The aim of this study from Taiwan was to evaluate the changes in sexual function of women with refractory IC/BPS who underwent a second-line intravesical HA therapy. A total of 103 women diagnosed with refractory IC/BPS were enrolled in this prospective, multicenter study. Sexual function was evaluated using the short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-9). Bladder-related symptoms and bother were assessed by the Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index

(ICPI), and a pain visual analog scale (VAS), respectively. Data were analyzed with univariate methods or multivariate logistic regression analysis accordingly. Changes in PISQ-9, ICSI, ICPI, and pain VAS scores after treatment were assessed. Mean age and duration of symptoms was  $43.6 \pm 11.8$  and  $5.1 \pm 5.0$  years, respectively. ICSI, ICPI, and pain VAS scores were significantly improved after 1 month and 6 months of treatment. Of the 87 (84.5%) sexually active women evaluated, PISQ-9 total scores improved significantly from the baseline, after 1 month, and 6-months of treatment. Significantly improved PISQ-9 items included "dyspareunia" and "negative reactions" during sexual intercourse, and "intensity" of sexual orgasms. After a logistic regression analysis, the authors found that a baseline PISQ-9 score was negatively correlated with the duration of IC/BPS symptoms. Meanwhile, the changes in PISQ-9 scores were positively correlated with the reduction in ICSI scores after treatment. It was concluded that intravesical HA is an effective treatment for refractory IC/BPS. A longer duration of IC/BPS symptoms may be a predictor of poor sexual function. However, intravesical HA may improve sexual function along with the reduction of IC/BPS symptoms.

**DECREASE OF URINARY NERVE GROWTH FACTOR BUT NOT BRAIN-DERIVED NEUROTROPHIC FACTOR IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME TREATED WITH HYALURONIC ACID.**

Jiang YH, Liu HT, Kuo HC. *PLoS One*. 2014 Mar 10;9(3):e91609. doi: 10.1371/journal.pone.0091609. eCollection 2014. PMID: 24614892

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The aim of this study from Taiwan was to investigate urinary nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) levels in interstitial cystitis/bladder pain syndrome (IC/BPS) patients after hyaluronic acid (HA) therapy. Thirty-three patients with IC/BPS were prospectively studied; a group of 45 age-matched healthy subjects served as controls. All IC/BPS patients received nine intravesical HA instillations during the 6-month treatment regimen. Urine samples were collected for measuring urinary NGF and BDNF levels at baseline and 2 weeks after the last HA treatment. The clinical parameters including visual analog scale (VAS) of pain, daily frequency nocturia episodes, functional bladder capacity (FBC) and global response assessment (GRA) were recorded. Urinary NGF and BDNF levels were compared between IC/BPS patients and controls at baseline and after HA treatment. Urinary NGF, NGF/Cr, BDNF, and BDNF/Cr levels were significantly higher in IC/BPS patients compared to controls. Both NGF and NGF/Cr levels significantly decreased after HA treatment. Urinary NGF and NGF/Cr levels significantly decreased in the responders with a VAS pain reduction by 2 (both  $p < 0.05$ ) and the GRA improved by 2 (both  $p < 0.05$ ), but not in non-responders. Urinary BDNF and BDNF/Cr did not decrease in responders or non-responders after HA therapy. It was concluded that urinary NGF, but not BDNF, levels decreased significantly after HA therapy; both of these factors remained higher than in controls even after HA treatment. HA had a beneficial effect on IC/BPS, but it was limited. The reduction of urinary NGF levels was significant in responders, with a reduction of pain and improved GRA.

**COMPARISON OF INTRAVESICAL APPLICATION OF CHONDROITIN SULPHATE AND COLCHICINE IN RAT PROTAMINE/LIPOPOLYSACCHARIDE INDUCED CYSTITIS MODEL.**

Sinanoglu O, Dogan Ekici I, Ekici S. *Urol J*. 2014 Mar 4;11(1):1296-300. PMID: 24595940

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The purpose of this study from Turkey was to investigate beneficial effect of the readily available colchicine through its intravesical application on protamine/lipopolysaccharide induced interstitial cystitis model in rats and to compare its efficacy to the chondroitin sulphate available for clinical use. Twenty-four Wistar female rats were assigned to control (C), interstitial cystitis (IC), chondroitin sulphate (CS) and colchicine (Col) groups. IC, CS and Col groups received protamine sulphate and lipopolysaccharide (PS/LPS) instillation. Testing agents CS and Col were administered a day after PS/LPS inoculation into the bladders. Rats in Group C received saline solution. CS and Col groups received 1 mL CS (0.2%) and 1 mL Col (0.05 mg/mL). The treatment agents were left in bladders for one hour's duration. Animals were sacrificed 5 days after the inoculation and the bladder tissues were examined histologically to evaluate the amount of extravasated leucocytes, mast cell concentration (by counting total number of cells per 10 high power field (hpf; 1 hpf =  $\times 400$  magnification) as well as interstitial tissue edema for each bladder. The results indicated that intravesical application of CS significantly reduced the leucocyte and mast cell infiltration as well as interstitial edema compared to group C. The level of reduction in leucocyte and mast cell infiltration in Col group was comparable to that of CS, although the interstitial edema was not resolved. It was concluded that intravesical administration of Col decreased



leucocyte and mast cell infiltration to the same extent of CS in PS/LPS induced bladder inflammation in rat. Col may be an alternative to other treatment modalities for painful bladder conditions.

#### **INTRAVESICAL TREATMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: FROM THE CONVENTIONAL REGIMENS TO THE NOVEL BOTULINUM TOXIN INJECTIONS.**

*Dellis A, Papatsoris AG. Expert Opin Investig Drugs. 2014 Apr 22. [Epub ahead of print] PMID: 24749738*

Dellis and Papatsoris from Greece note that none of the numerous existing oral and intravesical treatments have been effective for all of the BPS subtypes and therefore relevant research is ongoing. In this review, the authors analyze the existing literature for the intravesical treatment of BPS/IC with focus on the novel administration of botulinum toxin (BTX). Several intravesical drugs have been studied in the past, including lidocaine, heparin, pentosan polysulfate sodium, dimethyl sulfoxide, chondroitin sulfate, hyaluronic acid as well as investigational drugs such as GM-0111. Recently, intravesical submucosal injections of BTX have been studied in patients with BPS/IC. Most of the recent studies use BTX-A with no serious adverse effects and with satisfactory results in patients who do not respond to oral or standard intravesical therapy. Nevertheless, there is no consensus regarding the best dosage scheme of BTX, the injection sites and the treatment intervals. BTX intravesical administration in patients with BPS/IC is a safe and efficient treatment option; yet the level of evidence of the initial studies is not high. The authors emphasize that there is still a need for large randomized controlled studies so that a consensus can be reached for the ideal BTX dosage, injection sites and intervals between treatments.

#### **ULCERATIVE AND NONULCERATIVE FORMS OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS DO NOT DIFFER IN SYMPTOM INTENSITY OR RESPONSE TO ONABOTULINUM TOXIN A**

*Pinto R, Lopes T, Costa D, Barros S, Silva J, Silva C, Cruz C, Dinis P, Cruz F. Urology. 2014 May;83(5):1030-4. doi: 10.1016/j.urology.2014.01.018. PMID: 24767520*

The purpose of this study from Portugal was to determine whether intratrigenal Onabotulinum toxin A (OnabotA) injection produces a different symptomatic outcome and duration of effect on ulcerative (Ulc) and nonulcerative (NULc) bladder pain syndrome/interstitial cystitis (BPS/IC) patients and to compare the urinary levels of neurotrophines (NGF, BDNF, and GDNF) in response to OnabotA. Ten Ulc and 14 NULc bladder pain syndrome/interstitial cystitis patients were included in this study. OnabotA (100 U) was injected in 10 trigonal sites, each receiving 10 U in 1 mL of saline. Outcome measures included pain visual analog scale (0-10), a 3-day voiding chart, O'Leary-Sant Score (OSS), and quality of life (QoL) from International Prostate Symptoms Score assessed before treatment, 1 month after injection, and every 3 months afterwards. Urinary NGF, BDNF, and GDNF were accessed using ELISA, at same time points. Treatment duration was determined at the time patients requested another injection. The authors found that in this cohort Ulc and NULc patients had similar symptoms at baseline and comparable clinical response to intratrigenal OnabotA. These findings suggest that pain may not be directly related with ulcers themselves.

#### **USE AND EFFECTIVENESS OF COMPLEMENTARY THERAPIES AMONG WOMEN WITH INTERSTITIAL CYSTITIS.**

*Anderson R, Zinkgraf K. Urol Nurs. 2013 Nov-Dec;33(6):306-9, 311. PMID: 24592524*

Interstitial cystitis is a chronic condition that may go undiagnosed for years. Patients may turn to complementary therapies to find relief of symptoms. A survey was done at Waukesha Memorial Hospital, Waukesha, USA to assess the use and effectiveness of these therapies by adult women diagnosed with the disorder.

#### **EVALUATION OF SELECTIVE CANNABINOID CB1 AND CB2 RECEPTOR AGONISTS IN A MOUSE MODEL OF LIPOPOLYSACCHARIDE-INDUCED INTERSTITIAL CYSTITIS.**

*Tambaro S, Casu MA, Mastinu A, Lazzari P. Eur J Pharmacol. 2014 Apr 15;729:67-74. doi: 10.1016/j.ejphar.2014.02.013. Epub 2014 Feb 20. PMID: 24561047*

In this study, Tambaro and colleagues from Italy and the USA evaluated the anti-inflammatory effect of selective cannabinoid CB1 and CB2 receptor agonists in a mouse model of interstitial cystitis. Bladder inflammation was induced in mice by lipopolysaccharide (LPS) and whole bladders were removed 24h later. LPS induced a significant increase of the contractile amplitude in spontaneous activity and a hypersensitivity to exogenous acetylcholine-induced contraction of whole-isolated bladder. They then evaluated the anti-



inflammatory activity of cannabinoidergic compounds by pre-treating mice with CB1 or CB2 selective agonist compounds, respectively ACEA and JWH015. Interestingly, JWH015, but not ACEA, antagonized LPS-induced bladder inflammation. Additionally, anti-inflammatory activity was studied by evaluation, leukocytes mucosa infiltration, myeloperoxidase activity, and mRNA expression of pro-inflammatory interleukin (IL-1 $\alpha$  and IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ) and cannabinoid CB1 and CB2 receptors. JWH015 significantly decreased leukocytes infiltration in both submucosa and mucosa, as well as the myeloperoxidase activity, in LPS treated mice. JWH015 reduced mRNA expression of IL-1 $\alpha$ , IL-1 $\beta$ , and TNF- $\alpha$ . LPS treatment increased expression of bladder CB2 but not CB1 mRNA. Taken together, the authors are of the opinion that these findings strongly suggest that modulation of the cannabinoid CB2 receptors might be a promising therapeutic strategy for the treatment of bladder diseases and conditions characterized by inflammation, such as interstitial cystitis.

#### **INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: EPIDEMIOLOGY, PATHOPHYSIOLOGY AND EVIDENCE-BASED TREATMENT OPTIONS.**

*Davis NF, Brady CM, Creagh T. Eur J Obstet Gynecol Reprod Biol. 2014 Apr;175C:30-37. doi: 10.1016/j.ejogrb.2013.12.041. Epub 2014 Jan 13. PMID: 24480114*

Davis and colleagues from Ireland note that the prevalence of interstitial cystitis/painful bladder syndrome (IC/PBS) is believed to range from 52 to 500/100,000 in females compared to 8-41/100,000 in males, and its incidence is increasing globally. Treatment algorithms are sub-classified into behavioural, pharmacological, intravesical, interventional and surgical therapies. Short-term (i.e. <1 year) cure rates range from 50% to 75% for non-/minimally-invasive therapies, but repeat administration of a therapeutic agent is required. Although definitive surgical intervention is associated with greater long-term cure rates ( $\geq 80\%$ ); significant short- and long-term adverse effects occur more frequently. Clinicians are likely to experience increasing numbers of patients with IC/PBS as more is understood about its pathophysiology and evolving epidemiology. Therefore, the authors urge urogynaecologists to familiarise themselves with appropriate diagnostic criteria and evidence based therapies to optimise clinical outcomes in these patients.

#### **INTRAVESICAL LIPOSOME AND ANTISENSE TREATMENT FOR DETRUSOR OVERACTIVITY AND INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.**

*Tyagi P, Kashyap MP, Kawamorita N, Yoshizawa T, Chancellor M, Yoshimura N. ISRN Pharmacol. 2014 Jan 15;2014:601653. eCollection 2014. PMID: 24527221*

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The following review from Pittsburgh and Royal Oak, USA focuses on the recent advancements in intravesical drug delivery, which bring added benefit to the therapy of detrusor overactivity and interstitial cystitis/painful bladder syndrome (IC/PBS). Intravesical administration is a preferred route for restricting the action of extremely potent drugs like DMSO for patients with interstitial cystitis/painful bladder syndrome (IC/PBS) and botulinum toxin for detrusor overactivity. Patients who are either refractory to oral treatment or need to mitigate the adverse effects encountered with conventional routes of administration also choose this route. Its usefulness in some cases can be limited by vehicle (carrier) toxicity or short duration of action. Efforts have been underway to overcome these limitations by developing liposome platform for intravesical delivery of biotechnological products including antisense oligonucleotides. The authors conclude that adoption of forward-thinking approaches can achieve advancements in drug delivery systems targeted to future improvement in pharmacotherapy of bladder diseases. Latest developments in the field of nanotechnology can bring this mode of therapy from second line of treatment for refractory cases to the forefront of disease management.

#### **URINARY BLADDER MUCOSAL RESPONSES TO ISCHEMIA.**

*Sunagawa M, Wolf-Johnston A, Nomiya M, Sawada N, Andersson KE, Hisamitsu T, Birder LA. World J Urol. 2014 Apr 12. [Epub ahead of print] PMID: 24728265*

The objectives of this study from Pittsburgh were to examine the expression of various cellular proteins within the urothelium (UT) and lamina propria (LP) following chronic bladder ischemia in the rat urinary bladder. The authors report that their findings reveal that chronic ischemia alters a number of proteins within the UT and underlying LP. These proteins are involved in barrier function, remodeling, repair as well as intercellular communication. The increased expression of LP-vimentin-IR cells suggests that changes in cell-cell interactions could play a role in ischemia-induced changes in bladder activity.

### **BLADDER SENSORY PHYSIOLOGY: NEUROACTIVE COMPOUNDS/RECEPTORS, SENSORY TRANSDUCERS AND TARGET-DERIVED GROWTH FACTORS AS TARGETS TO IMPROVE FUNCTION.**

Gonzalez EJ, Merrill L, Vizzard MA. *Am J Physiol Regul Integr Comp Physiol.* 2014 Apr 23. [Epub ahead of print] PMID: 24760999

Urinary bladder dysfunction presents a major problem in the clinical management of patients suffering from pathological conditions and neurological injuries or disorders. Currently, the etiology underlying altered visceral sensations from the urinary bladder that accompany the chronic pain syndrome, bladder pain syndrome (BPS)/interstitial cystitis (IC), is not known. Bladder irritation and inflammation are histopathological features that may underlie BPS/IC that can change the properties of lower urinary tract sensory pathways (e.g., peripheral and central sensitization, neurochemical plasticity) and contribute to exaggerated responses of peripheral bladder sensory pathways. Among the potential mediators of peripheral nociceptor sensitization and urinary bladder dysfunction are neuroactive compounds (e.g., purinergic and neuropeptide/receptor pathways), sensory transducers (e.g., transient receptor potential channels) and target-derived growth factors (e.g., nerve growth factor). Gonzalez and colleagues from Vermont review studies related to the organization of the afferent limb of the micturition reflex and discuss neuroplasticity in an animal model of urinary bladder inflammation to increase the understanding of functional bladder disorders and to identify potential novel targets for development of therapeutic interventions. Given the heterogeneity of BPS/IC and the lack of consistent treatment benefits, it is unlikely that a single treatment directed at a single target in micturition reflex pathways will have a mass benefit. Thus, identification of multiple targets is a prudent approach and use of cocktail treatments directed at multiple targets should be considered.

### **HEALTH CARE SERVICE UTILIZATION AMONG PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS IN A SINGLE PAYER HEALTHCARE SYSTEM.**

Chung SD, Liu SP, Li HC, Lin HC. *PLoS One.* 2014 Jan 29;9(1):e87522. doi: 10.1371/journal.pone.0087522. eCollection 2014. PMID: 24489932

This study from Taiwan investigated the differences in the utilization of healthcare services between patients with bladder pain syndrome/interstitial cystitis (BPS/IC) and patients without BPS/IC, using a population-based database in Taiwan, with 350 patients with BPS/IC and 1,750 age-matched controls. Healthcare resource utilization was evaluated in the one-year follow-up period as follows: the number of outpatient visits and inpatient days, and the mean costs of outpatient and inpatient treatment. A multivariate regression analysis was used to evaluate the relationship between BPS/IC and total costs of health care services. Chung and colleagues found that patients with BPS/IC have a significantly higher number of healthcare-related visits, and have significantly higher healthcare related costs than age-matched controls. The high level of healthcare services utilization accrued with BPS/IC was not necessarily exclusive for BPS/IC, but may have also been associated with medical comorbidities.

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

Fan YH, Lin AT, Lu SH, Chuang YC, Chen KK. *Int J Urol.* 2014 Apr 13. doi: 10.1111/iju.12456. [Epub ahead of print] PMID: 24724573

This study by Fan and colleagues from Taiwan aimed to detect non-bladder conditions in patients with interstitial cystitis/hypersensitive bladder syndrome. A total of 122 female interstitial cystitis/hypersensitive bladder syndrome patients and a control group of 122 age-matched female patients with stress urinary incontinence completed screening questionnaires for irritable bowel syndrome, temporomandibular disorder, multiple chemical sensitivities, tension and migraine headache, localized myofascial pain disorder, and fibromyalgia. Interstitial cystitis/hypersensitive bladder syndrome patients also completed questionnaires on interstitial cystitis/hypersensitive bladder syndrome symptom severity, including the O'Leary-Sant symptom index, and the visual analog scale for pain and urgency. Interstitial cystitis/hypersensitive bladder syndrome patients were more likely to meet diagnostic criteria for irritable bowel syndrome than controls (37.5% vs 11.5%), and tension/migraine headache (38.7% vs 15.7%; all  $P < 0.001$ ). The prevalence of temporomandibular disorder, multiple chemical sensitivities, localized myofascial pain disorders and fibromyalgia did not reach a statistically significant difference between the two groups. In the multivariate model, associations were also

observed for irritable bowel syndrome and tension/migraine headache. Patients with more comorbid conditions had more severe and bothersome interstitial cystitis/hypersensitive bladder syndrome symptoms as measured by the visual analog scale of pain and O'Leary-Sant bother index. They concluded that interstitial cystitis/hypersensitive bladder syndrome patients are more likely to have multiple non-bladder conditions. These conditions correlate with the severity of interstitial cystitis/hypersensitive bladder syndrome symptoms.

#### **AUTONOMIC TESTING OF WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.**

*Chelimsky G, McCabe NP, Janata J, Elston R, Zhang L, Ialacci S, Chelimsky T. Clin Auton Res. 2014 Apr 30. [Epub ahead of print] PMID: 24781351*

Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by urinary urgency, frequency, nocturia, pain worsening as the bladder fills and improving after emptying. These features might suggest abnormal autonomic bladder control mechanisms. Chelimsky and colleagues from Wisconsin compared the structural integrity of the autonomic nervous system (ANS) in IC/BPS and control subjects. Differences in ANS integrity for IC/BPS subjects and controls were determined by modified Composite Autonomic Severity Score (CASS) that includes sudomotor, adrenergic and cardiovascular indices. Baseline heart rate (HR) and HRs from each of three 10 min upright segments of a tilt test were compared and trend analyses performed using t tests. Healthy and IC/BPS subjects were demographically similar. The two groups did not differ in modified-CASS scores but elevated average peak heart rate was evident during baseline (supine;  $p = 0.057$ ) for IC/BPS subjects prior to a tilt test. Difference at baseline was maintained at each interval during the tilt, with nearly identical slopes across intervals. The preliminary nature of this report denotes a small sample size and important differences may not be detected. The authors report that their findings show no structural ANS abnormalities in IC/BPS subjects. Higher baseline HR supports the concept of functional rather than structural change in the ANS, such as abnormality of sympathetic/parasympathetic balance that will require further evaluation.

#### **[RISK FACTORS FOR INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS PRESENTING FOR UROLOGIC CARE].**

[Article in Chinese]

*He Q, Yang Y, Xia M, Zhang N, Wu S, Xiao Y, Li G, Zhan S, Liu L, Xiao H, Zhao J. Zhonghua Yi Xue Za Zhi. 2014 Feb 14;94(6):428-32. PMID: 24754986*

The purpose of this study by He and colleagues from Beijing, China was to identify the risk factors in interstitial cystitis/painful bladder syndrome (IC/PBS) patients with lower urinary tract symptoms (LUTS) without urinary tract infection or benign prostate hyperplasia in China. A total of 954 outpatients with LUTS presenting for care to urology clinics at 8 hospitals throughout China from November 20, 2008 to August 24, 2012 were surveyed with a standardized questionnaire and validated outcome measures. The definitions for IC/PBS based on the O'Leary-Sant interstitial cystitis symptom and problem indices were used. The possible risk factors were analyzed with the Fisher's exact and Pearson chi-square tests. And multivariate predictive models were developed with binary Logistic regression methods. There were 491 females and 463 males. And 44.7% (427/954) met the criteria for IC/PBS. There was significant gender difference. After adjusting for confounding factors, bladder pain was significantly associated with stimulatory foods and anorectal disease in females. Caffeine beverage intake was the only modifiable association according to multivariate analysis of males. The authors conclude that stimulatory foods, anorectal disease and caffeine beverages are potential risk factors for IC/PBS. They note that further studies are necessary to determine their roles in the pathogenesis of this disorder.

#### **BLADDER PAIN SYNDROME: WHERE DO WE STAND NOW?**

*Chang Kit L. Curr Bladder Dysfunct Rep (2014) 9:32-40*

Bladder pain syndrome is one of the most challenging urological disorders to diagnose and manage. Symptoms can be highly debilitating for patients. The exact etiology remains unclear although there have been associations with other regional and global functional disorders. The magnitude and duration of symptom response to current therapies can be highly variable amongst patients, and even within an individual patient's course. A multidisciplinary approach is paramount and optimal therapy may involve multiple simultaneous treatments.

## URETHRAL PAIN SYNDROME

### ENIGMA OF URETHRAL PAIN SYNDROME: WHY ARE THERE SO MANY ASCRIBED ETIOLOGIES AND THERAPEUTIC APPROACHES?

Phillip H, Okewole I, Chilaka V. *Int J Urol*. 2014 Jan 21. doi: 10.1111/iju.12396. [Epub ahead of print] PMID: 24447292

Urethral pain syndrome has had several sobriquets, which have led to much confusion over the existence of this pathological condition and the useful options in the care of the afflicted patient. The aim of this study from the Department of Obstetrics and Gynecology, Royal Derby Hospital, Derby, UK was to explore the proposed etiologies of this syndrome, and to provide a critical analysis of each proposed etiology and present a balanced argument on the plausibility of the proposed etiology and therapeutic approaches. They carried out an English language electronic search using the following search terms: urethral syndrome, urethral diseases, urethra, urologic diseases etiology/etiology, presentation, treatment, outcome, therapeutics and treatment from 1951 to 2011. In excess of 200 articles were recovered. With the clearly defined objectives of analyzing the proposed etiologies and therapeutic regimes, two author(s) (HP and IO) perused the abstracts of all the recovered articles, selecting those that addressed the etiologies and therapeutic approaches to treating the urethral pain syndrome. The number of articles was reduced to 25. The full text of all 25 articles was retrieved and reviewed. This article endeavours to elucidate the most probable etiology of this condition whilst simultaneously, advancing a logical explanation for the apparent success in the treatment of this condition using a range of different therapeutic modalities. They hope that this narrative review will reduce some of the confusion around this clinical entity by combining the known facts about the disease.

## KETAMINE CYSTITIS/UROPATHY

### KETAMINE: AN UPDATE ON ITS ABUSE.

Bokor G, Anderson PD. *J Pharm Pract*. 2014 Mar 20. [Epub ahead of print] PMID: 24651639

Ketamine is a dissociative anesthetic and substance of abuse. Numerous effects can result from the abuse of ketamine. Death from acute direct toxicity is rare. Ketamine can alter numerous functions in the brain including color perception, memory, attention, cognition, reaction time, and sense of time and can produce psychological addiction. Chronic ketamine abuse can produce toxicity to the gastrointestinal and urinary tract. Gastrointestinal changes include epigastric pain, hepatic dysfunction, and impaired gallbladder activity. The most common urological condition from ketamine is cystitis but renal failure has been reported.

### EVALUATION OF THE EXTENT OF KETAMINE-INDUCED UROPATHY: THE ROLE OF CT UROGRAPHY.

Huang LK, Wang JH, Shen SH, Lin AT, Chang CY. *Postgrad Med J*. 2014 Apr;90(1062):185-90. doi: 10.1136/postgradmedj-2013-131776. Epub 2014 Jan 17. PMID: 24443558

With growing ketamine abuse, ketamine-induced uropathy (KIU) has become more prevalent in recent years. This research from Taiwan evaluates the presence, distribution and extent of KIU in the upper and lower urinary tracts by retrospectively reviewing CT urography (CTU) images. Patients diagnosed with KIU who underwent CT scanning from 1 January 2006 to 31 December 2011 were recruited. The CT protocols included three-phase CTU in six patients, split-bolus CTU in 17, two-phase CT in one and unenhanced CT in three. The CT images were retrospectively reviewed by two radiologists. A total of 27 patients participated in this study. The common CT findings included diffuse bladder wall thickening (88.9%), small bladder volume (66.7%) and perivesical inflammation (44.4%). Twelve patients (44.4%) were diagnosed with hydronephrosis, including three patients with unilateral hydronephrosis and nine with bilateral hydronephrosis. Of these patients, nine had ureteral wall thickening (33.3%) and two (7.4%) had ureterovesical junction involvement (ie, they had hydronephrosis but no ureteral wall thickening). One patient had a ureteral obstruction caused by a ureter stone. The correlation between upper urinary tract involvement and grading of the interstitial cystitis was statistically non-significant. Four patients (14.8%) had a vesicovaginal fistula which could be detected in the excretory phase only. The authors concluded that upper urinary tract involvement is common in patients with KIU. CTU might aid evaluation of the extent of KIU and prompt adequate management.

**ONE-STOP CLINIC FOR KETAMINE-ASSOCIATED UROPATHY: REPORT ON SERVICE DELIVERY MODEL, PATIENTS' CHARACTERISTICS AND NON-INVASIVE INVESTIGATIONS AT BASELINE BY A CROSS-SECTIONAL STUDY IN A PROSPECTIVE COHORT OF 318 TEENAGERS AND YOUNG ADULTS.**

*Tam YH, Ng CF, Pang KK, Yee CH, Chu WC, Leung VY, Wong GL, Wong VW, Chan HL, Lai PB. BJU Int. 2014 Feb 19. doi: 10.1111/bju.12675. [Epub ahead of print] PMID: 24552244*

The purpose of this article by Tam and colleagues from Hong Kong was to describe the service delivery model and report the baseline characteristics of patients investigated by a non-invasive approach for ketamine-associated uropathy. This was a cross-sectional study in a prospective cohort of patients who attended their first visit and underwent non-invasive investigations at a dedicated centre to treat ketamine-associated uropathy in Hong Kong from December 2011 to July 2013. Data regarding demographics, illicit ketamine use, symptoms scores and voiding function parameters at baseline were prospectively collected. Differences between active abusers and ex-abusers, and risk factors for the most symptomatic group were investigated by univariate and multivariate analysis. It was concluded that an effective service model for recruiting patients with ketamine-associated uropathy is possible. With such a service model as a platform, the authors suggest that further prospective studies are warranted to investigate the appropriate choice of treatment to this new clinical entity.

**SJÖGREN'S SYNDROME**

**CLASSIFICATION CRITERIA OF SJÖGREN'S SYNDROME.**

*Goules AV, Tzioufas AG, Moutsopoulos HM. J Autoimmun. 2014 Feb-Mar;48-49:42-5. doi: 10.1016/j.jaut.2014.01.013. Epub 2014 Jan 21.2014. PMID: 24456935*

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease that affects typically the exocrine glands causing mucosal dryness. Dry eyes and mouth are considered by far the most common and early symptoms of the disease but systemic complications may also occur. In 1993, the preliminary European criteria were proposed and widely accepted, consisting of both subjective and objective criteria. Almost ten years later, these classification criteria were revised by introducing more stringent rules and precise diagnostic procedures leading to the currently used American-European Consensus Group (AECG) criteria. The AECG criteria have been largely employed to conduct epidemiologic and clinical studies of patients with SS and proved to be more specific compared to the preliminary European criteria. The recent American College of Rheumatology/Sjögren's International Collaborative Clinical Alliance (ACR/SICCA) criteria that are based exclusively on objective tests, the stringency of the AECG criteria and the potential therapeutic use of biologic agents in SS clearly set the need for new classification criteria. Whether the new diagnostic approach will further encompass subclinical and early forms of the disease remains to be addressed by the scientific community.

**INTERSTITIAL CYSTITIS ASSOCIATED WITH PRIMARY SJÖGREN'S SYNDROME SUCCESSFULLY TREATED WITH A COMBINATION OF TACROLIMUS AND CORTICOSTEROID: A CASE REPORT AND LITERATURE REVIEW.**

*Ueda Y, Tomoe H, Takahashi H, Takahashi Y, Yamashita H, Kaneko H, Kano T, Mimori A. Mod Rheumatol. 2014 Apr 11. [Epub ahead of print] PMID: 24720552*

Ueda and colleagues from Japan report a case of interstitial cystitis (IC) associated with primary Sjögren's syndrome (SS) successfully controlled with combination therapy of tacrolimus and a corticosteroid. In 2011, a 69-year-old female, who had been diagnosed with primary SS 23 years ago, developed IC and was successfully treated with tacrolimus and prednisolone combination therapy. The mechanism of IC, including the involved autoimmunity, has not been elucidated. Clinical observation studies suggest a potential association between SS and IC. However, IC is currently thought to be underdiagnosed in patients with SS as well as in the general population. Based on their case and others reported previously, IC associated with SS responds well to immunosuppressive therapy. In particular, a combination of a calcineurin inhibitor (tacrolimus or cyclosporine) with a corticosteroid seems to be highly effective. Attention should be paid to the possibility of IC in patients with SS complaining of lower urinary tract symptoms without features of infection or other identifiable causes.

**COMPARISON OF PLASMA VITAMIN D LEVELS IN PATIENTS WITH SJÖGREN'S SYNDROME AND HEALTHY SUBJECTS.**



*Erten S, Sahin A, Altunoğlu A, Gemcioğlu E, Koca C. Int J Rheum Dis. 2014 Jan 28. doi: 10.1111/1756-185X.12298. [Epub ahead of print] PMID: 24467766*

Erten and colleagues from Turkey report that there is increasing evidence indicating that vitamin D is important in the initiation and propagation of a range of autoimmune diseases which may include Sjögren's syndrome (SS). The aim of this present study was to evaluate plasma vitamin D (vit D) levels in patients with SS and to compare this with a control group. One hundred and seven SS patients (97 [90.7%] female and 10 [9.3%] male) and 74 healthy controls (64 [86.5%] female and 10 [13.5%] male) were included into the study. Plasma baseline 25-hydroxy-vit D levels were measured by high-powered liquid chromatography method using an Agilent 1100 liquid chromatograph. The authors found that plasma vit D levels in SS patients were significantly lower than in the control group. Female SS patients had significantly lower vit D levels than controls but this difference was not present among the male patients and controls. There was no correlation between plasma vit D levels and erythrocyte sedimentation rate and C-reactive protein in SS patients. It was concluded that Vit D deficiency was frequent in patients with SS. In particular, female SS patients had the risk of vit D deficiency. It may be convenient to look for vit D deficiency and to correct vit D nutritional status in SS patients.

#### **RENAL TUBULAR DYSFUNCTION IN PATIENTS WITH PRIMARY SJÖGREN SYNDROME.**

*Duffles Amarante GB, Zotin MC, Rocha E, Delgado AG, Leite Jr M, Gomes CP. Clin Nephrol. 2014 Mar;81(3):185-91. doi: 10.5414/CN108142. PMID: 24424087*

Primary Sjögren's syndrome (pSS) is an important cause of renal tubular dysfunction in adults, mainly due to acquired type 1 distal renal tubular acidosis (RTA 1) and concentration defects (CD). This cross-sectional study evaluated renal tubular function of patients with pSS, by detecting proximal tubular injury (through measurements of urinary  $\beta_2$  microglobulin and albumin), RTA 1 (through an acidification protocol using furosemide and fludrocortisone), and CD (through water deprivation test, WDT). A total of 25 patients with pSS were evaluated and despite a preserved renal function, 24% were diagnosed as RTA 1. On the other hand, CD was diagnosed in 28% of the patients who presented worse renal function. Increased  $\beta_2$  microglobulin was found in 16% of the patients, and all of them had impaired renal function. These data showed a high prevalence of tubular dysfunction, mainly RTA 1 and CD, in patients with pSS, and suggest that patients with this disorder should be evaluated by the acidification protocol used in this study and WDT for proper diagnosis. Proximal tubular injury was less common, and probably associated with worsening of renal function.

#### **EVERYTHING YOU NEED TO KNOW ABOUT DISTAL RENAL TUBULAR ACIDOSIS IN AUTOIMMUNE DISEASE.**

*Both T, Zietse R, Hoom EJ, van Hagen PM, Dalm VA, van Laar JA, van Daele PL. Rheumatol Int. 2014 Mar 29. [Epub ahead of print] PMID: 24682397*

Renal acid-base homeostasis is a complex process, effectuated by bicarbonate reabsorption and acid secretion. Impairment of urinary acidification is called renal tubular acidosis (RTA). Distal renal tubular acidosis (dRTA) is the most common form of the RTA syndromes. Multiple pathophysiologic mechanisms, each associated with various etiologies, can lead to dRTA. The most important consequence of dRTA is (recurrent) nephrolithiasis. The diagnosis is based on a urinary acidification test. Potassium citrate is the treatment of choice.

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

### **GASTRO-INTESTINAL DISORDERS**

#### **ASSOCIATIONS AMONG GUT PERMEABILITY, INFLAMMATORY MARKERS, AND SYMPTOMS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME.**

*Shulman RJ, Jarrett ME, Cain KC, Broussard EK, Heitkemper MM. J Gastroenterol. 2014 Jan 17. [Epub ahead of print] PMID: 24435814*

Alterations in gastrointestinal (GI) permeability and immune measures are present in some patients with irritable bowel syndrome (IBS) but the relationship to symptoms is poorly defined. In adults with IBS, Shulman and colleagues from Texas compared permeability, unstimulated peripheral blood monocyte (PBMC) interleukin-10 (IL-10) levels, IBS life interference, and GI and psychological distress symptoms. In 88 women and 18 men with IBS, GI permeability was quantitated as percent recovery of urinary sucrose and the



lactulose/mannitol (L/M) ratio. IL-10 was measured in supernatants from 72-h incubated, unstimulated PBMCs. Participants completed a 4-week daily diary recording IBS life interference on daily activities and work, IBS symptoms, and psychological distress symptoms. They also completed the Brief Symptom Inventory. The L/M ratio but not percent sucrose recovery was significantly correlated with IBS interference with activities and work and retrospectively measured anxiety and depression. Unstimulated PBMC production of IL-10 correlated significantly with IBS interference with daily work, IBS symptom score, and abdominal pain. The authors identified a subgroup of IBS subjects with higher IL-10 and/or higher L/M ratio who had substantially higher IBS interference and IBS symptom scores. They concluded that their findings suggest a distinct subgroup of IBS patients with alterations in gut barrier function. This subgroup is characterized by increased GI permeability and/or increased PBMC production of IL-10. These physiologic alterations reflect more severe IBS as measured by interference of IBS with daily activities and daily IBS symptoms.

## VULVODYNIA

### VULVODYNIA AND PROCTODYNIA TREATED WITH TOPICAL BACLOFEN 5 % AND PALMITOYLETHANOLAMIDE.

*Keppel Hesselink JM, Kopsky DJ, Sajben NL. Arch Gynecol Obstet. 2014 Apr 2. [Epub ahead of print]. PMID: 24691823*

In this paper from the Netherlands, Keppel Hesselink and colleagues write that the prevalence of idiopathic vulvodynia and proctodynia is high. Pain management with anti-depressants and anti-epileptics may induce undesirable side effects. They suggest that topical baclofen cream and palmitoylethanolamide might be new therapeutic options. They refer to a case of a 33-year-old woman with intractable chronic vulvar and anal pain who had to abstain from sexual intercourse and could neither cycle nor sit for more than 5 min. The patient did not respond to standard treatments. They prescribed a combination of topical baclofen 5 % and palmitoylethanolamide 400 mg, three times daily. After 3 months her symptoms decreased more than 50 % and sexual intercourse was possible again without pain. They concluded that topical baclofen and palmitoylethanolamide can be a viable treatment option in chronic vulvodynia and proctodynia.

### 2013 VULVODYNIA GUIDELINE UPDATE.

*Stockdale CK, Lawson HW. J Low Genit Tract Dis. 2014 Apr;18(2):93-100. doi: 10.1097/LGT.000000000000021. PMID: 24633161*

In this guideline update, Stockdale and Lawson from the USA note that vulvodynia is a complex disorder that can be difficult to treat. Most patients describe it as burning, stinging, irritation, or rawness. Vulvodynia is a costly disease both economically and on its negative impact on patient quality of life. Although many treatment options are available, no one treatment is effective for all patients, thus the need to individualize management. Measures such as gentle vulvar care, medication, biofeedback training, physical therapy, sexual counselling and surgery, as well as complementary and alternative therapies are available to treat the condition with varying success.

### [WHAT IS THE CURRENT STAGE OF VULVOVAGINAL DISCOMFORT DIAGNOSTICS IN THE CZECH REPUBLIC? PILOT ANALYSIS].

#### [ARTICLE IN CZECH]

*Kestřánek J, Jílek P, Matula V, Buchta V, Gregor M, Spaček J. Ceska Gynekol. 2013 Dec;78(6):522-7. PMID: 24372429*

The purpose of this Czech study was to find out the level of the diagnostic effort of gynaecologists which is focused on the issue of vulvovaginal discomfort. This was a pilot questionnaire study at the Department of Obstetrics and Gynecology, Department of Clinical Microbiology, University Hospital and Medical Faculty Hradec Králové, Charles University, Prague, Department of Biological and Medical Sciences, FaF UK in Hradec Králové, concerning the evaluation of selected parameters of entrance questionnaire in patients with chronic vulvovaginal discomfort (itching, burning, discharge, vulvodynia more than 4 times a year). It has been confirmed, with the questionnaires, that almost no gynaecologists are interested in the issue of this matter. After evaluating the questionnaires a diversion of patient-tailored attitude has been found out, which can lead

to negative consequences, particularly, in the future. Overuse of antibacterial and antimycotic medication and blind treatment have been prevailing.

#### **FACTORS ASSOCIATED WITH VULVODYNIA INCIDENCE.**

*Reed BD, Legocki LJ, Plegue MA, Sen A, Haefner HK, Harlow SD. Obstet Gynecol. 2014 Feb;123(2 Pt 1):225-31. doi: 10.1097/AOG.000000000000066. PMID: 24402591*

In this study from Michigan, Reed and colleagues assessed incidence rates of and risk factors for vulvodynia. They conducted a longitudinal population-based study of women in southeast Michigan (Woman-to-Woman Health Study) using a validated survey-based screening test for vulvodynia that was repeated at 6-month intervals over 30 months. Unadjusted incidence rates were determined using Poisson models. Demographic and symptom-related risk factors for incidence were assessed using discrete time survival analysis. Women who screened negative for vulvodynia at baseline and were followed through at least one additional survey were assessed for onset of vulvodynia. The incidence rate was 4.2 cases per 100 person-years, and rates per 100 person-years were greater in women who were younger (7.6 cases per 100 person-years at age 20 years, compared with 3.3 cases per 100 person-years at age 60 years), Hispanic (9.5 cases per 100 person-years), married, or living as married (4.9 cases per 100 person-years); had reported symptoms of vulvar pain but did not meet vulvodynia criteria on the initial survey (11.5 cases per 100 person-years); or had reported past symptoms suggesting a history of vulvodynia (7.5 cases per 100 person-years). Increased risk of new-onset vulvodynia also included baseline sleep disturbance, chronic pain in general, specific comorbid pain disorders, and specific comorbid psychological disorders. It was concluded that the incidence rates of vulvodynia differ by age, ethnicity, and marital status. Onset is more likely among women with previous symptoms of vulvodynia or those with intermediate symptoms not meeting criteria for vulvodynia and among those with pre-existing sleep, psychological, and comorbid pain disorders. This suggests vulvodynia is an episodic condition with a potentially identifiable prodromal phase.

#### **PUDENDAL NEURALGIA**

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

*Pérez-López FR, Hita-Contreras F. Climacteric. 2014 Apr 9. [Epub ahead of print] PMID: 24716710*

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

##### **VARIABILITY OF PUDENDAL AND MEDIAN NERVE SENSORY PERCEPTION THRESHOLDS IN HEALTHY PERSONS.**

*Quaghebeur J, Wyndaele JJ. NeuroUrol Urodyn. 2014 Jan 25. doi: 10.1002/nau.22565. [Epub ahead of print] PMID: 24464871*

Normative current perception thresholds (CPTs) are used for the evaluation of sensory function in a variety of diseases. The purpose of this study from Antwerp was to evaluate the reproducibility of CPT measurements with sinusoidal current in healthy volunteers. Neuroselective CPT evaluations of the median and pudendal nerve in healthy volunteers were repeated with 1 week interval. Both nerves showed deviating values. CPT values with sinusoidal current assessed with 1 week interval, showed a weak intraclass correlation. This finding limits the use of CPT values with this current for longitudinal studies.

#### **CHRONIC (PELVIC) PAIN**

##### **PREVALENCE OF CHRONIC PELVIC PAIN AMONG WOMEN: AN UPDATED REVIEW.**

Ahangari A. *Pain Physician*. 2014 Mar-Apr;17(2):E141-7. PMID: 24658485

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Chronic pelvic pain (CPP), defined as a noncyclical pain lasting for more than 6 months can lead to lower physical performance and quality of life in women. CPP is a worldwide problem affecting women of all ages. However, health care professionals and researchers, due to its complex nature and the lack of knowledge surrounding the condition, frequently neglect CPP. Subsequently, basic data and knowledge regarding CPP remain incomplete. The purpose of this systematic review of CPP prevalence studies from Umea, Sweden was to update the review of the worldwide estimation of the CPP prevalence considering the World Health Organization systematic review by Latthe et al in 2006 as point of departure. From 140 studies, only 7 studies were about CPP prevalence. Their study design consisted of 3 cross sectional studies, one population based mailing questionnaire study, one survey study (computer assisted telephone interview), one data analysis by questionnaire, and one prospective community based study. This review was limited by the paucity of population based studies in addition to probability of existence of studies at the local level with limited access to worldwide databases, lack of consensus about definition of CPP among researchers and therapists, and non-inclusion of CPP related key words in databases such as PubMed. Based on these articles, prevalence in general ranged between 5.7% and 26.6%. There were many countries and regions without basic data in the field of CPP. This review shows the paucity of studies, especially multidisciplinary researches with multifactorial views on CPP. Multidisciplinary studies would provide more reliable data for estimating the prevalence of CPP and its psycho-socioeconomic burden, as well as finding its etiologies and characteristics. This would be the first step towards better treatment and care for women with CPP.

#### **NON-SURGICAL INTERVENTIONS FOR THE MANAGEMENT OF CHRONIC PELVIC PAIN.**

Cheong YC, Smotra G, Williams AC. *Cochrane Database Syst Rev*. 2014 Mar 5;3:CD008797. doi: 10.1002/14651858.CD008797.pub2. PMID: 24595586

Cheong and colleagues note that chronic pelvic pain is a common and debilitating condition; its aetiology is multifactorial, involving social, psychological and biological factors. The management of chronic pelvic pain is challenging, as despite interventions involving surgery, many women remain in pain without a firm gynaecological diagnosis. The purpose of this review study from Southampton, UK was to assess the effectiveness and safety of non-surgical interventions for women with chronic pelvic pain. Twenty-one RCTs were identified that involved non-surgical management of chronic pelvic pain: 13 trials were included in the review, and eight were excluded. The studies included a total of 750 women-406 women in the intervention groups and 344 in the control groups. The authors concluded that evidence of moderate quality supports progestogen as an option for chronic pelvic pain, with efficacy reported during treatment. In practice, this option may be most acceptable among women unconcerned about progestogenic adverse effects (e.g. weight gain and bloating which are the most common adverse effects). Although some evidence suggests possible benefit of goserelin when compared with progestogen, gabapentin as compared with amitriptyline, ultrasound versus 'wait and see' and writing therapy versus non-disclosure, the quality of evidence is generally low, and evidence is drawn from single studies. Given the prevalence and healthcare costs associated with chronic pelvic pain in women, RCTs of other medical, lifestyle and psychological interventions are urgently required.

#### **CLINICAL PHENOTYPE STRONGLY VALIDATES CLASS MEMBERSHIP IN STAGING CHRONIC PELVIC PAIN.**

Fenton BW, Grey S, McCarroll M, Von Gruenigen V. *Obstet Gynecol*. 2014 May;123 Suppl 1:27S. doi: 10.1097/01.AOG.0000447291.00168.ea. PMID: 24770155

An easily implemented, clinically applicable staging system for chronic pelvic pain remains elusive but extremely useful. The Patient Reported Outcome Measures Information System is a multidimensional, National Institutes of Health-supported method for assessment, independent of diagnosis. Previous work has demonstrated distinct clinical phenotypes in chronic pelvic pain based on latent class modelling of a semiquantitative physical examination. The purpose of this study from Akron was to validate a newly developed Patient Reported Outcome Measures Information System-based chronic pelvic pain staging system with an examination-based phenotype. 481 patients meeting the American College of Obstetricians and Gynecologists criteria for chronic pelvic pain completed Patient Reported Outcome Measures Information System testing and a phenotyping physical examination based on four regions: pelvic abdominal wall, vulva, pelvic floor muscles, and uterosacral ligaments. The authors found that patients with chronic pelvic pain can be

classified according to this novel, multidimensional assessment into three stages: low, moderate, and severe, which are strongly predicted by physical examination-based phenotype.

#### **TARGETING CELL SURFACE TRAFFICKING OF PAIN-FACILITATING RECEPTORS TO TREAT CHRONIC PAIN CONDITIONS.**

*Ma W, Quirion R. Expert Opin Ther Targets. 2014 Apr;18(4):459-72. doi: 10.1517/14728222.2014.887683. Epub 2014 Feb 10. PMID: 24512266*

Chronic pain conditions are serious clinical concerns. Its genesis is closely associated with sensitization of nociceptive primary sensory neurons (nociceptors) and dorsal horn neurons by various pain mediators produced during inflammation and tissue injury. Growing evidence showed that increasing cell surface trafficking of pain-facilitating receptors is an important mechanism underlying the peripheral and central sensitization. Ma and Quirion from Canada have summarized the progress of this area over the past decade by showing that inflammation, tissue damage or pain mediators facilitate cell surface trafficking of pain-facilitating receptors such as transient receptor potential vanilloid-1, transient receptor potential ankyrin-1, voltage-gated sodium channel 1.8, P2X3 and EP4 in primary sensory neurons, GluR1 and GluR2 of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, NR1 and NR2 of N-methyl-d-aspartate receptors and acid-sensing ion channels 1 in dorsal horn neurons and P2X4 in spinal microglia. The anti-allodynic effects of gabapentin was mediated by blocking surface trafficking of  $\alpha 2\delta 1$  and  $\alpha 2\delta 2$  subunits of voltage-gated calcium channels in primary sensory and dorsal horn neurons. Pain mediators stimulate forward surface trafficking of their own and/or other pain-facilitating receptors to amplify pain intensity and duration. Enhancing surface abundance of pain-facilitating receptors in nociceptors and dorsal horn neurons is an important mechanism underpinning chronic pain states. According to the authors, targeting specific trafficking events of pain-facilitating receptors may open a novel therapeutic avenue to more efficiently treat chronic pain conditions.

#### **DIFFERENTIAL METHYLATION OF THE TRPA1 PROMOTER IN PAIN SENSITIVITY.**

*Bell JT, Loomis AK, Butcher LM, Gao F, Zhang B, Hyde CL, Sun J, Wu H, Ward K, Harris J, Scollen S, Davies MN, Schalkwyk LC, Mill J; MuTHER Consortium, Williams FM, Li N, Deloukas P, Beck S, McMahon SB, Wang J, John SL, Spector TD. Collaborators: Ahmadi KR, Ainali C, Barrett A, Bataille V, Bell JT, Buil A, Deloukas P, Dermizakis ET, Dimas AS, Durbin R, Glass D, Grundberg E, Hassanali N, Hedman AK, Ingle C, Knowles D, Krestyaninova M, Lindgren CM, Lowe CE, McCarthy MI, Meduri E, di Meglio P, Min JL, Montgomery SB, Nestle FO, Nica AC, Nisbet J, O'Rahilly S, Parts L, Potter S, Sekowska M, Shin SY, Small KS, Soranzo N, Spector TD, Surdulescu G, Travers ME, Tsaprouni L, Tsoka S, Wilk A, Yang TP, Zondervan KT. Nat Commun. 2014;5:2978. doi: 10.1038/ncomms3978. PMID: 24496475*

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Chronic pain is a global public health problem, but the underlying molecular mechanisms are not fully understood. Here the authors examine genome-wide DNA methylation, first in 50 identical twins discordant for heat pain sensitivity and then in 50 further unrelated individuals. Whole-blood DNA methylation was characterized at 5.2 million loci by MeDIP sequencing and assessed longitudinally to identify differentially methylated regions associated with high or low pain sensitivity (pain DMRs). Nine meta-analysis pain DMRs show robust evidence for association (false discovery rate 5%) with the strongest signal in the pain gene TRPA1 ( $P=1.2 \times 10^{-13}$ ). Several pain DMRs show longitudinal stability consistent with susceptibility effects, have similar methylation levels in the brain and altered expression in the skin. The authors' approach identifies epigenetic changes in both novel and established candidate genes that provide molecular insights into pain and may generalize to other complex traits.

## **FIBROMYALGIA**

#### **FIBROMYALGIA: A CLINICAL REVIEW.**

*Clauw DJ. JAMA. 2014 Apr 16;311(15):1547-55. doi: 10.1001/jama.2014.3266. PMID: 24737367*

Fibromyalgia is present in as much as 2% to 8% of the population, is characterized by widespread pain, and is often accompanied by fatigue, memory problems, and sleep disturbances. The purpose of this article by Clauw from the USA was to review the epidemiology, pathophysiology, diagnosis, and treatment of fibromyalgia. The medical literature on fibromyalgia was reviewed from 1955 to March 2014 via MEDLINE and the Cochrane

Central Registry of Controlled Trials, with an emphasis on meta-analyses and contemporary evidence-based treatment guidelines. Treatment recommendations are based on the most recent evidence-based guidelines from the Canadian Pain Society and graded from 1 to 5 based on the level of available evidence. Clauw found that numerous treatments are available for managing fibromyalgia that are supported by high-quality evidence. These include nonpharmacological therapies (education, exercise, cognitive behavioral therapy) and pharmacological therapies (tricyclics, serotonin norepinephrine reuptake inhibitors, and gabapentinoids). The author concludes that fibromyalgia and other "centralized" pain states are much better understood now than ever before. Fibromyalgia may be considered as a discrete diagnosis or as a constellation of symptoms characterized by central nervous system pain amplification with concomitant fatigue, memory problems, and sleep and mood disturbances. Effective treatment for fibromyalgia is now possible.

**[SYMPATHETIC NERVOUS SYSTEM DYSFUNCTION IN FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, IRRITABLE BOWEL SYNDROME, AND INTERSTITIAL CYSTITIS: A REVIEW OF CASE-CONTROL STUDIES.](#)**

*Martínez-Martínez LA, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. J Clin Rheumatol. 2014 Apr;20(3):146-50. doi: 10.1097/RHU.000000000000089. PMID: 24662556*

Fibromyalgia often coexists and overlaps with other syndromes such as chronic fatigue, irritable bowel syndrome, and interstitial cystitis. Chronic stress has been implicated in the pathogenesis of these illnesses. The sympathetic nervous system is a key element of the stress response system. Sympathetic dysfunction has been reported in these syndromes, raising the possibility that such dysautonomia could be their common clustering underlying pathogenesis. The objective of this study from the Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico was to carry out a review of all published comparative case-control studies investigating sympathetic nervous system performance in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. A total of 196 articles are included in this review. The most often used methods to assess sympathetic functionality were heart rate variability analysis, sympathetic skin response, tilt table testing, and genetic studies. The majority of studies (65%) described sympathetic nervous system predominance in these overlapping syndromes. In contrast, 7% of the studies found parasympathetic predominance. This review demonstrates that sympathetic nervous system predominance is common in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. This concordance raises the possibility that sympathetic dysfunction could be their common underlying pathogenesis that brings on overlapping clinical features. The recognition of sympathetic predominance in these 4 syndromes may have potential clinical implications. It may be worth exploring the use of nonpharmacological measures as well as drug therapies aimed to regain autonomic balance.

**[CENTRAL PAIN SENSITIZATION, COMT VAL158MET POLYMORPHISM, AND EMOTIONAL FACTORS IN FIBROMYALGIA.](#)**

*Desmeules J, Chabert J, Rebsamen M, Rapiti E, Piguet V, Besson M, Dayer P, Cedraschi C. J Pain. 2014 Feb;15(2):129-35. doi: 10.1016/j.jpain.2013.10.004. Epub 2013 Oct 20. PMID: 24342707*

Neurobiological evidence points to altered central nervous system processing of nociceptive stimuli in fibromyalgia. Enzymes like catechol-O-methyl-transferase (COMT) are involved in the elimination of catecholamines playing a possible role in central sensitization and pain. Desmeules and colleagues from Switzerland used quantitative sensory testing to evidence central sensitization in fibromyalgia patients and test whether COMT Val158Met polymorphism, associated with a reduction in enzyme activity, plays a role in sensitized patients. Pain evaluation and quantitative sensory testing were performed including the spinal nociceptive flexion reflex, a physiologic correlate for the evaluation of central nociceptive pathways. Quality of life and distress questionnaires were used. A total of 137 fibromyalgia patients were assessed and compared to 99 matched controls. Central sensitization was present in 95/134 (71%) patients. Among them, COMT p.Val158Met polymorphism displayed a significant linear "genotype effect", with the Met/Met and Val/Val subgroups at the opposite ends of the nociceptive flexion reflex threshold and the Val/Met subgroup in between. Spontaneous moderate to severe pain was more likely to be associated with COMT Met/Met genotype. Patients showed important emotional distress compared to controls. In sensitized patients, the COMT Met/Met subgroup showed systematically-though not significantly-worse scores for all psychological variables. The authors are of the opinion that the association between COMT p.Val158Met polymorphism and

central sensitization in fibromyalgia is essential as it refers to the severity of central sensitization and may be a risk factor for treatment outcome.

**MARKED IMPROVEMENT OF PAIN FROM LONG-TERM FIBROMYALGIA WITH DEXTROAMPHETAMINE SULFATE IN A WOMAN WHO FAILED TO IMPROVE WITH CONVENTIONAL PHARMACOLOGIC TREATMENT.**

*Check JH, Cohen R. Clin Exp Obstet Gynecol. 2014;41(1):90-2. PMID: 24707694*

The purpose of this study was to determine if treatment with the sympathomimetic amine dextroamphetamine sulfate, which has been so effective in treating a variety of pain syndromes, including severe pelvic pain and interstitial cystitis in women with the sympathetic neural hyperalgesia edema syndrome, would also mitigate pain from fibromyalgia which was resistant to multiple therapies. Dextroamphetamine sulfate extended release capsules once daily was gradually increased to 25 mg per day in a woman with treatment resistant fibromyalgia of 20 years duration. Within a short time, the woman experienced dramatic relief of pain. Furthermore, her edema improved resulting in a 27 pound weight loss and her chronic fatigue improved. That authors concluded that fibromyalgia can be effectively treated with an innocuous dose of dextroamphetamine sulfate.

**PATIENT INFORMATION: CARTOONS**

**DEVELOPING CARTOONS FOR LONG-TERM CONDITION SELF-MANAGEMENT INFORMATION.**

*Kennedy A, Rogers A, Blickem C, Daker-White G, Bowen R. BMC Health Serv Res. 2014 Feb 8;14(1):60. [Epub ahead of print] PMID: 24507692*

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Advocating the need to adopt more self-management policies has brought with it an increasing demand for information about living with and making decisions about long-term conditions, with a significant potential for using cartoons. However, the purposeful use of cartoons is notably absent in many areas of health care as is evidence of their acceptability to patients and lay others. This paper outlines the process used to develop and evaluate cartoons and their acceptability for a series of self-management guidebooks for people with inflammatory bowel disease, irritable bowel syndrome, diabetes, chronic obstructive pulmonary disease and chronic kidney disease (CKD). Principles for a process to develop information and cartoons were developed. Cartoon topics were created using qualitative research methods to obtain lay views and experiences. The CKD guidebook was used to provide a detailed exemplar of the process. Focus group and trial participants were recruited from primary care CKD registers. The book was part of a trial intervention; selected participants evaluated the cartoons during in-depth interviews which incorporated think-aloud methods. In general, the cartoons developed by this process depict patient experiences, common situations, daily management dilemmas, making decisions and choices and the uncertainties associated with conditions. CKD cartoons were developed following two focus groups around the themes of getting a diagnosis; understanding the problem; feeling that facts were being withheld; and setting priorities. Think-aloud interviews with 27 trial participants found the CKD cartoons invoked amusement, recognition and reflection but were sometimes difficult to interpret. It was concluded that humour is frequently utilised by people with long-term conditions to help adjustment and coping. Cartoons can help provide clarity and understanding and could address concerns related to health literacy. Using cartoons to engage and motivate people is a consideration untapped by conventional theories with the potential to improve information to support self-management.

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