

International Painful Bladder Foundation

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

IPBF e-Newsletter and Research Update

Issue 44, January 2017

THE INTERNATIONAL PAINFUL BLADDER FOUNDATION (IPBF) WOULD LIKE TO WISH ITS e-NEWSLETTER READERS AROUND THE WORLD A HAPPY AND HEALTHY 2017!

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

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

- UK Joint RCOG/BSUG Guideline on Management of Bladder Pain Syndrome
- Updating the definition of pain: IASP proposes change in its pain definition
- International Pain Management Network
- Meeting Reviews
- News from the National Institutes of Health: MAPP Research Network Home Page and “LURN” Research Network
- Open access publications reminder
- Calendar of Upcoming Events
- Research Highlights
- Donations & Sponsoring

UK JOINT RCOG/BSUG GUIDELINE ON MANAGEMENT OF BLADDER PAIN SYNDROME

This is the first edition of this new IC/BPS Management Guideline from the United Kingdom. This guideline, which is a joint initiative of the Royal College of Obstetricians and Gynaecologists (BJOG) and the British Society of Urogynaecology (BSUG), aims to provide evidence-based information for both primary and secondary care clinicians on the symptoms and treatment options for bladder pain syndrome (BPS) in women. The guideline is available online at <http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.14310/epdf>. Patients and their organisations as well as health professionals may find it helpful and a useful addition to the global collection of guidelines, all of which are slightly different. What is particularly interesting about this very readable guideline is that it is also aimed at primary care clinicians and not simply urologists or urogynaecologists.

Ref: Tirlapur SA, Birch JV, Carberry CL, Khan KS, Latthe PM, Jha S, Ward KL, Irving A on behalf of the Royal College of Obstetricians and Gynaecologists. BJOG. 2017 Jan;124(2):e46-e72. doi: 10.1111/1471-0528.14310. Epub 2016 Dec 9. PMID: 27933722

RCOG Green-top Guideline No. 70

UPDATING THE DEFINITION OF PAIN: IASP PROPOSES CHANGE IN ITS PAIN DEFINITION

The definition of “pain” affects everyone who is diagnosing, treating or suffering from pain. Until now, the International Association for the Study of Pain’s most recent definition of pain has been:

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.

In an article published in the November 26 issue of Pain Journal, AC Williams and KD Craig propose a new IASP definition in light of recent advances in the understanding of pain. The definition they are proposing is:

“Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components.”

Everyone involved in the field of pain should now take this opportunity of looking at this new proposed definition to see if you feel that it really covers your field of pain. Like terminology, definitions are important. A lot can depend on them.

(See: Williams AC, Craig KD. *Updating the Definition of Pain. Pain. 2016 Nov;157(11):2420-2423. PMID: 27200490*)

INTERNATIONAL PAIN MANAGEMENT NETWORK (IPM NETWORK)

The purpose of the International Pain Management Network, a relatively new globally-oriented organization, is to increase awareness, understanding and management of pain worldwide. Its committee members and partners who come from different parts of the world and different pain-related organizations (including our own field of IC/BPS) have the aim of improving pain care globally by endeavouring to understand the problems faced by individual pain patients as well as cultural attitudes to pain and its treatment, and by drawing attention to the very diverse situations prevailing in different parts of the world. Watch this space because you will be hearing more from us!

Its new website can be found at: www.ipmnetwork.org

MEETING REVIEWS

INTERNATIONAL CONTINENCE SOCIETY (ICS) ANNUAL SCIENTIFIC MEETING + 6TH INTERNATIONAL CONSULTATION ON INCONTINENCE (ICI), 13-16 SEPTEMBER 2016, TOKYO, JAPAN.

The annual meeting of the International Continence Society (ICS) 2016 was held in Tokyo, Japan and chaired by Professor Yukio Homma from Tokyo. While this was a long trip for delegates from western countries, it was a home game for the East Asian and Australian-Pacific countries. The 2,146 registered delegates this year included a record 464 from Japan, with many physicians, physiotherapists and nurses from countries in the region such as Korea, Thailand, China, Taiwan and Australia and more besides. In recent years, the International Continence Society (ICS) has become a hub for discussion of chronic pelvic pain, including interstitial cystitis/bladder pain syndrome and hypersensitive bladder, together with presentation of new research in this field. [Click here](#) to read more.

ESSIC ANNUAL MEETING 2016 HELD IN INDIA, NEW DELHI, INDIA, 17-19 NOV 2016.

ESSIC (International Society for the Study of IC/BPS, chair Professor JJ Wyndaele) held its 2016 Annual Meeting in New Delhi, India, organized by Dr Rajesh Taneja and his team. With 250 registered guests, it was a well-attended meeting and included numerous presentations on diagnosis and treatment as well as the current hot topic of phenotyping these patients. Dr Nagendra Mishra, a pioneer in IC patient care and awareness in India, led a very successful parallel patient meeting with patient speakers.

The 2017 ESSIC meeting will be held in Budapest, Hungary. We will let you know as soon as we hear a definite date. www.essic.eu

1st MEETING OF THE SOCIETY FOR PELVIC RESEARCH, 5-6 DECEMBER 2016, CHARLESTON, USA

The Society for Pelvic Research (SPR) was founded by and for career basic and translational scientists interested in normal function and benign disease states of the pelvic viscera and pelvic floor. The Inaugural Meeting of the SPR was held December 5-6, 2016 in Charleston, South Carolina, USA. The one-and-a-half-day program was attended by fifty-five scientists and trainees from multiple disciplines representing different systems and approaches for the study of pelvic visceral and pelvic floor function and dysfunction. The cross-fertilization of ideas resulting from this unique conference engendered lively and productive discussion sessions. Meeting

highlights included Dr. William C. de Groat, PhD as Keynote Speaker, Drs. Kenton M. Sanders, PhD and Arthur L. Burnett, II, MD as State of the Art Speakers, and Drs. Tamara G. Bavendam, MD and Grannum R. Sant, MD as Special Guest Speakers. Three presentations were preselected from abstract submissions for extended podium presentations, and five oral and two poster presentations were selected for monetary awards. The enthusiasm generated by this meeting ensures the continuation of the society, and planning is currently underway for the 2nd Annual Meeting of the SPR.

The abstracts have been published online in TAU journal (Translational Andrology & Urology), Vol 5, Supplement 2 (December 2016) ([click here](#)) and there is to be a future issue in TAU with full length papers from the meeting presenters.

2016 meeting programme overview. <https://www.pelvicresearch.com/spr-2016.html>

NEWS FROM THE NATIONAL INSTITUTES OF HEALTH (NIH/NIDDK) IN THE USA

- MAPP RESEARCH NETWORK HOME PAGE

If you would like to know more about the MAPP Research Network and its work, [click here](#) to go to the home page.

- SYMPTOMS OF LOWER URINARY TRACT DYSFUNCTION RESEARCH NETWORK (LURN)

While most people have heard of the National Institutes of Health (NIH/NIDDK) MAPP Research Network project, many may not have heard of the Symptoms of Lower Urinary Tract Dysfunction Research Network, known for short as LURN.

LURN has four main goals:

1. Identify and explain the important subtypes of LUTS
2. Improve the measurement of patient experiences of LUTS
3. Disseminate novel findings to researchers, clinicians, and patients
4. Generate data, research tools, and biological samples for future studies

For the first of these goals, LURN has begun to examine disorders of urinary sensation (e.g., urgency) and their causes, a departure from most prior research. This will be achieved via an observational cohort study that is currently enrolling patients with LUTS.

A first explanatory paper was published last year. See: Yang CC, Weinfurt KP, Merion RM, Kirkali Z; [LURN Study Group](#). The Symptoms of Lower Urinary Tract Dysfunction Research Network. *J Urol*. 2016 Jul;196(1):146-52. doi: 10.1016/j.juro.2016.01.007. Epub 2016 Jan 16. PMID: 26784646
(See also under IPBF Research Highlights.)

FREE OPEN ACCESS JOURNAL SPECIAL ISSUE PUBLICATIONS REMINDER

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

- TRANSLATIONAL ANDROLOGY AND UROLOGY (TAU)

SUPPLEMENTS FOCUSED ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: PART I AND PART II:

PART I: TRANSLATIONAL ANDROLOGY AND UROLOGY VOL 4, NO 5 (OCTOBER 2015),

<http://www.amepc.org/tau/issue/view/362>. This link takes you to an overview of the articles with open access to HTML or pdf.

PART II: TRANSLATIONAL ANDROLOGY AND UROLOGY VOL 4, NO 6 (DECEMBER 2015)

<http://tau.amegroups.com/issue/view/374> This link takes you to an overview of the articles with open access to HTML or pdf.

- INTERNATIONAL JOURNAL OF UROLOGY

Special Issue: 3rd International Consultation on Interstitial Cystitis Japan (ICICJ) and International Society for the Study of Bladder Pain Syndrome (ESSIC) Joint Meeting, 21–23 March 2013, Kyoto, Japan April 2014
Volume 21, Issue Supplement S1 Pages 1–88, i–vi, A1–A25. Direct link:

<http://onlinelibrary.wiley.com/doi/10.1111/iju.2014.21.issue-s1/issuetoc>

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

CALENDAR OF UPCOMING EVENTS

EUROPEAN ASSOCIATION OF UROLOGY

24-28 March 2017, ExCel, London, United Kingdom

<http://eau17.uroweb.org>

AMERICAN UROLOGICAL ASSOCIATION

12-16 May 2017, Boston, USA

<http://www.aa2017.org>

SOCIETAL IMPACT OF PAIN (SIP) SYMPOSIUM 2017

“Structured co-operation to tackle the Societal Impact of Pain”,

8-9 June 2017, Valletta, Malta

<https://www.sip-platform.eu>

THE 6TH INTERNATIONAL CONGRESS ON NEUROPATHIC PAIN (NEUPSIG 2017), 15-18 JUNE 2017, GOTHENBURG, SWEDEN

<http://neupsig2017.kenes.com/>

THE 10TH CONGRESS OF THE EUROPEAN PAIN FEDERATION, EFIC® (EFIC 2017), 6-9 SEPTEMBER 2017, COPENHAGEN, DENMARK

<http://www.efic2017.kenes.com/SiteAssets/Top.jpg>

INTERNATIONAL CONTINENCE SOCIETY (ICS) 2017

12-15 September 2017, Florence, Italy

www.ics.org

3RD WORLD CONGRESS ON ABDOMINAL AND PELVIC PAIN

HOSTED BY THE INTERNATIONAL PELVIC PAIN SOCIETY (IPPS)

October 12 - 15, 2017, Renaissance Washington DC Downtown, Washington, DC

Further information: <http://pelvicpain.org/meetings/details.aspx?id=114>

ESSIC 2017

To be held in Budapest, Hungary. Date still to be announced.

www.essic.eu

RESEARCH HIGHLIGHTS

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME, HYPERSENSITIVE BLADDER, CHRONIC (PELVIC) PAIN AND RELATED DISORDERS

Most of these have a direct link to the PubMed abstract if you click on the title. An increasing number of scientific articles “In Press” or “Early View” are being published early online (on the Journal website) as “Epub ahead of print” sometimes long before they are published in the journals. While abstracts are usually available on PubMed, the pre-publication articles can

only be read online if you have online access to that specific journal. However, in some cases there may be [free access](#) to the full article online. Click on the title to go to the PubMed abstract or to the full article in the case of free access.

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

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

BRAIN WHITE MATTER CHANGES ASSOCIATED WITH UROLOGICAL CHRONIC PELVIC PAIN SYNDROME: MULTISITE NEUROIMAGING FROM A MAPP CASE-CONTROL STUDY

Huang L, Kutch JJ, Ellingson BM, Martucci KT, Harris RE, Clauw DJ, Mackey S, Mayer EA, Schaeffer AJ, Apkarian AV, Farmer MA. *Pain*. 2016 Dec;157(12):2782-2791. PMID: 27842046

Clinical phenotyping of urological chronic pelvic pain syndromes (UCPPSs) in men and women have focused on end organ abnormalities to identify putative clinical subtypes. Initial evidence of abnormal brain function and structure in male pelvic pain has necessitated large-scale, multisite investigations into potential UCPPS brain biomarkers. Huang and colleagues from the USA present the first evidence of regional white matter (axonal) abnormalities in men and women with UCPPS, compared with positive (irritable bowel syndrome, IBS) and healthy controls. Epidemiological and neuroimaging data were collected from participants with UCPPS, IBS, and healthy sex- and age-matched controls. White matter microstructure, measured as fractional anisotropy (FA), was examined by diffusion tensor imaging. Group differences in regional FA positively correlated with pain severity, including segments of the right corticospinal tract and right anterior thalamic radiation. Increased corticospinal FA was specific and sensitive to UCPPS, positively correlated with pain severity, and reflected sensory (not affective) features of pain. Reduced anterior thalamic radiation FA distinguished patients with IBS from those with UCPPS and controls, suggesting greater microstructural divergence from normal tract organization. Findings confirm that regional white matter abnormalities characterize UCPPS and can distinguish between visceral diagnoses, suggesting that regional axonal microstructure is either altered with ongoing pain or predisposes its development.

TRANSGENIC MICE EXPRESSING MCP-1 BY THE UROTHELIUM DEMONSTRATE BLADDER HYPERSENSITIVITY, PELVIC PAIN AND VOIDING DYSFUNCTION: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN RESEARCH NETWORK ANIMAL MODEL STUDY.

Xu S, Wang X, Wang Y, Lutgendorf S, Bradley C, Schrepf A, Kreder K, O'Donnell M, Luo Y. *PLoS One*. 2016 Sep 29;11(9):e0163829. doi: 10.1371/journal.pone.0163829. PMID: 27684718

Monocyte chemoattractant protein-1 (MCP-1) is one of the key chemokines that play important roles in diverse inflammatory and chronic pain conditions. Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic and debilitating inflammatory condition of the urinary bladder characterized by the hallmark symptoms of pelvic pain and voiding dysfunction. To facilitate IC/BPS research, Xu and colleagues from the USA used transgenic technology to develop a novel urothelial MCP-1 secretion mouse model (URO-MCP-1). A transgene consisting of the uroplakin II gene promoter and the mouse MCP-1 coding sequence with a secretory element was constructed and microinjected. URO-MCP-1 mice were found to express MCP-1 mRNA in the bladder epithelium and MCP-1 protein in the urine, and developed bladder inflammation 24 hours after intravesical administration of a single sub-noxious dose of lipopolysaccharide (LPS). The inflamed bladders of URO-MCP-1 mice exhibited elevated mRNAs for interleukin (IL)-1 β , IL-6, substance P precursor, and nerve growth factor as well as increased macrophage infiltration. In parallel with these phenotypic changes, URO-MCP-1 mice manifested significant functional changes at days 1 and 3 after cystitis induction. These functional changes included pelvic pain as measured by von Frey filament stimulation and voiding dysfunction (increased urinary frequency, reduced average volume voided per micturition, and reduced maximum volume voided per micturition) as measured by micturition cages. Micturition changes remained evident at day 7 after cystitis induction, although these changes were not statistically significant. Control wild-type C57BL/6

mice manifested no clear changes in histological, biochemical and behavioral features after similar cystitis induction with LPS. Taken together, they believe that their results indicate that URO-MCP-1 mice are hypersensitive to bladder irritants such as LPS and develop pelvic pain and voiding dysfunction upon cystitis induction, providing a novel model for IC/BPS research.

[EVIDENCE FOR THE ROLE OF MAST CELLS IN CYSTITIS-ASSOCIATED LOWER URINARY TRACT DYSFUNCTION: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN RESEARCH NETWORK ANIMAL MODEL STUDY.](#)

Wang X, Liu W, O'Donnell M, Lutgendorf S, Bradley C, Schrepf A, Liu L, Kreder K, Luo Y. *PLoS One*. 2016 Dec 21;11(12):e0168772. doi: 10.1371/journal.pone.0168772. eCollection 2016. PMID: 28002455

Bladder inflammation frequently causes cystitis pain and lower urinary tract dysfunction (LUTD) such as urinary frequency and urgency. Although mast cells have been identified to play a critical role in bladder inflammation and pain, the role of mast cells in cystitis-associated LUTD has not been demonstrated. Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic and debilitating inflammatory condition of the urinary bladder characterized by the hallmark symptoms of pelvic pain and LUTD. In this MAPP study, Wang and colleagues investigated the role of mast cells in LUTD using a transgenic autoimmune cystitis model (URO-OVA) that reproduces many clinical correlates of IC/BPS. URO-OVA mice express the membrane form of the model antigen ovalbumin (OVA) as a self-antigen on the urothelium and develop bladder inflammation upon introduction of OVA-specific T cells. To investigate the role of mast cells, they crossed URO-OVA mice with mast cell-deficient KitW-sh mice to generate URO-OVA/KitW-sh mice that retained urothelial OVA expression but lacked endogenous mast cells. They compared URO-OVA mice with URO-OVA/KitW-sh mice with and without mast cell reconstitution in response to cystitis induction. URO-OVA mice developed profound bladder inflammation with increased mast cell counts and LUTD, including increased total number of voids, decreased mean volume voided per micturition, and decreased maximum volume voided per micturition, after cystitis induction. In contrast, similarly cystitis-induced URO-OVA/KitW-sh mice developed reduced bladder inflammation with no mast cells and LUTD detected. However, after mast cell reconstitution URO-OVA/KitW-sh mice restored the ability to develop bladder inflammation and LUTD following cystitis induction. They further treated URO-OVA mice with cromolyn, a mast cell membrane stabilizer, and found that cromolyn treatment reversed bladder inflammation and LUTD in the animal model. The authors are of the opinion that their results provide direct evidence for the role of mast cells in cystitis-associated LUTD, supporting the use of mast cell inhibitors for treatment of certain forms of IC/BPS.

NIH/NIDDK LURN RESEARCH NETWORK

[SYMPTOMS OF LOWER URINARY TRACT DYSFUNCTION RESEARCH NETWORK.](#)

Yang CC, Weinfurt KP, Merion RM, Kirkali Z; [LURN Study Group](#). *J Urol*. 2016 Jul;196(1):146-52. doi: 10.1016/j.juro.2016.01.007. Epub 2016 Jan 16. PMID: 26784646

[Collaborators \(71\)](#)

In order to address gaps in understanding and treating lower urinary tract symptoms, the NIDDK created the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN). The goals of LURN are to work collaboratively to 1) identify and explain the important subtypes of lower urinary tract symptoms; 2) improve the measurement of patient experiences of lower urinary tract symptoms; 3) disseminate novel findings to researchers, clinicians and patients; and 4) generate data, research tools and biological samples for future studies. As a first step in understanding subtypes of lower urinary tract symptoms, LURN will focus on disorders of urinary sensation (eg urgency) and their causes. These are being examined with respect to patient experience, organism or systemic factors, genitourinary organs and tissues, and cellular/molecular factors. This is being achieved via an observational cohort study that is currently enrolling patients with lower urinary tract symptoms (target number 1,000) and that will extensively characterize patients with lower urinary tract symptoms. Future studies embedded within the observational cohort study will focus on neuroimaging and sensory testing, biomarkers and organ based factors. To advance the science of measurement of lower urinary tract symptoms, LURN is also developing and evaluating a comprehensive set of self-report questions to provide more granular assessments of lower urinary tract symptoms. LURN has taken its first steps by developing a framework for studying lower urinary tract symptom subtypes. In developing this framework,

LURN is choosing an initial domain on which to focus (sensory experiences), and creating and executing protocols designed to improve measurement of self-reported symptoms and identify patient subtypes.

GUIDELINES/ STANDARD TERMINOLOGY

MANAGEMENT OF BLADDER PAIN SYNDROME: GREEN-TOP GUIDELINE NO. 70.

RCOG/BSUG JOINT GUIDELINE. DECEMBER 2016

Tirlapur SA, Birch JV, Carberry CL, Khan KS, Latthe PM, Jha S, Ward KL, Irving A on behalf of the Royal College of Obstetricians and Gynaecologists. BJOG. 2017 Jan;124(2):e46-e72. doi: 10.1111/1471-0528.14310. Epub 2016 Dec 9. PMID: 27933722

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

This is the first edition of this guideline from the United Kingdom. This guideline, a joint initiative of the Royal College of Obstetricians and Gynaecologists (BJOG) and the British Society of Urogynaecology (BSUG), aims to provide evidence-based information for primary and secondary care clinicians on the symptoms and treatment options for bladder pain syndrome (BPS) in women.

AN INTERNATIONAL UROGYNECOLOGICAL ASSOCIATION (IUGA)/INTERNATIONAL CONTINENCE SOCIETY (ICS) JOINT REPORT ON THE TERMINOLOGY FOR THE CONSERVATIVE AND NONPHARMACOLOGICAL MANAGEMENT OF FEMALE PELVIC FLOOR DYSFUNCTION.

Bo K, Frawley HC, Haylen BT, Abramov Y, Almeida FG, Berghmans B, Bortolini M, Dumoulin C, Gomes M, McClurg D, Meijlink J, Shelly E, Trabuco E, Walker C, Wells A. Neurourol Urodyn. 2016 Dec 5. doi: 10.1002/nau.23107. [Epub ahead of print] PMID: 27918122

There has been an increasing need for the terminology on the conservative management of female pelvic floor dysfunction to be collated in a clinically based consensus report. This Report combines the input of members and elected nominees of the Standardization and Terminology Committees of two International Organizations, the International Urogynecological Association (IUGA) and the International Continence Society (ICS), assisted at intervals by many external referees. An extensive process of nine rounds of internal and external review was developed to exhaustively examine each definition, with decision-making by collective opinion (consensus). Before opening up for comments on the webpages of ICS and IUGA, five experts from physiotherapy, neurology, urology, urogynecology, and nursing were invited to comment on the paper. A Terminology Report on the conservative management of female pelvic floor dysfunction, encompassing over 200 separate definitions, has been developed. It is clinically based, with the most common symptoms, signs, assessments, diagnoses, and treatments defined. Clarity and ease of use have been key aims to make it interpretable by practitioners and trainees in all the different specialty groups involved in female pelvic floor dysfunction. Ongoing review is not only anticipated, but will be required to keep the document updated and as widely acceptable as possible. A consensus-based terminology report for the conservative management of female pelvic floor dysfunction has been produced, aimed at being a significant aid to clinical practice and a stimulus for research.

CUA GUIDELINE: DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Cox A, Golda N, Nadeau G, Curtis Nickel J, Carr L, Corcos J, Teichman J. Can Urol Assoc J. 2016 May-Jun;10(5-6):E136-E155. Epub 2016 May 12. PMID: 27790294

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

The Canadian Urological Association has published a guideline for the diagnosis and treatment of IC/BPS. The full text is available free online.

UPDATING THE DEFINITION OF PAIN.

Williams AC, Craig KD. Pain. 2016 Nov;157(11):2420-2423. PMID: 27200490

In light of recent advances in the understanding of pain, Williams and Craig are proposing a new IASP definition of pain: *Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components.*

REVIEW

BLADDER DYSFUNCTION IN 2016: NEW INSIGHTS INTO INTERSTITIAL CYSTITIS AND CHRONIC PELVIC PAIN SYNDROMES.

Jhang JF, Kuo HC. Nat Rev Urol. 2016 Nov 29. doi: 10.1038/nrurol.2016.249. [Epub ahead of print] PMID: 27898100

In 2016, immunohistochemical evidence revealed major differences in the inflammatory characteristics of Hunner and non-Hunner interstitial cystitis/bladder pain syndrome (IC/BPS). Evidence has also emerged that an isomer of testosterone, etio-S, might be a urinary biomarker of IC/BPS. Intravesical botulinum toxin injections became a standard treatment of IC/BPS. Furthermore, the International Continence Society has published a new Standard for Terminology for Chronic Pelvic Pain Syndromes.

Further info: <http://www.nature.com/nrurol/journal/vaop/ncurrent/full/nrurol.2016.249.html>

TREATMENT REIMBURSEMENT ISSUES

CONTESTED EVIDENCE: A DUTCH REIMBURSEMENT DECISION TAKEN TO COURT.

Moes F, Houwaart E, Delnoij D, Horstman K. Health Econ Policy Law. 2016 Nov 15:1-20. [Epub ahead of print] PMID: 27842620

This paper examines a remarkable lawsuit in health care rationing. The Patients Association for Interstitial Cystitis (ICP) sued the Dutch National Health Care Institute for alleged misconduct against Interstitial Cystitis patients, as the Institute decided that bladder instillations with chondroitin sulphate or hyaluronic acid are no longer covered by the basic health insurance. The patients' organisation challenged the Institute for basing its standpoint on scientific evidence, overruling clinical expertise and patients' experiences. While scientific advice is often solicited in public health issues, simultaneously, the authority of scientific advice is increasingly being questioned in the public domain. Also, the judiciary is frequently called upon to adjudicate in rationing decisions. Based on an ethnographic study of the National Health Care Institute, drawing on insights from the field of Science and Technology Studies, Moes and colleagues analyse this lawsuit as a negotiation of what knowledge counts in reimbursement decisions.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

SU-G-IEP1-10: PERMEABILITY EVALUATION OF INTERSTITIAL CYSTITIS BY DCE-MRI OF THE BLADDER.

Wu D, Vo J, North J, Towner R, Hurst R. Med Phys. 2016 Jun;43(6):3646. doi: 10.1118/1.4956970. PMID: 28048092

Interstitial cystitis (IC) is a chronic and painful condition that can lead to bladder pain syndrome (BPS) in women. IC and BPS have been known to manifest after physiological changes after giving birth. In this project, Wu and colleagues from Oklahoma, USA pioneered and advanced a new clinical utility using DCE-MRI to assess bladder permeability. At first IC/BPS perfusion methods were with ratio signal evaluation, the authors now incorporate pharmacokinetics techniques to allow for further assessment. In this pilot study, female patients and volunteers (IC=4, Control=3) underwent imaging with a clinical GE 3T 750W MRI system. This project was approved by the OUHSC IRB. Multiple TR Images series were acquired. Images were analyzed in the coronal plane at 0-, 3-, 6-, 9-, 12-, 15-, 20-, 25-, and 30-minute intervals. The authors used a three-compartmental pharmacokinetic model with these data. The compartments included: a) bladder interior site of injection, b) bladder wall, and c) external psoas muscle. The signal was transformed and corrected for T1-relaxation based on a multi-TR exponential regression before pharmacokinetic analysis. Significant differences were detected with relative means for T1 concentration changes on the outflow between the k13 transfer coefficient, which represents the injection leakage to the external parenchyma. Trend differences were found in permeability between the bladder injection site to the rim. They also found changes in the kurtosis of the histograms of regional perfusion. No detectable changes were found in the reverse directions for the above compartments (k21, k31). This study illustrates early detectable evidence for a possible DCE-MRI tool that can detect permeability differences with pharmacokinetics measurement of k13. These techniques are intended to advance quantitative imaging methods for IC/BPS, per the goals/objectives of the Quantitative Imaging Biomarker Alliance (QIBA) and other AAPM and RSNA initiatives.

THE BURDEN OF BLADDER PAIN IN FIVE EUROPEAN COUNTRIES: A CROSS-SECTIONAL STUDY.

Hakimi Z, Houbiers J, Pedersini R, Vietri J. Urology. 2017 Jan;99:84-91. doi: 10.1016/j.urology.2016.08.038. Epub 2016 Sep 8. PMID: 27616606

The aim of this study was to estimate the burden of illness associated with bladder pain in 5 European countries: France, Germany, Italy, Spain, and the United Kingdom. Patients with a diagnosis of bladder pain (ie, unpleasant sensation, pain, pressure, or discomfort related to the urinary bladder) were identified from data collected by the cross-sectional National Health and Wellness Survey performed in 2013. Propensity score matching was used to construct a comparator group without bladder pain (1 case: 2 controls). Assessments were performed for several outcomes including health-related quality of life (HRQoL; 36-item Short-Form, version 2), work-related function (Work Productivity and Activity Impairment questionnaire), employment status, and all-cause healthcare resource use. Hakimi and colleagues identified 275 patients with a physician diagnosis of bladder pain, 274 of whom were successfully matched to 548 controls without bladder pain. Compared with matched controls, patients with bladder pain had significantly impaired HRQoL. Overall work productivity loss was significantly greater in patients with bladder pain compared with matched controls. Patients with bladder pain were also significantly more likely to use all-cause healthcare resources and make more visits to healthcare providers in the previous 6 months than matched controls. The authors concluded that bladder pain is associated with a considerable burden in Europe in terms of impaired HRQoL and work productivity, and increased healthcare resource use.

PATHOMECHANISM OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND MAPPING THE HETEROGENEITY OF DISEASE.

Jhang JF, Kuo HC. Int Neurourol J. 2016 Nov;20(Suppl 2):S95-104. Epub 2016 Nov 22. PMID: 27915472

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

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a heterogeneous syndrome which is usually characterized by urinary frequency, nocturia, and bladder pain. Several pathomechanisms have been proposed, including uroepithelial dysfunction, mast cell activation, neurogenic inflammation, autoimmunity, and occult urinary tract infections. It is possible that an inflammatory process alters regulation of urothelial homeostasis and results in dysfunction of the bladder epithelium. Different phenotypes of IC/BPS have been explored including Hunner and non-Hunner type IC, hypersensitive bladder, and bladder pain both with and without functional somatic syndrome. Different gene expressions have also been found in different IC phenotypes. Abnormal expressions of uroplakin, chondroitin sulfate and adhesive protein E-cadherin, tight junction protein zonula occludens-1 in IC/BPS bladder suggest abnormal epithelial differentiation in this bladder disease. Analysis of inflammatory proteins, or cytokines in the urine or serum provides another diagnostic foundation for IC/BPS subtypes. The involvement of IC/BPS in systemic functional somatic syndrome and other pelvic organ diseases might also subdivide subtypes of IC/BPS. Chronic inflammation, increased urothelial apoptosis, and abnormal urothelial function are closely associated in IC bladders. This article from Taiwan reviews recent research on the pathomechanisms of IC, which might help us in mapping the heterogeneity of the disease.

DIFFERENTIAL EXPRESSION OF ROMK AND KCNQ1 POTASSIUM CHANNELS IN BLADDER UROTHELIUM OF PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.

Lee JD, Lee MH, Yang WK, Wang KL, Lee TH. Urology. 2016 Nov 14. pii: S0090-4295(16)30825-1. doi: 10.1016/j.urology.2016.11.010. [Epub ahead of print] PMID: 27856205

The purpose of this study from Taiwan was to investigate the changes including expression and localization of two potassium channels, renal outer medullary K⁺ channel (ROMK) and voltage-gated K⁺ channel 7.1 (KCNQ1), after increased urinary potassium leakage in patients with interstitial cystitis/painful bladder syndrome (IC/PBS). The study group included 24 patients with IC/PBS and a control group consisting of 12 volunteers without any IC/PBS symptoms. Bladder biopsies were taken from both groups. The authors determined the protein expression and distribution of potassium channels using immunoblotting, immunohistochemistry, and immunofluorescent staining under confocal laser microscopy. The results revealed that ROMK was predominantly expressed in apical cells of the bladder urothelium at significantly higher levels (3.3-fold) in the study group than in the control group. In contrast, KCNQ1 was expressed in the basolateral membrane according to confocal microscopy results and did not significantly differ between groups. The authors note that

their data showed that the abundance of ROMK protein in apical cells was increased in the IC/PBS group, whereas KCNQ1, which was distributed in the basolateral membrane of the bladder urothelium, showed similar abundance between groups. These results suggest that upregulation of the ROMK channel in apical cells might permit avid potassium flux into the bladder lumen to maintain intracellular K⁺ homeostasis in the dysfunctional urothelium.

PAIN RELIEF AFTER TRIAMCINOLONE INFILTRATION IN PATIENTS WITH BLADDER PAIN SYNDROME WITH HUNNER'S ULCERS.

Mateu L, Izquierdo L, Franco A, Costa M, Lawrentschuk N, Alcaraz A. *Int Urogynecol J.* 2016 Dec 6. [Epub ahead of print] *Int Urogynecol J.* 2016 Dec 6. [Epub ahead of print] PMID: 27924374

Bladder pain syndrome (BPS) is a chronic condition with severe implications in the patient's quality of life with no definitive treatment. The objective of this retrospective study from Spain was to assess pain relief after triamcinolone injection in patients with BPS with Hunner's ulcers (HU) (Hunner Lesion). They found that triamcinolone injection for HU in patients with BPS is associated with significant pain reduction. However, most patients will require retreatment.

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

Fry CH, Vahabi B. *Basic Clin Pharmacol Toxicol.* 2016 Oct;119 Suppl 3:57-62. doi: 10.1111/bcpt.12626. Epub 2016 Aug 5. PMID: 27228303

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

CLINICAL IMPLICATIONS OF THE MICROBIOME IN URINARY TRACT DISEASES.

Hiergeist A, Gessner A. *Curr Opin Urol.* 2016 Nov 24. [Epub ahead of print] PMID: 27898455

This review from Germany outlines and evaluates the most recent literature on the role of the microbiome in urinary tract diseases. High throughput molecular DNA sequencing of bacterial 16S rRNA genes enabled the analysis of complex microbial communities inhabiting the human urinary tract. Several recent studies have identified bacterial taxa of the urinary microbiome to impact urinary tract diseases including interstitial cystitis, urgency urinary incontinence or calcium oxalate stone formation. Furthermore, treatment of urinary tract infections by antibiotics globally impacts community profiles of the intestinal microbiota and might indirectly influence human health. Alternative treatment options like application of probiotics for the treatment of urinary tract infections are currently under investigation. The urinary microbiome and its relationship to urinary tract diseases is currently under comprehensive investigation. Further studies are needed to shed light on the role of commensal microbiota for urinary tract infections.

SPINAL ASTROCYTIC ACTIVATION CONTRIBUTES TO MECHANICAL ALLODYNIA IN A RAT MODEL OF CYCLOPHOSPHAMIDE-INDUCED CYSTITIS.

Liu B, Su M, Tang S, Zhou X, Zhan H, Yang F, Li W, Li T, Xie J. *Mol Pain.* 2016 Nov 15;12. pii: 1744806916674479. Print 2016. PMID: 27852964

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

Previous studies have demonstrated that glial cells play an important role in the generation and maintenance of neuropathic pain. Activated glial cells produce numerous mediators such as proinflammatory cytokines that facilitate neuronal activity and synaptic plasticity. Similarly, bladder pain syndrome/interstitial cystitis shares many characteristics of neuropathic pain. However, related report on the involvement of spinal glia in bladder pain syndrome/interstitial cystitis-associated pathological pain and the underlying mechanisms are still lacking. This study by Liu and colleagues from China investigated spinal glial activation and underlying molecular mechanisms in a rat model of bladder pain syndrome/interstitial cystitis. A rat model of bladder pain syndrome/interstitial cystitis was established via systemic injection with cyclophosphamide. Mechanical allodynia was tested with von Frey monofilaments and up-down method. Moreover, Western blots and double immunofluorescence were used to detect the expression and location of glial fibrillary acidic protein, OX42/Iba1, P-P38, NeuN, interleukin (IL)-1 β , phosphorylation of N-methyl-D-aspartate receptor 1 (P-NR1), and IL-1 receptor I (IL-1RI) in the L6-S1 spinal cord. The authors found that glial fibrillary acidic protein rather than OX42/Iba1 or P-P38 was significantly increased in the spinal cord of cyclophosphamide-induced cystitis. L-alpha-aminoadipate but not minocycline markedly attenuated the allodynia. Furthermore, spinal IL-1 β was dramatically increased in cyclophosphamide-induced cystitis, and activated astrocytes were the only source of IL-1 β release, which contributed to allodynia in cystitis rats. Besides, spinal P-NR1 was statistically increased in cyclophosphamide-induced cystitis and only localized in IL-1RI positive neurons in spinal dorsal horn. Additionally, NR antagonist significantly attenuated the cystitis-induced pain. Interestingly, the time course of the P-NR1 expression paralleled to that of IL-1 β or glial fibrillary acidic protein. They report that their results demonstrated that astrocytic activation but not microglial activation contributed to the allodynia in cyclophosphamide-induced cystitis and IL-1 β released from astrocytes might bind to its endogenous receptor on the neurons inducing the phosphorylation of NR1 subunit, leading to sensory neuronal hyperexcitability and pathological pain.

[A PROSPECTIVE RANDOMIZED CONTROLLED MULTICENTRE TRIAL COMPARING INTRAVESICAL DMSO AND CHONDROÏTIN SULPHATE 2% FOR PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS.](#)

Tutolo M, Ammirati E, Castagna G, Klockaerts K, Plancke H, Ost D, Van der Aa F, De Ridder D. Int Braz J Urol. 2016 Nov 2. doi: 10.1590/S1677-5538.IBJU.2016.0302. [Epub ahead of print] PMID: 27819752

The purpose of this study from Belgium and Italy was to compare effectiveness of intravesical chondroitin sulphate (CS) 2% and dimethyl sulphoxide (DMSO) 50% in patients with painful bladder syndrome/interstitial cystitis (PBS/IC). Patients were randomized to receive either 6 weekly instillations of CS 2% or 50% DMSO. The primary endpoint was the difference in proportion of patients achieving score 6 (moderately improved) or 7 (markedly improved) in both groups using the Global Response Assessment (GRA) scale. Secondary parameters were mean 24-hours frequency and nocturia on a 3-day micturition diary, changes from baseline in O'Leary-Sant questionnaire score and visual analog scale (VAS) for supra-pubic pain. Thirty-six patients took part (22 in CS and 14 in DMSO group). In the DMSO group, 57% withdrew consent and only 6 concluded the trial. Major reasons were pain during and after instillation, intolerable garlic odor and lack of efficacy. In the CS group, 27% withdrew consent. Compared with the DMSO group, more patients in the CS group reported moderate or marked improvement and achieved a reduction in VAS scores. The CS group performed significantly better in pain reduction and nocturia and better in total O'Leary reduction. CS was better tolerated. The trial was stopped due to high number of drop-outs with DMSO. It was concluded that intravesical CS 2% is viable treatment for PBS/IC with minimal side effects. DMSO should be used with caution and with active monitoring of side effects. More randomized controlled studies on intravesical treatments are needed.

[LONG-TERM OUTCOMES OF INTRAVESICAL DIMETHYL SULFOXIDE/HEPARIN/HYDROCORTISONE THERAPY FOR INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Lim YN, Dwyer P, Murray C, Karmakar D, Rosamilia A, Thomas E. Int Urogynecol J. 2016 Dec 16. [Epub ahead of print] PMID: 27987022

For decades, intravesical dimethyl sulfoxide (DMSO) cocktail therapy has been used for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS), but little is known about its long-term efficacy. Lim and colleagues from Australia looked at the long-term efficacy of intravesical DMSO/heparin/hydrocortisone/bupivacaine therapy in patients with IC/BPS. Patients with IC/BPS from the

authors' institutions who underwent this therapy with >2 years follow-up were surveyed with O'Leary-Sant interstitial cystitis symptom and problem index questionnaires before and after therapy. Chart reviews and telephone surveys were then conducted to determine their posttherapy course. Of 68 eligible women, 55 with a median follow-up of 60 months were surveyed. Their mean age at therapy onset was 44.8 years and their mean body mass index was 26.2 kg/m². There were statistically significant improvements in O'Leary-Sant and pain scores of 23-47% at both 6 weeks and the end of the follow-up period. At the end of the follow-up period, 19 of the 55 women were cured (requiring no further treatment) and 12 were significantly improved (requiring only ongoing oral medication). Univariate and multivariate analyses showed that DMSO treatment failure was more likely in patients with pretreatment day-time urinary frequency more than 15 episodes per day, nocturia more than two episodes per night, maximum bladder diary voided volume <200 ml and bladder capacity under anaesthesia <500 ml. At a median follow-up of 60 months, intravesical DMSO cocktail therapy appeared moderately effective for the treatment of IC/BPS. Treatment failure was more frequent in patients with pretreatment symptoms of reduced bladder capacity.

[STUDY OF THE APOPTOTIC EFFECT OF URINE AS A DIAGNOSTIC BIOMARKER IN PATIENTS WITH INTERSTITIAL CYSTITIS.](#) [Article in English, Spanish]

Di Capua-Sacoto C, Sanchez-Llopis A, O'Connor E, Martinez A, Ruiz-Cerdá JL. Actas Urol Esp. 2016 Nov;40(9):570-576. doi: 10.1016/j.acuro.2016.03.010. Epub 2016 May 9. PMID: 27174573

The main objective of this Spanish study was to assess the apoptotic effect of urine from patients with interstitial cystitis (IC) in cell cultures and to study its value as a diagnostic biomarker for IC. This prospective study included 57 patients diagnosed with IC and 50 healthy patients from the Hospital Clinic of Barcelona and the La Paz University Hospital. The urine of these patients was exposed to cell cultures, and its ability to induce apoptosis in the cultures was analysed. Using flow cytometry, they then measured the degree of apoptosis, quantified by the percentage of cells of the cell cycle in phase sub G0. The cell cultures exposed to the urine of patients with IC had a sub G1 peak and a G2 phase, which was significantly greater than that of the control group, and a significantly lower percentage in the S phase than the control group. The mean apoptosis values in the urine cultures from patients with IC were significantly higher than those of the control group. Using a value >10% of the apoptosis test as a positive result, they observed a specificity of 96% and a positive predictive value of 92%. They concluded that the urine of patients with IC exerts an apoptotic effect on tumour cell cultures that is significantly greater than that exerted by the urine of healthy control patients. A ≥10% cutoff for the apoptosis test presented very low sensitivity (40%) but had a very high specificity (96%), thereby able to confirm the diagnosis of IC when positive.

[SPECIFIC INHIBITION OF ICAM-1 EFFECTIVELY REDUCES BLADDER INFLAMMATION IN A RAT MODEL OF SEVERE NON-BACTERIAL CYSTITIS.](#)

Zhang X, He H, Lu G, Xu T, Qin L, Wang X, Jin X, Liu B, Zhao Z, Shen Z, Shao Y. Sci Rep. 2016 Oct 26;6:35672. doi: 10.1038/srep35672. PMID: 27782122

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

The development and progression of bladder pain syndrome/interstitial cystitis (BPS/IC) is closely related to bladder inflammation. Intercellular adhesion molecule 1 (ICAM-1) is associated with bladder inflammation in BPS/IC. Zhang and colleagues from China investigated the effect of specific inhibition of ICAM-1 using an anti-ICAM-1 antibody (AIA) on bladder inflammation in a rat model of severe non-bacterial cystitis (NBC) resembling BPS/IC by evaluating the bladder inflammation grade, mast cell infiltration and related cytokines and receptors. They also compared the effects of AIA with the COX-2 inhibitor celecoxib and the neurokinin-1 receptor (NK1R) inhibitor aprepitant. Their NBC model was established by intraperitoneal injection of cyclophosphamide combined with intravesical protamine/lipopolysaccharide, which resulted in severe bladder inflammation and increased mast cell infiltration, similar to the pathological changes of BPS/IC. Inhibition of ICAM-1 by AIA significantly decreased the bladder inflammation grade and mast cell counts, which was accompanied by a reduction of purinergic receptors (P2X2/P2X3), prostaglandin E2, EP1/EP2 receptors, TNF-α, NK1R, and ICAM-1. Moreover, AIA showed superior effects to those of celecoxib and aprepitant treatment in improving the bladder inflammatory response. According to the authors, their results suggest that ICAM-1 may play a critical role in bladder inflammation in severe NBC and may be used as a novel therapeutic target in non-bacterial bladder inflammation such as BPS/IC.

MANIPULATING THE EXTRACELLULAR MATRIX: AN ANIMAL MODEL OF THE BLADDER PAIN SYNDROME.

Offiah I, Didangelos A, O'Reilly BA, McMahon SB. Pain. 2017 Jan;158(1):161-170. PMID: 27992393

Bladder pain syndrome (BPS) is associated with breakdown of the protective uroepithelial barrier of the urinary bladder allowing urinary constituents access to bladder sensory neurons. Although there are several animal models of cystitis, none specifically relates to BPS. Here, Offiah and colleagues from the UK and Ireland aimed to create such a model using enzymatic digestion of the barrier proteoglycans (PGs) in the rat. Twenty female Wistar rats were anaesthetized and transurethral catheterized. Ten animals were treated with 0.25IU of intravesical chondroitinase ABC and heparanase III to digest chondroitin sulphate and heparin sulphate PGs, respectively. Ten animals received saline. Following PG deglycosylation, bladders showed irregular loss of the apical uroplakin and a significant increase in neutrophils, not evident in the control group. Spinal cord sections were also collected for c-fos analysis. A large and significant increase in fos immunoreactivity in the L6/S1 segments in the treatment vs control bladders was observed. Cystometry was performed on 5 treatment and 5 control animals. Analysis revealed a significant increase in micturition reflex excitability postdeglycosylation. On a further group of 10 animals, von Frey mechanical withdrawal thresholds were tested on abdominal skin before and after PG digestions. There was a significant decrease in abdominal mechanical withdrawal threshold postdeglycosylation compared with controls. The results of this animal study suggest that many of the clinical features of BPS are seen after PG digestion from the bladder lumen. This model can be used to further understand mechanisms of pain in patients with BPS and to test new therapeutic strategies.

NONINVASIVE EXPERIMENTAL BLADDER PAIN ASSESSMENT IN PAINFUL BLADDER SYNDROME.

Tu FF, Kane JN, Hellman KM. BJOG. 2017 Jan;124(2):283-291. doi: 10.1111/1471-0528.14433. PMID: 28012262

The purpose of this prospective observational study was to compare bladder sensitivity between patients with pelvic pain and patients who were pain free, undergoing noninvasive, controlled bladder distension via diuresis. Tu and colleagues from the USA also sought to measure potential mechanisms underlying bladder sensitivity. Reproductive-age women with non-bladder chronic pelvic pain, painful bladder syndrome, and pelvic pain-free controls took part in the study. Participants were compared on cystometric capacity, pelvic floor pressure-pain thresholds (PPTs), pelvic muscle function, O'Leary-Sant bladder questionnaire, and psychosocial instruments using Wilcoxon rank-sum tests. Multivariate regression was used to identify factors underlying bladder pain phenotypes. Participants with PBS exhibited higher bladder distension pain than those with CPP, with both groups reporting higher pain levels than controls. No significant associations were found between bladder distension pain and pelvic muscle structure or pain sensitivity measures; however, bladder distension pain positively correlates with both vaginal PPTs adjacent to the bladder and pain with transvaginal bladder palpation. Pain at maximal distension was less influenced by somatic sensitivity than bladder symptoms. Multivariate regression identified three independent components of bladder symptoms in PBS: bladder distension pain, bladder sensation, and somatic symptoms. The authors concluded that diuresis-induced bladder pain differentiates CPP from PBS. Experimental bladder pain is not predicted by pelvic floor sensitivity. Compared with patient-reported outcomes it appears less influenced by psychological factors. Further study is needed to determine whether screening for experimental bladder pain sensitivity could predict future risk of PBS.

TRANSURETHRAL RESECTION ALONE VS RESECTION COMBINED

WITH THERAPEUTIC HYDRODISTENTION AS TREATMENT FOR ULCERATIVE INTERSTITIAL CYSTITIS:

INITIAL EXPERIENCE WITH PROPENSITY SCORE MATCHING STUDIES.

Lee SW, Kim WB, Lee KW, Kim JM, Kim YH, Lee B, Kim JH. Urology. 2017 Jan;99:62-68. doi: 10.1016/j.urology.2016.09.038. Epub 2016 Oct 5. PMID: 27720770

This study from Korea compared the therapeutic efficacy of transurethral resection (TUR) alone with that of TUR combined with therapeutic hydrodistention in patients with ulcerative interstitial cystitis (IC). The study subjects were 44 female patients newly diagnosed with IC who underwent TUR to treat ulcerative IC and who were available for follow-up, without recurrence of disease for 12 months. Lee and colleagues retrospectively studied both patients who underwent TUR alone (group I) and those who underwent TUR combined with therapeutic hydrodistention (group II). Improvements in pain and voiding symptoms were retrospectively evaluated using a 10-point visual analog scale for pain and a 3-day micturition chart. Group I included 22

patients and group II included 22 patients of mean ages 58.45 ± 11.01 and 56.27 ± 11.86 years, respectively. Use of a 10-point visual analog scale showed that pain decreased after the procedures in both groups, but the improvement did not differ between groups. The maximum functional bladder capacities of patients in group I were 161.36, 192.47, and 204.12 mL, respectively, before, at 6 months, and at 12 months after the operation; the maximum functional bladder capacities of patients in group II were 175.45, 263.14, and 291.17 mL, respectively. The voiding frequencies of group I were 12.59, 10.67, and 9.89 times daily, respectively, before, at 6 months, and at 12 months after the operation; the voiding frequencies of group II were 12.95, 9.5, and 8.29 times daily, respectively. TUR combined with therapeutic hydrodistention increased bladder capacity and improved voiding symptoms more so than did TUR alone for ulcerative IC.

[INTERSTITIAL CYSTITIS-ASSOCIATED URINARY METABOLITES IDENTIFIED BY MASS-SPECTROMETRY BASED METABOLOMICS ANALYSIS.](#)

Kind T, Cho E, Park TD, Deng N, Liu Z, Lee T, Fiehn O, Kim J. *Sci Rep.* 2016 Dec 15;6:39227. doi: 10.1038/srep39227. PMID: 27976711

[Full free text, click on title.](#)

This international study on interstitial cystitis (IC) aimed to identify a unique urine metabolomic profile associated with IC. Although the burden of IC on the American public is immense in both human and financial terms, there is no clear diagnostic test for IC, but rather it is a disease of exclusion. Very little is known about the clinically useful urinary biomarkers of IC, which are desperately needed. Untargeted comprehensive metabolomic profiling was performed using gas-chromatography/mass-spectrometry to compare urine specimens of IC patients or health donors. The study profiled 200 known and 290 unknown metabolites. The majority of the thirty significantly changed metabolites before false discovery rate correction were unknown compounds. Partial least square discriminant analysis clearly separated IC patients from controls. The high number of unknown compounds hinders useful biological interpretation of such predictive models. Given that urine analyses have great potential to be adapted in clinical practice, research has to be focused on the identification of unknown compounds to uncover important clues about underlying disease mechanisms.

[PULSED RADIOFREQUENCY TREATMENT OF THE SUPERIOR HYPOGASTRIC PLEXUS IN AN INTERSTITIAL CYSTITIS PATIENT WITH CHRONIC PAIN AND SYMPTOMS REFRACTORY TO ORAL AND INTRAVESICAL MEDICATIONS AND BLADDER HYDRODISTENSION: A CASE REPORT.](#)

Kim JH, Kim E, Kim BI. *Medicine (Baltimore).* 2016 Dec;95(49):e5549. PMID: 27930554

Although a variety of therapeutic modalities are available for the treatment of interstitial cystitis, the less invasive therapies are usually ineffective, whereas the invasive ones carry potential risks of serious side effects and complications. Kim and colleagues from Korea report that pulsed radiofrequency (PRF) treatment of the superior hypogastric plexus may be an alternative to conventional treatments, as it provides nondestructive neuromodulation to the superior hypogastric plexus, which transmits the majority of pain signals from the pelvic viscera. In this case report, they describe a 35-year-old female patient who for 7 years had been experiencing lower abdominal pain provoked by urinary bladder filling, perivulvar pain developing spontaneously during sleep or upon postural change, urinary urgency and frequency with 15- to 60-min intervals between urinations, and nocturia with 10 voids per night. Hydrodistension of the bladder, monthly intravesical administration of sterile sodium chondroitin sulfate, and oral medications including gabapentin and pentosan polysulfate had not been effective in managing the pain and symptoms. Given the satisfactory result of a diagnostic block of the superior hypogastric plexus, 2 sessions of PRF treatment of the superior hypogastric plexus, which applied radiofrequency pulses with a pulse frequency of 2 Hz and a pulse width of 20 ms for 120 s twice per session to maintain the tissue temperature near the electrode at 42°C, were performed at a 6-month interval. This treatment relieved the pain and symptoms for 2 years and 6 months. The authors concluded that PRF treatment of the superior hypogastric plexus results in long-term improvements in the pain and symptoms associated with interstitial cystitis.

[UROPLAKINS AND THEIR POTENTIAL APPLICATIONS IN UROLOGY.](#)

Matuszewski MA, Tupikowski K, Dołowy Ł, Szymañska B, Dembowski J, Zdrojowy R. *Cent European J Urol.* 2016;69(3):252-257. Epub 2016 Jul 8. PMID: 27729990

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Urothelium is a highly specialized type of epithelium covering the interior of the urinary tract. One of the structures responsible for its unique features are urothelial plaques formed from glycoprotein heteropolymers, the uroplakins. Four types of uroplakins are known - UPIa, UPIb, UPII, UPIII. Matuszewski and colleagues from Poland review the current status of knowledge about uroplakins and discuss their potential clinical applications. Uroplakins can be detected in tissue, urine and blood. The process of urothelial plaque formation is complex and its disturbances resulting in incorrect plaque formation might be responsible for some pathological states. Additionally, uroplakins might be associated with other pathological processes i.e. urothelial cancer or infections of the urinary tract. Uroplakins as the end-product of urothelial cells have unique features and a complex structure. These glycoproteins can be involved in some diseases of the urinary tract and as such can be used as potential targets for intervention and markers of the disease.

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

Jhang JF, Hsu YH, Kuo HC. Urology. 2016 Dec;98:44-49. doi: 10.1016/j.urology.2016.08.029. Epub 2016 Aug 26. PMID: 27575016

The purpose of this study from Taiwan was to investigate the urothelium function and sensory receptors difference between interstitial cystitis/bladder pain syndrome (IC/BPS) patients with or without Hunner's lesion. Fourteen female IC/BPS patients with Hunner's lesion (Hunner IC) and 14 age-matched IC/BPS patients without Hunner's lesions (non-Hunner IC) were enrolled. Bladder mucosa biopsies were obtained. Bladder inflammation, eosinophil infiltration, and urothelial denudation were graded on a 4-point scale after staining with hematoxylin and eosin. Adhesive protein E-cadherin, tryptase, and zonula occludens-1 in the bladder tissues were assessed with immunofluorescence staining. Urothelial muscarinic receptors M2, M3, endothelial nitric oxide synthase (eNOS), and purinergic receptor P2X3 were evaluated by Western blotting. Hunner IC patients had a significantly higher mean visual analog scale pain score and smaller cystometric bladder capacity than non-Hunner IC patients. The Hunner IC bladder specimens showed more severe or moderate eosinophilic infiltration and urothelial denudation than the non-Hunner IC bladder specimens did. The E-cadherin expression was significantly lower, and eNOS expression was significantly higher in the Hunner IC bladder samples than in the non-Hunner IC samples suggesting that eNOS expression difference may implicate different pathogenesis in 2 types of IC. The other functional proteins or sensory receptors did not differ between groups.

CLINICAL PHENOTYPING DOES NOT DIFFERENTIATE HUNNER LESION SUBTYPE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A RELOOK AT THE ROLE OF CYSTOSCOPY.

Dairon RC, Tolls V, Irvine-Bird K, Kelly KL, Nickel JC. J Urol. 2016 Oct;196(4):1136-40. doi: 10.1016/j.juro.2016.04.067. Epub 2016 Apr 23. PMID: 27117441

Identifying Hunner lesions in patients with interstitial cystitis/bladder pain syndrome presents an opportunity for objective classification into Hunner lesion interstitial cystitis/bladder pain syndrome (classic interstitial cystitis) and nonHunner lesion bladder pain syndrome. While currently the former diagnosis requires cystoscopy, limited data suggest that these subtypes can be distinguished without endoscopy based on the degree of bladder focused centricity and the infrequent association with generalized pain conditions. Patients in a prospective, single center database of interstitial cystitis/bladder pain syndrome who had documented cystoscopic findings were categorized with Hunner lesion interstitial cystitis/bladder pain syndrome or nonHunner lesion bladder pain syndrome. Demographics, pain and symptom scores, voiding symptoms, irritable bowel syndrome and clinical UPOINT (urinary, psychosocial, organ specific, infection, neurological and tenderness) scoring were comparatively analyzed. The authors reviewed the records of 469 patients, including 359 with documented local anesthetic cystoscopic findings, 44 (12.3%) with Hunner lesion interstitial cystitis/bladder pain syndrome and 315 (87.7%) with nonHunner bladder pain syndrome. Patients with Hunner lesions were older and had greater urinary frequency, more nocturia and higher ICSI (Interstitial Cystitis Symptom Index) scores. Hunner lesion prevalence was significantly lower in those younger than 50 years vs those 50 years old or older. There was no difference in the number of UPOINT phenotype domains reported, overall UPOINT scores or the prevalence of irritable bowel syndrome between the groups. A subtype of interstitial cystitis with Hunner lesions has worse bladder centric symptoms but did not show a distinct bladder centric phenotype. Given the management implications of distinguishing classic interstitial cystitis from

nonHunner lesion bladder pain syndrome, the authors recommend cystoscopy with local anesthesia in patients diagnosed with interstitial cystitis/bladder pain syndrome.

FUNCTIONAL UROLOGICAL DISORDERS

FUNCTIONAL UROLOGICAL DISORDERS: A SENSITIZED DEFENCE RESPONSE IN THE BLADDER-GUT-BRAIN AXIS.

Leue C, Kruimel J, Vrijens D, Masclee A, van Os J, van Koeveringe G. Nat Rev Urol. 2016 Dec 6. doi: 10.1038/nrurol.2016.227. [Epub ahead of print] PMID: 27922040

Leue and colleagues from the Netherlands and UK note that functional urological and gastrointestinal disorders are interrelated and characterized by a chronic course and considerable treatment resistance. Urological disorders associated with a sizeable functional effect include overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS), and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Poor treatment outcomes might be attributable to untreated underlying psychological and psychiatric disorders, as the co-occurrence of functional urological and gastrointestinal disorders with mood and anxiety disorders is common. The hypothetical bladder-gut-brain axis (BGBA) is a useful framework under which this interaction can be studied, suggesting that functional disorders represent a sensitized response to earlier threats such as childhood adversity or previous traumatic events, resulting in perceived emotional and bodily distress - the symptoms of functional disorders. Psychological and physical stress pathways might contribute to such alarm falsification, and neuroticism could be a risk factor for the co-occurrence of functional disorders and affective conditions. Additionally, physical threat - either from external sources or internal sources such as infection - might contribute to alarm falsification by influencing body-brain crosstalk on homeostasis and, therefore, affecting mood, cognition, and behaviour. Multidisciplinary research and an integrated care approach is, therefore, required to further elucidate and remediate functional urological and gastrointestinal polymorphic phenotypes.

UROLOGIC/NEUROLOGIC

UROLOGIC SYMPTOMS AND FUNCTIONAL NEUROLOGIC DISORDERS.

Hoeritzauer I, Phé V, Panicker JN. Handb Clin Neurol. 2017;139:469-481. doi: 10.1016/B978-0-12-801772-2.00038-2. PMID: 27719863

The term functional urologic disorders covers a wide range of conditions related broadly to altered function rather than structure of the lower urinary tract, mainly of impaired urine voiding or storage. Confusingly, for a neurologic readership, these disorders of function may often be due to a urologic, gynecologic, or neurologic cause. However, there is a subset of functional urologic disorders where the cause remains uncertain and, in this chapter, Hoeritzauer and colleagues from the UK and France describe the clinical features of these disorders in turn: psychogenic urinary retention; Fowler's syndrome; paruresis (shy-bladder syndrome); dysfunctional voiding; idiopathic overactive bladder, and interstitial cystitis/bladder pain syndrome. Some of these overlap in terms of symptoms, but have become historically separated. Psychogenic urinary retention in particular has now largely been abandoned as a concept, in part because of the finding of specific urethral electromyogram findings in patients with this symptom now described as having Fowler's syndrome, and their successful treatment with sacral neurostimulation. In this chapter, they review the poorly researched interface between these "idiopathic" functional urologic disorders and other functional disorders (e.g., irritable-bowel syndrome, fibromyalgia) as well as specifically functional neurologic disorders. They conclude that there may be a relationship and overlap between them and that this requires further research, especially in those idiopathic functional urologic disorders which involve disorders of the urethral sphincter (i.e., voluntary muscle).

CROSS ORGAN SENSITIZATION

ACUTE SACRAL NERVE STIMULATION REDUCES VISCERAL MECHANOSENSITIVITY IN A CROSS-ORGAN SENSITIZATION MODEL.

Langlois LD, Le Long E, Meleine M, Antor M, Atmani K, Dechelotte P, Leroi AM, Gourcerol G. Neurogastroenterol Motil. 2016 Nov 7. doi: 10.1111/nmo.12987. [Epub ahead of print] PMID: 27997083

Sacral nerve stimulation (SNS) is a surgical treatment of fecal and urinary incontinence that consists of inserting a stimulating electrode into one of the s3 or s4 sacral holes. In addition to the benefit of SNS in the treatment of incontinence, recent studies showed that SNS is effective in the treatment of irritable bowel syndrome as well as bladder pain syndrome. The aim of this study from Rouen, France was to evaluate the effect of SNS on visceral mechanosensitivity in a cross-organ sensitization rat model. Hypersensitive model was obtained by instillation of acetic acid into the bladder of rats during 5 minutes, 30 minutes before the start of the experiments. Visceral sensitivity was assessed by monitoring the change in mean arterial pressure in response to graded isobaric colorectal distension series. To decipher the mechanisms underlying SNS effect, rats were administered intravenously either a nonselective opioid receptor antagonist (naloxone) or a nitric oxide synthesis antagonist (L-NAME). Neuronal activation in the dorsal horn of the sacral spinal cord was measured by counting c-fos immunoreactive cells in response to colorectal distension and NMS. Intravesical acetic acid instillation increased mean arterial pressure variation in response to colorectal distension when compared to saline group. SNS reduced the variation in arterial pressure. Colorectal distension induced a rise in c-fos immunoreactive cells in the dorsal horn of the spinal cord. This effect was reduced by SNS. It was therefore concluded that SNS reduces visceral mechanosensitivity in a cross-organ sensitization model.

BLADDER HYPERACTIVITY, CYSTITIS AND PAIN

BLOCKING MAMMALIAN TARGET OF RAPAMYCIN ALLEVIATES BLADDER HYPERACTIVITY AND PAIN IN RATS WITH CYSTITIS.

Liang S, Li J, Gou X, Chen D. Mol Pain. 2016 Oct 25;12. pii: 1744806916668868. Print 2016. PMID: 27780878

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

Bladder disorders associated with interstitial cystitis are frequently characterized by increased contractility and pain. The purposes of this study from China were to examine (1) the effects of blocking mammalian target of rapamycin (mTOR) on the exaggerated bladder activity and pain evoked by cystitis and (2) the underlying mechanisms responsible for the role of mTOR in regulating cystic sensory activity. The expression of p-mTOR, mTOR-mediated phosphorylation of p70 ribosomal S6 protein kinase 1 (p-S6K1), 4 E-binding protein 4 (p-4 E-BP1), as well as phosphatidylinositol 3-kinase (p-PI3K) pathway were amplified in cyclophosphamide rats as compared with control rats. Blocking mTOR by intrathecal infusion of rapamycin attenuated bladder hyperactivity and pain. In addition, blocking PI3K signal pathway attenuated activities of mTOR, which was accompanied with decreasing bladder hyperactivity and pain. Inhibition of either mTOR or PI3K blunted the enhanced spinal substance P and calcitonin gene-related peptide in cyclophosphamide rats. The data for the first time revealed specific signalling pathways leading to cyclophosphamide-induced bladder hyperactivity and pain, including the activation of mTOR and PI3K. Inhibition of these pathways alleviates cystic pain. Targeting one or more of these signalling molecules may present new opportunities for treatment and management of overactive bladder and pain often observed in cystitis.

KETAMINE CYSTITIS

THE PUTATIVE INVOLVEMENT OF ACTIN BINDING PROTEINS AND CYTOSKELETON PROTEINS IN PATHOLOGICAL MECHANISMS OF KETAMINE CYSTITIS - REVEALED BY A PROSPECTIVE PILOT STUDY USING PROTEOMIC APPROACHES.

Yang HH, Zhai WJ, Kuo HC. Proteomics Clin Appl. 2016 Nov 10. doi: 10.1002/prca.201600085. [Epub ahead of print] PMID: 27863071

The underlying pathophysiological mechanism(s) of Ketamine Cystitis (KC) is still unclear. The purpose of this pilot study from Taiwan was to elucidate the possible pathophysiological mechanism(s) of KC through proteomic techniques. Bladder tissues were obtained from 7 patients with KC, 7 patients with interstitial cystitis/bladder pain syndrome, and 5 control subjects who underwent videourodynamic study followed by augmentation enterocystoplasty to increase bladder capacity. 2DE/MS/MS based approach, functional classifications, and network analyses were used for proteomic and bioinformatics analyses and protein validation was carried out by Western blot analysis. Among the proteins identified, bioinformatics analyses revealed that several actin binding related proteins such as cofilin-1, myosin light polypeptide 9, filamin A, gelsolin, lamin A were involved in the apoptosis. Besides, the contractile proteins and cytoskeleton proteins

such as myosin light polypeptide 9, filamin A, and calponin were found downregulated in KC bladders. Increased apoptosis in KC might be mediated by actin binding proteins and a Ca²⁺-activated protease. Rapid detrusor contraction in KC might be induced by contractile proteins and cytoskeleton proteins.

KETAMINE: A CAUSE OF URINARY TRACT DYSFUNCTION.

Myers FA Jr, Bluth MH, Cheung WW. Clin Lab Med. 2016 Dec;36(4):721-744. doi: 10.1016/j.cll.2016.07.008. PMID: 27842789

Drug addiction as a result of improper use of prescribed and illicit use has been on the increase globally. The effects of such use have implications in the urologic disease space. To this end, Ketamine has been reported to affect urologic function, causing a number of voiding symptoms. It may also confound the differential diagnosis of urologic diseases, such as interstitial cystitis, among others.

PAIN EVALUATION

WORDS THAT DESCRIBE CHRONIC MUSCULOSKELETAL PAIN: IMPLICATIONS FOR ASSESSING PAIN QUALITY ACROSS CULTURES.

Sharma S, Pathak A, Jensen MP. J Pain Res. 2016 Nov 16;9:1057-1066. eCollection 2016. PMID: 27895511

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

While this article is specifically concerned with descriptions of musculoskeletal pain, it is of course applicable to any field of pain. It is particularly interesting in today's world of multicultural societies. According to Sharma and colleagues, people from different cultures who speak different languages may experience pain differently. This possible variability has important implications for evaluating the validity of pain quality measures that are directly translated into different languages without cultural adaptations. The aim of this study was to evaluate the impact of language and culture on the validity of pain quality measures by comparing the words that individuals with chronic pain from Nepal use to describe their pain with those used by patients from the USA. A total of 101 individuals with chronic musculoskeletal pain in Nepal were asked to describe their pain. The rates of the different pain descriptor domains and phrases used by the Nepali sample were then compared to the published rates of descriptors used by patients from the USA. The content validity of commonly used measures for assessing pain quality was then evaluated. While there was some similarity between patients from Nepal and the USA in how they describe pain, there were also important differences, especially in how pain quality was described. For example, many patients from Nepal used metaphors to describe their pain. Also, the patients from Nepal often used a category of pain descriptor - which describes a physical state - not used by patients from the USA. Only the original McGill Pain Questionnaire was found to have content validity for assessing pain quality in patients from Nepal, although other existing pain quality measures could be adapted to be content valid by adding one or two additional descriptors, depending on the measure in question. The findings indicate that direct translations of measures that are developed using samples of patients from one country or culture are not necessarily content valid for use in other countries or cultures; some adaptations may be required in order for such measures to be most useful in new language and culture.

CHRONIC (PELVIC) PAIN

COMORBID CHRONIC PAIN AND DEPRESSION: PATIENT PERSPECTIVES ON EMPATHY.

Sternke EA, Abrahamson K, Bair MJ. Pain Manag Nurs. 2016 Dec;17(6):363-371.

doi: 10.1016/j.pmn.2016.07.003. Epub 2016 Oct 19. PMID: 27769812

Clinician empathy is a well-documented component of effective patient/provider communication. Evidence surrounding the association between patient perspectives on clinician empathy and perception of pain management is currently limited, particularly among patients with chronic pain and depression. The aim of this study from the USA was to analyze patients' perspectives on the emergent theme of empathy and describe how patients construct their experiences and expectations surrounding empathic interactions. A secondary analysis of focus group data was designed using grounded theory methodology. Study participants highly valued empathy and two types of empathic interactions: empathic listening and empathic action. Patients who provided examples of empathic interactions claimed that others understood, valued, and cared for them. In contrast, patients who perceived a lack of empathy and empathic interactions felt frustrated and

uncared for by others (including their physicians) physically and emotionally. Patients with chronic pain and depression claimed that empathy helped them feel understood, believed, taken seriously, and that their needs were met. In demonstrating empathy and engaging in empathic interactions with patients, providers relate better to patients, better understand their life experience, and provide patient-centred care that is meaningful for patients, providers, and the health care systems within which they interact. Future research is needed to purposefully study the effects of empathic interactions on outcomes for patients with chronic pain and comorbid depression.

A PILOT COMPARISON OF A SMARTPHONE APP WITH OR WITHOUT 2-WAY MESSAGING AMONG CHRONIC PAIN PATIENTS: WHO BENEFITS FROM A PAIN APP?

Jamison RN, Jurcik DC, Edwards RR, Huang CC, Ross EL. Clin J Pain. 2016 Nov 24. [Epub ahead of print] PMID: 27898460

The overall aim of this study from Boston USA was to determine the effect of introducing a smartphone pain app, for both Android and iPhone devices that enables chronic pain patients to assess, monitor, and communicate their status to their providers. This study recruited 105 chronic pain patients to use a smartphone pain app and half of the subjects had 2-way messaging available through the app. All subjects completed baseline measures and were asked to record their progress every day for 3 months, with the opportunity to continue for 6 months. All participants were supplied a Fitbit to track daily activity. Summary line-graphs were posted to each of the patients' electronic medical records and physicians were notified of their patient's progress. Ninety patients successfully downloaded the pain app. Average age of the participants was 47.1 (range 18-72), 63.8% were female and 32.3% reported multiple pain sites. Adequate validity and reliability was found between the daily assessments and standardized questionnaires and in repeated daily measures. The app was found to be easily introduced and well tolerated. Those patients assigned to the 2-way messaging condition on average tended to use the app more and submit more daily assessments, but differences between groups were not significant. Pain-app satisfaction ratings overall were high. This study highlights some of the challenges and benefits in utilizing smartphone apps to manage chronic pain patients, and provides insight into those individuals who might benefit from mHealth technology.

ANORECTAL AND PELVIC PAIN.

Bharucha AE, Lee TH. Mayo Clin Proc. 2016 Oct;91(10):1471-1486. doi: 10.1016/j.mayocp.2016.08.011. PMID: 27712641

Although pelvic pain is a symptom of several structural anorectal and pelvic disorders (eg, anal fissure, endometriosis, and pelvic inflammatory disease), this comprehensive review from the USA focuses on the 3 most common nonstructural, or functional, disorders associated with pelvic pain: functional anorectal pain (ie, levator ani syndrome, unspecified anorectal pain, and proctalgia fugax), interstitialcystitis/bladder pain syndrome, and chronic prostatitis/chronic pelvic pain syndrome. The first 2 conditions occur in both sexes, while the latter occurs only in men. They are defined by symptoms, supplemented with levator tenderness (levator ani syndrome) and bladder mucosal inflammation (interstitial cystitis). Although distinct, these conditions share several similarities, including associations with dysfunctional voiding or defecation, comorbid conditions (eg, fibromyalgia, depression), impaired quality of life, and increased health care utilization. Several factors, including pelvic floor muscle tension, peripheral inflammation, peripheral and central sensitization, and psychosocial factors, have been implicated in the pathogenesis. The management is tailored to symptoms, is partly supported by clinical trials, and includes multidisciplinary approaches such as lifestyle modifications and pharmacological, behavioral, and physical therapy. Opioids should be avoided, and surgical treatment has a limited role, primarily in refractory interstitial cystitis.

CENTRAL AND PERIPHERAL PAIN GENERATORS IN WOMEN WITH CHRONIC PELVIC PAIN: PATIENT CENTERED ASSESSMENT AND TREATMENT.

Hoffman D. Curr Rheumatol Rev. 2015;11(2):146-66. PMID: 26088216

Women with chronic pelvic pain (CPP) often present without obvious cause on imaging studies, laboratory values or physical exam. Dysfunctional sensory processing in the central nervous system (CNS) may explain pain of unclear origin. Central sensitization (CS), a mechanism of centrally mediated pain, describes this abnormal processing of sensory information. Women with CPP often present with several seemingly unrelated

symptoms. This can be explained by co-existing chronic pain syndromes occurring in the same patient. Central sensitization occurs in all of these pain syndromes, also described as dysfunctional pain syndromes, and thus may explain why several often occur in the same patient. Six of the most common pain disorders that co-exist in CPP include endometriosis, painful bladder syndrome/interstitial cystitis, vulvodynia, myofascial pain/pelvic floor hypertonus, irritable bowel syndrome, and primary dysmenorrhea. Central pain generators, (pain originating from CS) and peripheral pain generators, (pain from local tissue damage), can both occur in each of these six conditions. These pain generators will be described. Chronic pain, specifically dysfunctional sensory processing, is recognized as a systemic disease process like diabetes to be managed as opposed to a local problem to be "fixed" or cured. A multi-disciplinary approach to assessment and treatment with a focus on improving emotional, physical and social functioning instead of focusing strictly on pain reduction is more effective in decreasing disability. This is best achieved by determining the patient's needs and perspective through a patient-centred approach. Algorithms for such an approach to assessment and treatment are outlined.

MULTIFACTORIAL CONTRIBUTORS TO THE SEVERITY OF CHRONIC PELVIC PAIN IN WOMEN.

Yosef A, Allaire C, Williams C, Ahmed AG, Al-Hussaini T, Abdellah MS, Wong F, Lisonkova S, Yong PJ. Am J Obstet Gynecol. 2016 Dec;215(6):760.e1-760.e14. doi: 10.1016/j.ajog.2016.07.023. Epub 2016 Jul 18. PMID: 27443813

Chronic pelvic pain affects some 15% of women, and is associated with significant societal cost and impact on women's health. Identifying factors involved in chronic pelvic pain is challenging due to its multifactorial nature and confounding between potential factors. For example, while some women with endometriosis have chronic pelvic pain, there may be comorbid conditions that are implicated in the chronic pelvic pain rather than the endometriosis itself. Yosef and colleagues from Canada sought to explore multifactorial variables independently associated with the severity of chronic pelvic pain in women. They used baseline cross-sectional data from an ongoing prospective cohort, collected from patient online questionnaires, physical examination, and physician review of medical records. Participants were recruited from a tertiary referral center for endometriosis and chronic pelvic pain in Vancouver, British Columbia, Canada, from December 2013 through April 2015. Exclusion criteria included menopausal status or age >50 years. Primary outcome was self-reported severity of chronic pelvic pain in the last 3 months. Potential associated factors ranged from known pain conditions assessed by standard diagnostic criteria, validated psychological questionnaires, musculoskeletal physical exam findings, as well as pain-related, reproductive, medical/surgical, familial, demographic, and behavioural characteristics. Mann-Whitney, Kruskal-Wallis, or Spearman test were used to identify variables with an association with the primary outcome, followed by multivariable linear regression to control for confounding and to identify independent associations with the primary outcome. Overall, 656 women were included (87% consent rate), of whom 55% were diagnosed with endometriosis. The following factors were independently associated with higher severity of chronic pelvic pain: abdominal wall pain, pelvic floor tenderness, painful bladder syndrome, higher score on Pain Catastrophizing Scale, adult sexual assault, higher body mass index, current smoking, and family history of chronic pain. Severity of chronic pelvic pain was similar between women with and without endometriosis. Multifactorial variables independently associated with severity of chronic pelvic pain were identified, ranging from myofascial/musculoskeletal, urological, family history, and psycho-social factors. Continued research is required to validate these factors and to determine whether any are potentially modifiable for the management of chronic pelvic pain.

PAIN MANAGEMENT

CHARACTERIZATION OF THE ADVERSE EFFECTS INDUCED BY ACETAMINOPHEN AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS BASED ON THE ANALYSIS OF THE JAPANESE ADVERSE DRUG EVENT REPORT DATABASE.

Nagai J, Uesawa Y, Shimamura R, Kagaya H. Clin J Pain. 2016 Nov 24. [Epub ahead of print] PMID: 27898459

Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are antipyretic analgesics with established adverse effects; however, only a few studies have compared their adverse effects simultaneously. Nagai and colleagues from Japan aimed to compare the adverse effects of these medications to confirm the respective frequencies of both rare and major adverse effects. They used a high-quality database for spontaneous adverse

drug event reporting in Japan. Data were extracted regarding the adverse effects of acetaminophen and NSAIDs to compare the tendency of the appearance of those adverse effects between the drugs. They also performed a principal component analysis (PCA) using the adverse effects data to assess the characteristics of major adverse effects. Cutaneous disorders and hepatic disorders were the most common adverse effects induced by acetaminophen and NSAIDs, with gastrointestinal tract disorders also common with NSAID use. PCA quantitatively showed the tendencies of specific adverse effects, and it helped demonstrate the characteristics of adverse effects. Acetaminophen and NSAIDs showed different tendencies in the occurrence of adverse effects. Each NSAID was plotted based on the tendency of the appearance of major adverse effects, and adverse effects were classified by their likelihood of being pharmacological or idiosyncratic. These authors concluded that these findings may help clinicians select an appropriate drug for patients considering their backgrounds, instead of choosing merely based on the class of the drug, e.g., COX selectivity. This selection, based on the characteristic information on adverse effects occurring in clinical settings, might be more suitable for patients.

FIBROMYALGIA

[IDENTIFYING FIBROMYALGIA SUBGROUPS USING CLUSTER ANALYSIS: RELATIONSHIPS WITH CLINICAL VARIABLES.](#)

Yim YR, Lee KE, Park DJ, Kim SH, Nah SS, Lee JH, Kim SK, Lee YA, Hong SJ, Kim HS, Lee HS, Kim HA, Joung CI, Kim SH, Lee SS. Eur J Pain. 2016 Sep 15. doi: 10.1002/ejp.935. [Epub ahead of print] PMID: 27633925

Patients with fibromyalgia (FM) exhibit significant clinical heterogeneity, in terms of physical, social and psychological functions, as well as therapeutic responses. Here, Yim and colleagues examined FM patients in terms of pain, physical, social and psychological variables to identify clinical subgroups that may be predictive of treatment patterns. They identified four subgroups of FM patients based on pain, physical, social and psychological function. These subgroups had different clinical symptoms and medication profiles, suggesting that FM may be better managed using a more comprehensive assessment of an individual patient's symptoms. They concluded that FM patients can be clustered into four distinct subgroups based on clinically measurable variables - pain, physical involvement, psychological function and social support. These subgroups had different clinical symptoms and medication profiles.

[A COMPARISON OF COPING STRATEGIES IN PATIENTS WITH FIBROMYALGIA, CHRONIC NEUROPATHIC PAIN, AND PAIN-FREE CONTROLS.](#)

Baastrup S, Schultz R, Brødsgaard I, Moore R, Jensen TS, Vase Toft L, Bach FW, Rosenberg R, Gormsen L. Scand J Psychol. 2016 Dec;57(6):516-522. doi: 10.1111/sjop.12325. Epub 2016 Aug 25. PMID: 27558974

Patients suffering from chronic pain may benefit from learning adaptive coping strategies. Consensus on efficient strategies for this group of patients is, however, lacking, and previous studies have shown inconsistent results. This study from Denmark examined coping strategies in two distinctly different groups of chronic pain patients and a group of healthy controls. Thirty neuropathic pain (NP) patients, 28 fibromyalgia (FM) patients, and 26 pain-free healthy controls completed the Coping Strategy Questionnaire (CSQ-48/27) and rated their daily pain. The results showed that FM and NP patients did not cope differently with pain. The only difference between the groups was that FM patients felt more in control of their pain than NP patients. Both patient groups used more maladaptive/passive coping strategies, but surprisingly also more adaptive/active coping strategies than healthy controls. However, FM patients with high levels of passive strategies felt less in control than FM patients with low levels of passive strategies. This was not seen in NP patients. An important implication for clinical practice is therefore that passive coping strategies should be restructured into active ones, especially for FM patients. Otherwise, the same psychological treatment model can be applied to both groups since they use similar coping styles.

VULVODYNIA/VULVAL PAIN SYNDROME

[THE VULVAR PAIN ASSESSMENT QUESTIONNAIRE INVENTORY.](#)

Dargie E, Holden RR, Pukall CF. Pain. 2016 Dec;157(12):2672-2686. PMID: 27780177

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Millions suffer from chronic vulvar pain (ie vulvodynia). Vulvodynia represents the intersection of 2 difficult subjects for health care professionals to tackle: sexuality and chronic pain. Those with chronic vulvar pain are often uncomfortable seeking help, and many who do so fail to receive proper diagnoses. The current research developed a multidimensional assessment questionnaire, the Vulvar Pain Assessment Questionnaire (VPAQ) inventory, to assist in the assessment and diagnosis of those with vulvar pain. A large pool of items was created to capture pain characteristics, emotional/cognitive functioning, physical functioning, coping skills, and partner factors. The item pool was subsequently administered online to 288 participants with chronic vulvar pain. Of those, 248 participants also completed previously established questionnaires that were used to evaluate the convergent and discriminant validity of the VPAQ. Exploratory factor analyses of the item pool established 6 primary scales: Pain Severity, Emotional Response, Cognitive Response, and Interference with Life, Sexual Function, and Self-Stimulation/Penetration. A brief screening version accompanies a more detailed version. In addition, 3 supplementary scales address pain quality characteristics, coping skills, and the impact on one's romantic relationship. When relationships among VPAQ scales and previously researched scales were examined, evidence of convergent and discriminant validity was observed. These patterns of findings are consistent with the literature on the multidimensional nature of vulvodynia. The VPAQ can be used for assessment, diagnosis, treatment formulation, and treatment monitoring. In addition, the VPAQ could potentially be used to promote communication between patients and providers, and point toward helpful treatment options and/or referrals.

RECENT ADVANCES IN UNDERSTANDING PROVOKED VESTIBULODYNIA.

Lev-Sagie A, Witkin SS. F1000Res. 2016 Oct 26;5:2581. eCollection 2016. PMID: 27853523

Vulvodynia refers to pain in the vulva of at least 3 months' duration in the absence of a recognized underlying cause. Provoked, localized vestibulodynia is the term used to describe superficial pain confined to the vulvar vestibule, provoked by touch. This review will focus on provoked vestibulodynia with regard to its suggested causative factors and will discuss the role of inflammation, vulvovaginal infections, mucosal nerve fiber proliferation, hormonal associations, central pain mechanisms, pelvic floor muscle dysfunction, and genetic factors. Clinical observations, epidemiological studies, and data from basic research emphasize the heterogeneity of vulvar pain syndromes. There is a critical need to perform prospective, longitudinal studies that will allow better diagnostic criteria and subgrouping of patients that would lead to improvements in our understanding of provoked vestibulodynia and its treatment.

SJOGREN'S SYNDROME

2016 AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM CLASSIFICATION CRITERIA FOR PRIMARY SJÖGREN'S SYNDROME: A CONSENSUS AND DATA-DRIVEN METHODOLOGY INVOLVING THREE INTERNATIONAL PATIENT COHORTS.

Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, Rasmussen A, Scofield H, Vitali C, Bowman SJ, Mariette X; International Sjögren's Syndrome Criteria Working Group. Collaborators (47). Arthritis Rheumatol. 2016 Oct 26. doi: 10.1002/art.39859. [Epub ahead of print] PMID: 27785888

Shiboski and colleagues developed and validated an international set of classification criteria for primary Sjögren's syndrome (SS) using guidelines from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). These criteria were developed for use in individuals with signs and/or symptoms suggestive of SS. They assigned preliminary importance weights to a consensus list of candidate criteria items, using multi-criteria decision analysis. They tested and adapted the resulting draft criteria using existing cohort data on primary SS cases and non-SS controls, with case/non-case status derived from expert clinical judgment. They then validated the performance of the classification criteria in a separate cohort of patients. The authors concluded that by using methodology consistent with other recent ACR/EULAR-approved classification criteria, they developed a single set of data-driven consensus classification criteria for primary SS, which performed well in validation analyses and are well-suited as criteria for enrollment in clinical trials.

CONNECTIVE TISSUE DISEASES: NEW CELLULAR PLAYERS IN SJÖGREN SYNDROME PATHOGENESIS.

McHugh J. Nat Rev Rheumatol. 2016 Oct 27. doi: 10.1038/nrrheum.2016.182. [Epub ahead of print] PMID: 27784892

Scientists have identified two novel PD1+ CD4+ T cell subsets in the target tissue of primary Sjögren syndrome (pSS), one corresponding to a population of regulatory T cells and the other to a pathogenic T cell subset. The findings provide new insights into the pathogenesis of the disease and could help in the design of future therapies

[PHYSICAL FATIGUE CHARACTERISES PATIENT EXPERIENCE OF PRIMARY SJÖGREN'S SYNDROME.](#)

Arends S, Meiners PM, Moerman RV, Kroese FG, Brouwer E, Spijkervet FK, Vissink A, Bootsma H. Clin Exp Rheumatol. 2016 Dec 28. [Epub ahead of print] PMID: 28032845

Besides ocular and oral dryness, fatigue is a major symptom in patients with primary Sjögren's syndrome (pSS). The aim of this study from Groningen, Netherlands was to investigate the importance of fatigue in relation to other symptoms experienced as well as to evaluate the effect of rituximab treatment on fatigue in pSS patients with active disease. This analysis was based on data from their open-label rituximab study in 28 pSS patients. Symptoms of dryness, physical fatigue, pain, and mental fatigue were scored on 0-10 scales (according to ESSPRI). Systemic disease activity was assessed with ESSDAI. At baseline, 24 (86%) patients rated physical fatigue as the complaint most eligible for improvement (median importance of 10), followed by pain, dryness, and mental fatigue. After rituximab treatment, physical fatigue showed maximum improvement of 2.5 points and 31% in median values at group level, and 10 (36%) patients reached physical fatigue score <5 representing patient-acceptable symptom state (PASS). In comparison, systemic disease activity improved 5.5 points and 73% at group level, and 22 (79%) patients reached ESSDAI <5 representing low disease activity. GEE analysis over time revealed that physical fatigue was significantly associated with absolute number of B cells, dryness and mental fatigue, but not with ESSDAI, IgG levels and IgM-RF. Physical fatigue characterises patient experience of pSS. Rituximab treatment resulted in significant improvement of patient-reported symptoms. However, the large majority of patients still experienced physical fatigue at an unsatisfactory level, above the cut-off value for PASS. Therefore, attention for optimal management of this prominent symptom is warranted.

LEGAL/ETHICS

[LEGAL AND ETHICAL ISSUES OF USING BRAIN IMAGING TO DIAGNOSE PAIN](#)

Davis, Karen D. PAIN Reports: October 2016 - Volume 1 - Issue 4 - p e577

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Pain, by definition, is a subjective experience, and as such its presence has usually been based on a self-report. However, limitations of self-reports for pain diagnostics, particularly for legal and insurance purposes, has led some to consider a brain-imaging-based objective measure of pain. This review will provide an overview of (1) differences between pain and nociception, (2) intersubject variability in pain perception and the associated brain structures and functional circuits, and (3) capabilities and limitations of current brain-imaging technologies. I then discuss how these factors impact objective proxies of pain. Finally, the ethical, privacy, and legal implications of a brain-imaging-based objective measure of pain are considered as potential future technological developments necessary to create a so-called "painometer test."

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