

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 39, April 2015

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

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

- **Publications of interest**
 - Books
 - Thesis
 - Special edition on pelvic pain syndromes
 - NIH report on opioids
 - IASP chronic pain classification for ICD-11
 - IASP Pain Clinical Update
 - RCOG scientific impact paper on chronic pelvic pain
- Upcoming Events
- Research Highlights
- Donations & Sponsoring

IPBF: NEW CORRESPONDENCE ADDRESS.

The IPBF recently moved house! Please note that the IPBF's correspondence address is now:
Mahlerlaan 4, 1411 HW Naarden, The Netherlands.

PUBLICATIONS OF INTEREST

- BOOKS

ABDOMINAL AND PELVIC PAIN: FROM DEFINITION TO BEST PRACTICE

Editors: Bert Messelink, Andrew Baranowski, John Hughes

ISBN 13: 978-1-4963-0618-0

Published by: Wolters Kluwer; IASP Press, 2015

329 pages

<http://www.lww.com/Product/9781496306180>

This useful reference book is in part a congress review of presentations at the 1st World Congress on Abdominal and Pelvic Pain held in Amsterdam in 2013, but also a textbook containing the most up-to-date information on abdominal and pelvic pain and an authoritative guide on the current science and management of abdominal,

pelvic and visceral pain. The book also contains a chapter on the role of patient organisations by patient advocates representing organizations that are members of the International Pelvic Pain Partnership (IPPP). This publication can also be purchased from the IASP website as an e-book.

- THESIS

Dr Jörgen Quaghebeur from Antwerp, an osteopath with a special interest in chronic pelvic pain syndromes including IC/BPS, recently published his PhD thesis (*Quaghebeur J. Research on diagnostic techniques used in CPPS patients. PhD thesis. Antwerp University, Faculty of Medicine and Health Sciences; 2014*), and also a summary “A Review of Techniques used for Evaluating Lower Urinary Tract Symptoms and the Level of Quality of Life in Patients with Chronic Pelvic Pain Syndrome”. This summary is available online at: <http://www.smartscitech.com/index.php/IP/article/view/659>

- SPECIAL JOURNAL EDITION

SPECIAL JOURNAL EDITION ON PELVIC PAIN SYNDROMES, CURRENT BLADDER DYSFUNCTION REPORTS, MARCH 2015

Dr Jeannette Potts and Dr Christopher Payne from California co-edited a special journal edition this year on pelvic pain syndromes for Current Bladder Dysfunction Reports, released in March 2015. Topics and authors included:

Male Pelvic Pain Syndrome: Escaping the Snare of Prostatocentric Thinking

Potts JM. Current Bladder Dysfunction Reports. March 2015, Volume 10, Issue 1, pp 75-80

Decades of prostatocentric research and publications have hampered care for men with genital or pelvic pain syndromes who are often misdiagnosed with prostatitis. The prostatitis classification system as well as other misuse of terminology may have direct and indirect influence on physicians and lay persons alike. Thankfully, there is growing interest and evidence to show that male pelvic pain can and should be approached more broadly, even as a nonurological condition.

A New Approach to Urologic Chronic Pelvic Pain Syndromes: Applying Oncologic Principles to “Benign” Conditions

Payne CK. Current Bladder Dysfunction Reports. March 2015, Volume 10, Issue 1, pp 81-86

The urologic chronic pelvic pain syndromes—interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome—continue to be both a major cause of morbidity in patients and huge challenge to clinicians. A new approach is needed. Utilizing principles borrowed from our oncologic colleagues to UCPPS patients can improve all aspects of care.

Myofascial Pelvic Pain: Rationale and Treatment

Kotarinos RK. Current Bladder Dysfunction Reports. March 2015, Volume 10, Issue 1, pp 87-94

Myofascial pelvic pain can develop as a result of a trigger point within the pelvic floor musculature or from extra-pelvic muscles that can refer into the pelvic region. Identification and appropriate therapeutic management of the myofascial trigger points is paramount to successful treatment of the pain and symptoms associated with chronic pelvic pain.

Classic Interstitial Cystitis: Unrelated to BPS

Fall M, Peeker RE. Current Bladder Dysfunction Reports. March 2015, Volume 10, Issue 1, pp 95-102

When first recognized, more than one hundred years ago, the term interstitial cystitis (IC) was reserved for subjects with a special type of deep inflammation of the bladder wall. Later, the scope of IC widened, including all kinds of bladder pain syndromes (BPS), giving rise to a lot of confusion and difficulties in research as well as in clinical practice. For the benefit of our patients, in BPS/IC, it is time for a final separation of the concepts BPS and IC. Classic IC is a well-defined entity with multiple unique characteristics, those characteristics having a potential for development of a specific rational, pharmacological, and surgical treatment algorithm if further investigated. BPS, on the other hand, seems to include a heterogenic composition of conditions calling for broad attempts to be more closely explored.

[Patient Heal Thyself: Engaging in a Team Approach](#)

Meijlink JM. Current Bladder Dysfunction Reports. March 2015, Volume 10, Issue 1, pp 103-108

Interstitial cystitis/bladder pain syndrome is a chronic condition for which conventional treatment is highly individualistic, may have a limited effect if any, and is often a question of trial and error. The impact on the patient's life is far-reaching and often greatly underestimated. The limitations of effectiveness, availability, reimbursement and affordability of conventional treatments mean that desperate patients actively seek alternative solutions, with or without professional guidance.

- NIH REPORT

NATIONAL INSTITUTES OF HEALTH (NIH): PATHWAYS TO PREVENTION WORKSHOP: THE ROLE OF OPIOIDS IN THE TREATMENT OF CHRONIC PAIN FINAL REPORT

An unbiased, independent panel developed a final report of the 2014 NIH Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain, which summarizes the workshop and identifies future research priorities. [Download the Final Report \(PDF - 527 KB\)](#).

Further information:

<https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/opioids-chronic-pain/workshop-resources#finalreport>

- INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN (IASP) TASK FORCE ON CHRONIC PAIN CLASSIFICATION

A CLASSIFICATION OF CHRONIC PAIN FOR ICD-11.

An International Association for the Study of Pain (IASP) Task Force has developed a new Classification of Chronic Pain for ICD-11 (scheduled for publication in the June issue of PAIN) in an effort to address shortcomings in the current version of the International Classification of Diseases (ICD) of the World Health Organization (WHO). For further information, go to the IASP website, [click here](#). This chronic pain classification for ICD-11 is naturally of great importance to the field of IC/BPS. We will provide further details in the next Newsletter.

- IASP PAIN CLINICAL UPDATE

EXPANDING PATIENTS' ACCESS TO HELP IN MANAGING THEIR CHRONIC PAIN

Vol XXIII, No 1, February 2015.

This clinical update from the International Association for the Study of Pain (www.iasp-pain.org) is available online in English and French. Click on title to access. The authors note that experts have strongly argued that interventions for people with disabling pain should not only address their pain experience but also their mood and disability, as well as any modifiable contributing factors.

- RCOG SCIENTIFIC IMPACT PAPER CPP

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS (RCOG) RELEASE (SCIENTIFIC IMPACT PAPER NUMBER 46): TREATMENT FOR WOMEN WITH CHRONIC PELVIC PAIN SHOULD CONSIDER THE KEY ROLE OF THE CENTRAL NERVOUS SYSTEM, SUGGESTS A NEW SCIENTIFIC OPINION PAPER

When assessing and planning treatment for women with chronic pelvic pain, a condition affecting more than one million women in the UK, the key role of the central nervous system must be considered, suggests a new Scientific Impact Paper (SIP) published by the Royal College of Obstetricians and Gynaecologists (RCOG).

- REMINDERS – USEFUL REFERENCE WORK

INTERNATIONAL JOURNAL OF UROLOGY (IJU) SPECIAL ISSUE WITH FREE ACCESS

International Painful Bladder Foundation

The proceedings of the 3rd International Consultation on Interstitial Cystitis, Japan (ICICJ) and the International Society for the Study of Bladder Pain Syndrome (ESSIC) Joint Meeting, held 21–23 March 2013, Kyoto, Japan, have been published in a special issue of the International Journal of Urology, April 2014, Volume 21, Supplement S1. [Click here](#) for the state-of-the-art in the field of IC/BPS and associated disorders or go to <http://onlinelibrary.wiley.com/doi/10.1111/iju.2014.21.issue-s1/issuetoc>.

All articles in this special supplement have free access.

BLADDER PAIN SYNDROME, A GUIDE FOR CLINICIANS

Jørgen Nordling, Jean-Jacques Wyndaele, Joop P van de Merwe, Pierre Bouchelouche, Mauro Cervigni, Magnus Fall (Editors.)

Published by Springer 2013, 365 p.

ISBN 978-1-4419-6929-3

[Click here](#) for the Content of the book

<http://www.springer.com/medicine/urology/book/978-1-4419-6928-6>

UPCOMING EVENTS

AMERICAN UROLOGICAL ASSOCIATION (AUA) ANNUAL MEETING

15-19 May, New Orleans. USA

<http://www.aua2015.org/>

13TH INTERNATIONAL SYMPOSIUM ON SJÖGREN'S SYNDROME

The 13th International Symposium on Sjögren's Syndrome will be held 19-22 May, 2015 in Bergen, Norway. This will include a meeting of patient organisations.

Further information is available at <http://www.sicca.org/iss2015/>

EURORDIS MEMBERSHIP MEETING (EMM) 2015 MADRID

The EURORDIS Membership Meeting 2015 will take place at Hotel Rafael Antocha, Madrid, Spain, May 29 and 30. The meeting's working language will be English, with simultaneous translation of the Plenary Session on Friday 29 May into Spanish. <http://www.eurordis.org/content/membership-meetings>.

2nd WORLD CONGRESS ON ABDOMINAL AND PELVIC PAIN (WCAPP), 11-13 JUNE 2015, NICE, FRANCE

Following the great success of the 1st WCAPP held in Amsterdam, this 2nd multidisciplinary WCAPP (President Dr Jean-Jacques Labat) will be organised 11-13 June 2015 in Nice, France by Convergences PP in collaboration with IPPS and APP-IASP. This meeting will also include a patient workshop.

www.pelvicpain-meeting.com.

2ND GLOBAL CONGRESS ON LOWER URINARY TRACT DYSFUNCTION 2015

The Second Global Congress on LUTD will be held 24-26 June 2015 in Rome, Italy.

<http://lutd.org>

ESSIC ANNUAL MEETING 2015

The ESSIC Annual Meeting 2015 will be held in Rome, Italy from Thursday 17 September at 13.00 hours to Saturday 19 September 2015 at 13.30 hours. Further details and preliminary programme are available on the ESSIC website www.essic.eu

45th INTERNATIONAL CONTINENCE SOCIETY (ICS) ANNUAL SCIENTIFIC MEETING

This year's meeting will be held 6-9 October in Montreal, Canada. Further information and preliminary programme can be found at <http://www.ics.org/2015>.

MIPS 3RD ANNUAL MEETING, LJUBLJANA, SLOVENIA, 10-12 DECEMBER, 2015

The Mediterranean Incontinence and Pelvic Floor Society will be holding its 3rd annual meeting in Slovenia this year. Further information at: <http://www.mipsnet.org>.

RESEARCH HIGHLIGHTS

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

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

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

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

UROLOGICAL CHRONIC PELVIC PAIN SYNDROME FLARES AND THEIR IMPACT: QUALITATIVE ANALYSIS IN THE MAPP NETWORK.

Sutcliffe S, Bradley CS, Clemens JQ, James AS, Konkle KS, Kreder KJ, Lai HH, Mackey SC, Ashe-McNalley CP, Rodriguez LV, Barrell E, Hou X, Robinson NA, Mullins C, Berry SH. *Int Urogynecol J.* 2015 Mar 20. [Epub ahead of print] PMID: 25792349

Although in-depth qualitative information is critical to understanding patients' symptom experiences and to developing patient-centered outcome measures, only one previous qualitative study has assessed urological chronic pelvic pain syndrome (UCPPS) symptom exacerbations ("flares"). This team from the MAPP Network conducted eight focus groups of female UCPPS (interstitial cystitis/bladder pain syndrome) patients at four sites from the MAPP Research Network to explore the full spectrum of flares and their impact on patients' lives. Flare experiences were common and varied widely in terms of UCPPS symptoms involved, concurrent non-pelvic symptoms (e.g. diarrhoea), symptom intensity (mild to severe), duration (minutes to years), and frequency (daily to < once/year), although the most commonly described flares were painful flares lasting days. These latter flares were also most disruptive to participants' lives, causing some to cancel social events, miss work or school, and in the worst cases, go to the emergency room or on disability leave. Participants also reported a longer-term impact of flares, including negative effects on their sexual functioning and marital, family, and social relationships; and the loss of employment or limited career or educational advancement. Emerging themes included the need for a sense of control over unpredictable symptoms and reduced social engagement. Given their negative impact, future research should focus on approaches to prevent flares, and to reduce their frequency, severity, and/or duration. Patients' quality of life may also be improved by providing them with a sense of control over their symptoms through ready access to flare medications/therapy, and by engaging them socially.

TOLL-LIKE RECEPTOR 4 AND COMORBID PAIN IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN RESEARCH NETWORK STUDY.

Schrepf A, Bradley CS, O'Donnell M, Luo Y, Harte SE, Kreder K, Lutgendorf S; Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. *Brain Behav Immun.* 2015 Mar 11. pii: S0889-1591(15)00074-4. doi: 10.1016/j.bbi.2015.03.003. [Epub ahead of print] PMID: 25771510

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a condition characterized by pelvic pain and urinary symptoms. Some IC/BPS patients have pain confined to the pelvic region, while others suffer widespread pain. Inflammatory processes have previously been linked to pelvic pain in IC/BPS, but their association with widespread pain in IC/BPS has not been characterized. Sixty-six women meeting criteria for IC/BPS completed self-report measures of pain as part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP), collected 3 days of saliva for cortisol assays, and provided blood samples. Peripheral blood

mononuclear cells (PBMCs) were stimulated with Toll-like Receptor (TLR) 2 and 4 agonists and cytokines were measured in supernatant; IL-6 was also measured in plasma. Associations between inflammatory variables and the likelihood of endorsing extra-pelvic pain, or the presence of a comorbid syndrome, were tested by logistic regression and General Linear Models, respectively. A subset of patients completed Quantitative Sensory Testing. A one standard deviation increase in TLR-4 inflammatory response was associated with a 1.59 greater likelihood of endorsing extra-pelvic pain. Participants with comorbid syndromes also had higher inflammatory responses to TLR-4 stimulation in PBMCs. Lower pressure pain thresholds were marginally associated with higher TLR-4 inflammatory responses, and significantly associated with higher IL-6 in plasma. TLR-4 inflammatory responses in PBMCs are a marker of widespread pain in IC/BPS, and should be explored in other conditions characterized by medically unexplained pain.

BRAIN WHITE MATTER ABNORMALITIES IN FEMALE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: A MAPP NETWORK NEUROIMAGING STUDY.

Farmer MA, Huang L, Martucci K, Yang CC, Maravilla KR, Harris RE, Clauw DJ, Mackey S, Ellingson BM, Mayer EA, Schaeffer AJ, Apkarian AV; MAPP Research Network. J Urol. 2015 Feb 21. pii: S0022-5347(15)00392-4. doi: 10.1016/j.juro.2015.02.082. [Epub ahead of print] PMID: 25711200

Farmer and colleagues note that several chronic pain conditions may be distinguished by condition specific brain anatomical and functional abnormalities on imaging, which are suggestive of underlying disease processes. This MAPP Research Network team presents what they believe to be the first characterization of interstitial cystitis/bladder pain syndrome (IC/BPS) associated white matter (axonal) abnormalities based on multicenter neuroimaging from the MAPP Research Network. They assessed 34 women with interstitial cystitis/bladder pain syndrome and 32 healthy controls using questionnaires on pain, mood and daily function. White matter microstructure was evaluated by diffusion tensor imaging to model directional water flow along axons or fractional anisotropy. Regions correlating with clinical parameters were further examined for gender and syndrome dependence. They found that women with IC/BPS showed numerous white matter abnormalities that correlated with pain severity, urinary symptoms and impaired quality of life. IC/BPS was characterized by decreased fractional anisotropy in aspects of the right anterior thalamic radiation, the left forceps major and the right longitudinal fasciculus. Increased fractional anisotropy was detected in the right superior and bilateral inferior longitudinal fasciculi. This MAPP team concludes that given that white matter abnormalities closely correlated with hallmark symptoms of IC/BPS, including bladder pain and urinary symptoms, brain anatomical alterations suggest that there are neuropathological contributions to chronic urological pelvic pain.

SEARCH FOR MICROORGANISMS IN MEN WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROME: A CULTURE-INDEPENDENT ANALYSIS IN THE MAPP RESEARCH NETWORK.

Nickel JC, Stephens A, Landis JR, Chen J, Mullins C, van Bokhoven A, Lucia MS, Melton-Kreft R, Ehrlich GD; The MAPP Research Network. J Urol. 2015 Jan 14. pii: S0022-5347(15)00058-0. doi: 10.1016/j.juro.2015.01.037. [Epub ahead of print] PMID: 25596358

Nickel and colleagues used next-generation, state-of-the-art, culture-independent methodology to survey urine microbiota of UCPPS males and control participants enrolled in the MAPP Network to investigate a possible microbial etiology. Male UCPPS patients and matched controls were asked to provide VB1, VB2 and VB3 urine specimens. Specimens were analyzed with Ibis T-5000 Universal Biosensor technology to provide comprehensive identification of bacterial and select fungal species. Differences between UCPPS and control study participants for presence of species or species variation within a higher taxonomic grouping (genus) were evaluated using permutational multivariate analysis of variance and logistic regression. The authors conclude that assessment of baseline culture-independent microbiological data from male subjects enrolled in the MAPP Network has identified over representation of B cenocepacia in UCPPS. Future studies are planned to further evaluate microbiota associations with variable and changing UCPPS symptom patterns.

Explanatory note:

VB1 - voided bladder 1, which represents the urethra.

VB2 - voided bladder 2, which represents the bladder.

VB3 - voided bladder 3, which also represents the prostate.

RELATIONSHIP BETWEEN CHRONIC NONUROLOGICAL ASSOCIATED SOMATIC SYNDROMES AND SYMPTOM SEVERITY IN UROLOGICAL CHRONIC PELVIC PAIN SYNDROMES: BASELINE EVALUATION OF THE MAPP STUDY.

Krieger JN, Stephens AJ, Landis JR, Clemens JQ, Kreder K, Lai HH, Afari N, Rodriguez L, Schaeffer A, Mackey S, Andriole GL, Williams DA; MAPP Research Network. Collaborators (117). J Urol. 2015 Apr;193(4):1254-62. doi: 10.1016/j.juro.2014.10.086. Epub 2014 Oct 22. PMID: 25444992

Krieger and colleagues used MAPP data to identify participants with urological chronic pelvic pain syndromes only or a chronic functional nonurological associated somatic syndrome in addition to urological chronic pelvic pain syndromes. They characterized these 2 subgroups and explored them using 3 criteria, including 1) MAPP eligibility criteria, 2) self-reported medical history or 3) RICE criteria. Self-reported cross-sectional data were collected on men and women with urological chronic pelvic pain syndromes, including predominant symptoms, symptom duration and severity, nonurological associated somatic syndrome symptoms and psychosocial factors. Of 424 participants with urological chronic pelvic pain syndromes 162 (38%) had a nonurological associated somatic syndrome, including irritable bowel syndrome in 93 (22%), fibromyalgia in 15 (4%), chronic fatigue syndrome in 13 (3%) and multiple syndromes in 41 (10%). Of 233 females 103 (44%) had a nonurological associated somatic syndrome compared to 59 of 191 males (31%) ($p = 0.006$). Participants with a nonurological associated somatic syndrome had more severe urological symptoms and more frequent depression and anxiety. Of 424 participants 228 (54%) met RICE criteria. Of 228 RICE positive participants 108 (47%) had a nonurological associated somatic syndrome compared to 54 of 203 RICE negative patients (28%) with a nonurological associated somatic syndrome ($p < 0.001$). It was concluded that nonurological associated somatic syndromes represent important clinical characteristics of urological chronic pelvic pain syndromes. Participants with a nonurological associated somatic syndrome have more severe symptoms, longer duration and higher rates of depression and anxiety. RICE positive patients are more likely to have a nonurological associated somatic syndrome and more severe symptoms. Because nonurological associated somatic syndromes are more common in women, future studies must account for this potential confounding factor in urological chronic pelvic pain syndromes.

COMPARISON OF BASELINE UROLOGICAL SYMPTOMS IN MEN AND WOMEN IN THE MAPP RESEARCH COHORT.

Clemens JQ, Clauw DJ, Kreder K, Krieger JN, Kusek JW, Lai HH, Rodriguez L, Williams DA, Hou X, Stephens A, Landis JR; MAPP Research Network. J Urol. 2015 May;193(5):1554-8. doi: 10.1016/j.juro.2014.11.016. Epub 2014 Nov 13. PMID: 25463989

The clinical features of the interstitial cystitis/bladder pain syndrome are similar to those of the chronic prostatitis/chronic pelvic pain syndrome. However, Clemens and colleagues note that to their knowledge no studies have directly compared the characteristics of these syndromes in men and women. The MAPP Research Network recruited 191 men and 233 women with IC/BPS or CP/CPPS. Baseline data included demographics, Interstitial Cystitis Symptom Index and Problem Index scores; Genitourinary Pain Index score; American Urological Association Symptom Index score; Likert scales to assess urinary urgency, frequency, pain and overall symptom severity; and a single question about the most bothersome pelvic symptom. After adjustment for age, income and symptom duration, measures of pain severity were similar across genders. Mean scores for the ICSI, ICPI and AUASI were significantly higher in women than in men, reflecting more bladder focused symptoms in women. The most bothersome single symptom in men as well as in women was pain in the pubic/bladder area (men 34%, women 58%). The characteristics of the men and women in the MAPP cohort were similar to those reported in other research cohorts for IC/BPS and CP/CPPS. The authors report that their findings indicate that pain severity is similar for both genders and that bladder focused symptoms (urgency, suprapubic pain, frequency) are more common in women. However, a substantial proportion of men also reported these types of bladder symptoms.

PRELIMINARY STRUCTURAL MRI BASED BRAIN CLASSIFICATION OF CHRONIC PELVIC PAIN: A MAPP NETWORK STUDY.

Bagarinao E, Johnson KA, Martucci KT, Ichesco E, Farmer MA, Labus J, Ness TJ, Harris R, Deutsch G, Apkarian AV, Mayer EA, Clauw DJ, Mackey S. Pain. 2014 Dec;155(12):2502-9. doi: 10.1016/j.pain.2014.09.002. Epub 2014 Sep 19. PMID: 25242566

Neuroimaging studies have shown that changes in brain morphology often accompany chronic pain conditions. However, brain biomarkers that are sensitive and specific to chronic pelvic pain (CPP) have not yet been adequately identified. Using data from the Trans-MAPP Research Network, Bagarinao and colleagues examined the changes in brain morphology associated with CPP. They used a multivariate pattern classification approach to detect these changes and to identify patterns that could be used to distinguish participants with CPP from age-matched healthy controls. In particular, they used a linear support vector machine (SVM) algorithm to differentiate gray matter images from the 2 groups. Regions of positive SVM weight included several regions within the primary somatosensory cortex, pre-supplementary motor area, hippocampus, and amygdala were identified as important drivers of the classification with 73% overall accuracy. Thus, they have identified a preliminary classifier based on brain structure that is able to predict the presence of CPP with a good degree of predictive power. Their regional findings suggest that in individuals with CPP, greater grey matter density may be found in the identified distributed brain regions, which are consistent with some previous investigations in visceral pain syndromes. They emphasize that future studies are needed to improve upon their identified preliminary classifier with integration of additional variables and to assess whether the observed differences in brain structure are unique to CPP or generalizable to other chronic pain conditions.

IC/BPS BASIC SCIENCE, DIAGNOSIS AND TREATMENT

[DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: AUA GUIDELINE AMENDMENT.](#)

Hanno PM, Erickson D, Moldwin R, Faraday MM. J Urol. 2015 Jan 23. pii: S0022-5347(15)00176-7. doi: 10.1016/j.juro.2015.01.086. [Epub ahead of print] PMID: 25623737

The purpose of this amendment is to provide an updated clinical framework for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome based upon data received since the publication of original guideline in 2011. A systematic literature review using the MEDLINE® database (search dates 1/1/83-7/22/09) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of IC/BPS. This initial review yielded an evidence base of 86 treatment articles after application of inclusion/exclusion criteria. The AUA update literature review process, in which an additional systematic review is conducted periodically to maintain guideline currency with newly published relevant literature, was conducted in July 2013. This review identified an additional 31 articles, which were added to the evidence base of this Guideline. Newly incorporated literature describing the treatment of IC/BPS was integrated into the Guideline with additional treatment information provided as Clinical Principles and Expert Opinions when insufficient evidence existed. The diagnostic portion of the Guideline remains unchanged from the original publication and is still based on Expert Opinions and Clinical Principles. The management of IC/BPS continues to evolve as can be seen by an expanding literature on the topic. This document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the individual clinician and patient. As the science relevant to IC/BPS evolves and improves, the strategies presented will require amendment to remain consistent with the highest standards of care.

[NUMBER OF ACTIVE ELECTRODES AT TIME OF STAGED TINED LEAD INTERSTIM IMPLANT DOES NOT IMPACT CLINICAL OUTCOMES.](#)

Gillera JP, Killinger K, Boura J, Peters KM. NeuroUrol Urodyn. 2015 Apr 6. doi: 10.1002/nau.22766. [Epub ahead of print] PMID: 25850568

The purpose of this study from the William Beaumont Hospital, Royal Oak, Michigan was to determine: (1) if obtaining motor response on <4 tined lead electrodes at time of placement affects subjective and objective clinical outcome and (2) voltage requirements to elicit motor response at implant and first postoperative visit number based on number of responding electrodes. They reviewed their prospective neuromodulation database to identify patients with unilateral S3 lead placement and motor response (bellows ± toe flexion) on stimulation of 1-4 electrodes, then grouped by number of active electrodes at lead placement. Stage 1 success, reoperation and reprogramming rates, mean voltage at implant and first postoperative visit, and Interstitial Cystitis Symptom/Problem Indices (ICSI-PI) were analyzed using Pearson's Chi-square, Fisher's exact, Kruskal-Wallis or Wilcoxon rank tests. Two hundred forty four patients met inclusion criteria, categorized into 1-2

(n = 25), 3 (n = 48), and 4 active electrodes (n = 171). There were no significant differences between groups in terms of age, indications for neuromodulation, or stage 1 success. At implant, patients with <4 active electrodes required higher mean voltages for motor responses (5.9, 4.9, and 3.9 volts for each group respectively). Mean voltages for sensory threshold at first postoperative programming were 1.5 ± 1.5 , 0.9 ± 1.0 , and 0.8 ± 1.0 , respectively. Overall reoperation rates, and reprogramming sessions at 24 months did not differ. ICSI-PI scores improved similarly in all groups. Motor response on four electrodes is not necessary for successful stage 1 trial. Despite higher voltage requirements in those with <4 active electrodes at implant, this difference was not observed at initial postoperative programming.

HYALURONIC ACID DECREASES IL-6 AND IL-8 SECRETION AND PERMEABILITY IN AN INFLAMMATORY MODEL OF INTERSTITIAL CYSTITIS.

Rooney P, Srivastava A, Watson L, Quinlan LR, Pandit A. *Acta Biomater.* 2015 Mar 26. pii: S1742-7061(15)00113-0. doi: 10.1016/j.actbio.2015.02.030. [Epub ahead of print] PMID: 25818949

Hyaluronic acid (HA) has received a lot of attention recently as a biomaterial with applications in wound healing, drug delivery, vascular repair and cell and/or gene delivery. Interstitial cystitis (IC) is characterised by an increase in the permeability of the bladder wall urothelium due to loss of the glycosaminoglycan (GAG) layer. The degradation of the urothelium leads to chronic pain and urinary dysfunction. The aetiology of the degradation of the GAG layer in this instance is currently unknown. At a clinical level, GAG replacement therapy using a HA solution is currently utilised as a treatment for IC. However, there is a significant lack of data on the mechanism of action of HA in IC. This study from Ireland investigates the mechanistic effect of clinically relevant HA treatment on an in vitro model of IC using urothelial cells, examining cytokine secretion, GAG secretion and trans-epithelial permeability. This study demonstrates that HA can significantly decrease induced cytokine secretion (4-5 fold increase), increase sulphated GAG production (2-fold increase) and without altering tight junction expression, decrease trans-epithelial permeability, suggesting that the HA pathway is a clinical target and potential treatment vector.

HYALURONIC ACID-CHONDROITIN SULFATE: A POTENTIAL FACTOR TO SELECT PURE STRESS URINARY INCONTINENCE IN PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME AND MIXED INCONTINENCE SYMPTOMS.

Morelli M, Mocciaro R, Venturella R, Albano A, Sacchinelli A, Zullo F. *Minerva Ginecol.* 2015 Apr;67(2):121-5. PMID: 25763801

The purpose of this study from Italy was to validate the Hyaluronic acid-Chondroitin sulfate (HA-CS) as ex adjuvantibus criteria to identify patients with urgency symptoms related to interstitial cystitis/painful bladder syndrome (IC/PBS) and to obtain a population of patients with pure stress urinary incontinence. Morelli and colleagues retrospectively analysed clinical data of 17 patients with clinical suspect of IC/PBS, who received intravesical HA-CS to reduce pelvic pain and urgency symptoms waiting for surgical treatment for stress urinary incontinence. The main outcomes were reduction of urinary frequency, urgency, and bladder pain. Compared to baseline, a significant decrease in pain, urgency and frequency was observed. Of the 17 patients, 82.3% reported resolution of pain and urge symptoms and in patients with persistence of urge symptoms the urodynamic assessment showed an overactive bladder syndrome (OAB). HA-CS treatment induces an improvement in pain and urgency symptoms in patients with IC/PBS with stress urinary incontinence. Therefore, HA-CS treatment could be used as clinical adjunctive parameter to select patients with pure stress urinary incontinence.

HEPARIN AND ALKALINIZED LIDOCAINE VERSUS ALKALINIZED LIDOCAINE FOR TREATMENT OF INTERSTITIAL CYSTITIS SYMPTOMS.

Parsons CL, Koziol JA, Proctor JG, Zupkas P, Argade S. *Can J Urol.* 2015 Apr;22(2):7739-44. PMID: 25891339

This pilot study by Parsons and colleagues from San Diego was undertaken to determine if the combination of heparin and alkalized lidocaine (heparin-lidocaine) was more efficacious than alkalized lidocaine at relieving pain and urgency symptoms associated with IC and also capable of yielding higher lidocaine absorption. A single blind study was conducted on 14 IC patients with a heparin-lidocaine combination versus alkalized lidocaine instilled intravesically. In a separate study serum lidocaine levels for heparin-alkalized lidocaine combination versus USP lidocaine only were determined by high performance liquid chromatography.

Alkalinized lidocaine and heparin have been reported to provide relief from pain and urgency symptoms associated with IC. The heparin-lidocaine combination significantly reduced the % of bladder pain (38% versus 13%) and urgency (42% versus 8%) compared to lidocaine. In addition the GAR was significantly better for the heparin-lidocaine combination at both 1 hr % improved (77% versus 50%) and 24 hrs (57% versus 23%) after study drug treatment. Serum lidocaine levels for the heparin-lidocaine combination were significantly higher compared to USP lidocaine (unalkalinized). The authors report that in this pilot study the heparin-lidocaine combination results in significantly better relief of IC symptoms compared to alkalinized lidocaine and the combination yields higher lidocaine absorption than USP lidocaine.

[ARTEMIN IMMUNOTHERAPY IS EFFECTIVE IN PREVENTING AND REVERSING CYSTITIS-INDUCED BLADDER HYPERALGESIA VIA TRPA1 REGULATION.](#)

DeBerry JJ, Saloman JL, Dragoo BK, Albers KM, Davis BM. J Pain. 2015 Apr 16. pii: S1526-5900(15)00627-6. doi: 10.1016/j.jpain.2015.03.014. [Epub ahead of print] PMID: 25892657

Injury- or disease-induced artemin (ARTN) signaling can sensitize primary afferents and contribute to persistent pain. DeBerry and colleagues from Pittsburgh demonstrate that administration of an anti-artemin (α -ARTN) neutralizing antibody can block the development of, and reverse already established, bladder hyperalgesia associated with cyclophosphamide (CYP)-induced cystitis in mice. They further demonstrate that α -ARTN therapy blocks upregulation of TRPA1, an ion channel contributing to persistent bladder pain during CYP-induced cystitis, and decreases phospho-ERK1/2 (pERK) immunoreactivity in regions of the spinal cord receiving bladder afferent input. They suggest that α -ARTN may be a promising novel therapeutic approach for treatment of bladder hyperalgesia that may be associated with interstitial cystitis (IC)/painful bladder syndrome (PBS), as well as cystitis associated with anti-tumor or immunosuppressive CYP therapy. α -ARTN therapy effectively prevented and reversed ongoing bladder hyperalgesia in an animal model of cystitis, indicating its potential as an efficacious treatment strategy for ongoing bladder pain associated with IC/PBS.

[CORRELATION OF CYSTOSCOPICALLY CONFIRMED PERIURETERALLY LOCATED HUNNER LESION WITH VESICoureTERAL REFLUX: PRELIMINARY STUDY IN PATIENTS WITH INTERSTITIAL CYSTITIS.](#)

Lee JE, Yi BH, Lee HK, Lee MH, Kim YH. AJR Am J Roentgenol. 2015 Apr;204(4):W457-60. doi: 10.2214/AJR.14.13108. PMID: 25794095

The purpose of this study from Korea was to evaluate the incidence of vesicoureteral reflux (VUR) in patients with interstitial cystitis (IC) and to explore the correlation between periureterally located Hunner lesions and ipsilateral VUR. Lee and colleagues evaluated 344 patients with IC who underwent cystoscopy (March 2012 to July 2013). Among these patients, 25 underwent voiding cystourethrography (VCUG) to check for the presence of VUR. They reviewed the cystoscopy findings (grade and location of Hunner lesions) and the results of VCUG (presence and grade of VUR). The relationship between VUR and periureterally located Hunner lesions and the association between cystoscopic grading of IC and VUR were evaluated. Of the 25 patients with IC, seven (28%) had VUR (two bilateral and five unilateral). Among nine separate ureters with VUR, seven (78%) had associated periureterally located Hunner lesions, as evaluated cystoscopically. The median bladder capacity was 200 mL for patients with VUR and 230 mL for patients without VUR, with no statistically significant difference between the two groups. There was a strong correlation between the presence of VUR and ipsilateral periureterally located Hunner lesions. However, there was no association between the severity of cystoscopy grading and the presence of VUR. The authors report that, according to their study, VUR is not an uncommon complication in patients with IC, and there is a statistically significant correlation between VUR and periureterally located Hunner lesions. They assume that, along with the decrease in bladder capacity, a periureterally located Hunner lesion may be an important factor in the development of VUR.

[PHLOROGLUCINOL PROTECTS THE URINARY BLADDER VIA INHIBITION OF OXIDATIVE STRESS AND INFLAMMATION IN A RAT MODEL OF CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL CYSTITIS.](#)

He YQ, Zhang WT, Shi CH, Wang FM, Tian XJ, Ma LL. Chin Med J (Engl). 2015 5th Apr;128(7):956-962. doi: 10.4103/0366-6999.154316. PMID: 25836618

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Phloroglucinol plays an important role in oxidative stress and inflammatory responses. The effects of phloroglucinol have been proven in various disease models. The aim of this study from Beijing, China was to

investigate the efficacy and possible mechanisms of phloroglucinol in the treatment of interstitial cystitis (IC). Thirty-two female Sprague-Dawley (SD) rats were used in this study. IC was induced by intraperitoneal injection of cyclophosphamide (CYP). Rats were randomly allocated to one of four groups (n = 8 per group): A control group, which was injected with saline (75 mg/kg; i.p.) instead of CYP on days 1, 4, and 7; a chronic IC group, which was injected with CYP (75 mg/kg; i.p.) on days 1, 4, and 7; a high-dose (30 mg/kg) phloroglucinol-treated group; and a low-dose (15 mg/kg) phloroglucinol-treated group. On day 8, the rats in each group underwent cystometrography (CMG), and the bladders were examined for evidence of oxidative stress and inflammation. Statistical analysis was performed by analysis of variance (ANOVA) followed by least square difference multiple comparison post-hoc test. Histological evaluation showed that bladder inflammation in CYP-treated rats was suppressed by phloroglucinol. CMG revealed that the CYP treatment induced overactive bladder in rats that was reversed by phloroglucinol. Up-regulated tumor necrosis factor- α and interleukin-6 expression in the CYP-treated rats were also suppressed in the phloroglucinol treated rats. CYP treatment significantly increased myeloperoxidase activity as well as the decreased activities of catalase of the bladder, which was reversed by treatment with phloroglucinol. The authors concluded that the application of phloroglucinol suppressed oxidative stress, inflammation, and overactivity in the bladder. This may provide a new treatment strategy for IC.

[MESENCHYMAL STEM CELL THERAPY ALLEVIATES INTERSTITIAL CYSTITIS BY ACTIVATING WNT SIGNALING PATHWAY.](#)

Song M, Lim J, Yu HY, Park J, Chun JY, Jeong J, Heo J, Kang H, Kim Y, Cho YM, Kim SW, Oh W, Choi SJ, Jang SW, Park S, Shin DM, Choo MS. Stem Cells Dev. 2015 Apr 9. [Epub ahead of print] PMID: 25745847

Interstitial cystitis (IC) is a syndrome characterized by urinary urgency, frequency, pelvic pain, and nocturia in the absence of bacterial infection or identifiable pathology. IC is a devastating disease that certainly decreases quality of life. However, the causes of IC remain unknown and no effective treatments or cures have been developed. This study from Korea evaluated the therapeutic potency of using human umbilical cord-blood-derived mesenchymal stem cells (UCB-MSCs) to treat IC in a rat model and to investigate its responsible molecular mechanism. IC was induced in 10-week-old female Sprague-Dawley rats via the instillation of 0.1 M HCl or phosphate-buffered saline (PBS; sham). After 1 week, human UCB-MSC (IC+MSC) or PBS (IC) was directly injected into the submucosal layer of the bladder. A single injection of human UCB-MSCs significantly attenuated the irregular and decreased voiding interval in the IC group. Accordingly, denudation of the epithelium and increased inflammatory responses, mast cell infiltration, neurofilament production, and angiogenesis observed in the IC bladders were prevented in the IC+MSC group. The injected UCB-MSCs successfully engrafted to the stromal and epithelial tissues and activated Wnt signaling cascade. Interference with Wnt and epidermal growth factor receptor activity by small molecules abrogated the benefits of MSC therapy. This is the first report that provides an experimental evidence of the therapeutic effects and molecular mechanisms of MSC therapy to IC using an orthodox rat animal model. The authors believe that their findings not only provide the basis for clinical trials of MSC therapy to IC but also advance their understanding of IC pathophysiology.

[DETRUSOR MYOCYTE AUTOPHAGY PROTECTS THE BLADDER FUNCTION VIA INHIBITING THE INFLAMMATION IN CYCLOPHOSPHAMIDE-INDUCED CYSTITIS IN RATS.](#)

Zhao J, Song Q, Wang L, Dong X, Yang X, Bai X, Song B, Damaser M, Li L. PLoS One. 2015 Apr 1;10(4):e0122597. doi: 10.1371/journal.pone.0122597. eCollection 2015. PMID: 25830308.

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Autophagy, a highly conserved homeostatic cellular process that removes and recycles damaged proteins and organelles in response to cellular stress, is believed to play a crucial role in the immune response and inflammation. The role of autophagy in bladder cystitis, however, has not well been clarified. Zhao and colleagues from China and the USA investigated the role of detrusor myocytes autophagy (DMA) in cyclophosphamide-induced cystitis animal model. 164 female Sprague-Dawley rats were randomized into three experimental groups and compared to three control groups, respectively. The expressions of microtubule-associated protein 1 light chain 3 (LC3), p-p70s6k (the phosphorylated form of ribosomal protein S6), SOD2 (superoxide dismutase 2) in the bladder muscular layer were measured using western blot. The co-location of LC3, alpha-smooth muscle actin (α -SMA), and autophagic vacuoles were investigated with double-labelled immunofluorescence and transmission electron microscopy (TEM). The expression of IL-1 β , IL-6, IL-8,

malondialdehyde (MDA), and glutathione (GSH) in the detrusor layer were analyzed using ELISA. The bladder inflammation and the number of mast cells in the muscular layer were analyzed by histology. The bladder function was evaluated using cystometry. In cyclophosphamide-induced cystitis, autophagy was detected in detrusor myocytes by increased LC3, p-p70s6k expression, and autophagosomes. However, the presence of enhanced inflammation and oxidative stress in the cyclophosphamide-treated group suggest autophagy of detrusor myocytes may not be sufficiently activated. Inflammation and oxidative stress were significantly decreased and the bladder histology and micturition function were significantly improved with rapamycin (RAPA, autophagy agonist) pre-treatment. In contrast, inflammation and oxidative stress were dramatically increased and the bladder histology and function were negatively affected with chloroquine (CQ, autophagy blocker) pre-treated. According to the authors, these findings preferentially provide evidence of the association between DMA and cyclophosphamide-induced cystitis in rats. The autophagy agonist RAPA significantly decreased the inflammation and protected the bladder function, which might be considered as a potential treatment for interstitial cystitis.

[A NOVEL METHOD FOR ASSESSING BLADDER-RELATED PAIN REVEALS THE INVOLVEMENT OF NERVE GROWTH FACTOR IN PAIN ASSOCIATED WITH CYCLOPHOSPHAMIDE-INDUCED CHRONIC CYSTITIS IN MICE.](#)

Fujita M, Kasai E, Omachi S, Sakaguchi G, Shinohara S. Eur J Pain. 2015 Mar 29. doi: 10.1002/ejp.693. [Epub ahead of print] PMID: 25820250

Pain is a prominent feature of interstitial cystitis/painful bladder syndrome (IC/PBS), but the underlying mechanisms are not fully understood. There is a lack of well-characterized research tools, such as pain evaluation methods and experimental animal models, for investigating non-ulcerative cystitis. Fujita and colleagues from Japan developed a novel method for evaluating bladder pain in mice with cyclophosphamide (CYP)-induced cystitis. Cystitis was produced by a single intraperitoneal injection of CYP (300 mg/kg) or repeated injections of CYP (150 mg/kg once daily for 4 days). Blunt stimulation with a cotton probe was applied to the abdominal region, and the thresholds for withdrawal responses were measured quantitatively using an anaesthesiometer. The single injection of CYP provoked acute cystitis with severe bladder inflammation in mice. In these mice, the authors could detect an increased sensitivity to blunt stimulation, which was abolished by intravesical lidocaine. The stimulation induced phosphorylation of extracellular signal-regulated kinases in bladder-projecting sensory neurons. Chronic treatment with CYP produced persistent pain responses to the blunt stimulus. Although there were few signs of bladder inflammation in these mice, the concentration of nerve growth factor (NGF) was elevated in bladder tissue, and NGF antiserum inhibited the hypersensitivity. The authors concluded that the blunt probe method is useful for evaluating bladder pain signalling in mice, and revealed the involvement of an NGF-sensitive pain pathway in chronic cystitis pain. This assessment method may be useful for studying the pathophysiology of bladder pain and for developing therapeutic strategies for non-ulcerative IC/PBS in patients.

[\[INTERSTITIAL CYSTITIS IN UROLOGY CLINIC: CURRENT STATUS AND PROBLEMS\].](#)

[Article in Japanese]

Nanri M, Nanri M, Nanri K. Nihon Hinyokika Gakkai Zasshi. 2014 Oct;105(4):178-82. PMID: 25757347

Nanri and colleagues from Japan examined complications in the diagnosis and treatment of interstitial cystitis in daily clinical practice. This study included 82 patients who were suspected of having interstitial cystitis at the authors' hospital from March 2002 to April 2013. All hydrodistention procedures were performed with the aid of an anesthesiologist, as recommended by the Ministry of Health, Labour, and Welfare since April 2010. Of the 82, 20 patients were male and 62 were female, (mean age at diagnosis 53 years.) Six of the suspected cases did not have interstitial cystitis. Of the 67 patients diagnosed with interstitial cystitis during hydrodistention, 29 (43%) did not experience pain. The time taken to diagnose these asymptomatic patients was longer than that taken for those who experienced pain. Twenty-eight patients (42%) discontinued treatment because it was ineffective. Interstitial cystitis has been widely recognized, but general physicians are unable to provide a diagnosis and suggest aggressive treatment because of difficulty associated in the treatment and diagnosis. To resolve these issues, physicians should keep in mind that interstitial cystitis involves a hypersensitive bladder, and that some patients may not experience pain. Furthermore, knowledge about Hunner's ulcer is essential. The authors believe that the most important points are improving health insurance about facility criteria of hydrodistention, and evaluating behavioural modification and dietary manipulation.

POLAPREZINC ATTENUATES CYCLOPHOSPHAMIDE-INDUCED CYSTITIS AND RELATED BLADDER PAIN IN MICE.

Murakami-Nakayama M, Tsubota M, Hiruma S, Sekiguchi F, Matsuyama K, Kimura T, Moriyama M, Kawabata A. J Pharmacol Sci. 2015 Feb;127(2):223-8. doi: 10.1016/j.jpshs.2015.01.004. Epub 2015 Jan 28. PMID: 25727961
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Cav3.2 T-type Ca(2+) channels targeted by H₂S, a gasotransmitter, participate in cyclophosphamide-induced cystitis and bladder pain. Given that zinc selectively inhibits Cav3.2 among T-channel isoforms and also exhibits antioxidant activity, the authors examined whether polaprezinc (zinc-l-carnosine), a medicine for peptic ulcer treatment and zinc supplementation, reveals preventive or therapeutic effects on bladder inflammation and/or pain in the mouse with cyclophosphamide-induced cystitis, a model for interstitial cystitis. Systemic administration of cyclophosphamide caused cystitis-related symptoms including increased bladder weight and vascular permeability, and histological signs of bladder edema, accompanied by bladder pain-like nociceptive behavior/referred hyperalgesia. All these symptoms were significantly attenuated by oral preadministration of polaprezinc at 400 mg/kg. The same dose of polaprezinc also prevented the increased malondialdehyde level, an indicator of lipid peroxidation, and protein upregulation of cystathionine-γ-lyase, an H₂S-generating enzyme, but not occludin, a tight junction-related membrane protein, in the bladder tissue of cyclophosphamide-treated mice. Oral posttreatment with polaprezinc at 30-100 mg/kg reversed the nociceptive behavior/referred hyperalgesia in a dose-dependent manner without affecting the increased bladder weight. Murakami-Nakayama from Japan report that together their data show that zinc supplementation with polaprezinc prevents the cyclophosphamide-induced cystitis probably through the antioxidant activity, and, like T-channel blockers, reverses the established cystitis-related bladder pain in mice, suggesting novel therapeutic usefulness of polaprezinc.

THE AMYGDALA CENTRAL NUCLEUS IS REQUIRED FOR ACUTE STRESS-INDUCED BLADDER HYPERALGESIA IN A RAT VISCERAL PAIN MODEL.

DeBerry JJ, Robbins MT, Ness TJ. Brain Res. 2015 May 5;1606:77-85. doi: 10.1016/j.brainres.2015.01.008. Epub 2015 Feb 17. PMID: 25698616

Chronic stress has been implicated in the pathogenesis of chronic visceral pain conditions, such as interstitial cystitis (IC), and bouts of acute stress exacerbate clinical urological pain. Studies using animal models have shown that exposure to chronic footshock stress augments reflex responses to urinary bladder distension (UBD) in animal models, however acute effects in animal models are largely unknown, as are the central nervous system mechanisms of stress-related increases in nociception. The amygdala is a salient structure for integration of sensory and cognitive/emotional factors. The present study determined the role of the central nucleus of the amygdala (CeA) in stress-related bladder hypersensitivity. DeBerry and colleagues from the USA examined the effects of CeA manipulations (lesions and chemical stimulation) on visceromotor responses (abdominal muscle contractions) to UBD in adult, female Sprague-Dawley rats. They report that acute footshock stress produces bladder hyperalgesia that can be prevented by bilateral CeA lesions, despite no effect of lesions on baseline somatic sensation, as indicated by flinch/jump thresholds to electrical shock. Further, acute glucocorticoid stimulation of the CeA recapitulated stress-induced hyperalgesia. Of note is that CeA lesions, but not chemical stimulation, significantly affected HPA axis activation, as indicated by measurements of circulating corticosterone. Their findings conclusively show that the CeA is necessary for the generation of bladder hyperalgesia in response to acute stress. The CeA may play multiple stress-related roles in nociceptive modulation, i.e., via direct facilitation of the HPA axis during acute stress, or via modulation of other systems that augment acute stress responsiveness.

INTRAVESICAL INJECTION OF BOTULINUM TOXIN A FOR TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: 10 YEARS OF EXPERIENCE AT A SINGLE CENTER IN CHINA.

Gao Y, Liao L. Int Urogynecol J. 2015 Feb 18. [Epub ahead of print] PMID: 25690160

The aim of this study from Beijing, China was to evaluate the efficacy and safety of the intravesical injection of Chinese botulinum toxin A (BTX-A) in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Between January 2003 and June 2013, 124 women with IC/BPS were studied. Of these 124 patients, 66 were treated with BTX-A and 58 underwent bladder hydrodistention plus sodium hyaluronate (Cystistat) instillation. Intravesical injection of 100 U of Chinese BTX-A was immediately followed by cystoscopic hydrodistention

under intravenous general anesthesia. The patients were evaluated using the O'Leary-Saint score, a visual analog scale pain score, a urinary frequency record and a quality of life questionnaire before treatment and 1 week, and 1, 3, 6 and 12 months after treatment. Of the patients who received BTX-A injection, only 2 had acute urinary retention, 23 received a repeat injection, and 20 were lost to follow-up. Of the patients treated with hydrodistention plus Cystistat instillation, 2 had urinary tract infection, 11 switched to BTX-A injection at 6 months, and 23 were lost to follow-up. BTX-A was shown to remain effective for up to 6 months after treatment. After repeated Chinese BTX-A injections, symptoms improved significantly. Hydrodistention plus Cystistat remained effective for up to 3 months after treatment. The authors concluded that intravesical injection of Chinese BTX-A is a safe and effective therapeutic option for patients with IC/BPS. The average duration of the effect of one dose of Chinese BTX-A amongst the responders was 6 months. Repeated injection of Chinese BTX-A is safe and effective.

INCREASED RISKS OF HEALTHCARE-SEEKING BEHAVIORS OF ANXIETY, DEPRESSION AND INSOMNIA AMONG PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A NATIONWIDE POPULATION-BASED STUDY.

Chuang YC, Weng SF, Hsu YW, Huang CL, Wu MP. Int Urol Nephrol. 2015 Jan 11. [Epub ahead of print] PMID: 25577231

The purpose of this study from Taiwan was to explore the association between bladder pain syndrome/interstitial cystitis (BPS/IC) and the risk of subsequent healthcare-seeking behaviour for common mental disorders in Taiwan using a population-based administrative database. Both BPS/IC subjects and age- and sex-matched non-BPS/IC control subjects who had no previous insomnia and mental diseases, including anxiety, depression, were examined for these mental disorders by psychiatrists from the recruited date between 2002 and 2010. The risk of outcomes was assessed with Kaplan-Meier curves; and the impact of BPS/IC was estimated with Poisson regression analysis and Cox proportional hazards models. The authors included 16,185 BPS/IC subjects and 32,370 non-BPS/IC subjects, with a mean age of 46 years and 73.5 % of women. Difference in the prevalence of hypertension, diabetes, chronic kidney disease, and hyperlipidemia between the groups was not significant. Subjects with BPS/IC had a significantly higher incidence rate of anxiety, depression, and insomnia than the matched controls. After adjusting for age, sex, and common comorbidities in multivariable analysis, BPS/IC remained a significant predictor with hazard ratio and 95 % confidence incidence, 2.4, 2.4, and 2.1 for anxiety, depression, and insomnia, respectively. The authors conclude that BPS/IC patients are at risk of development of anxiety, depression, and insomnia and suggest that these findings can help guide urologists, urogynaecologists, and psychiatrists towards early identification and treatment of psychological complications that may develop in BPS/IC patients.

PREGNANCY AND DELIVERY AFTER VESICO ILEOCYSTOPLASTY--A CASE REPORT.

Vucinic OK, Kovacevic G, Sulovic N, Kovacevic-Vukolic Lj, Vukolic D, Radunovic N. Clin Exp Obstet Gynecol. 2014;41(6):727-9. PMID: 25551974

Neobladder is a continent urinary reservoir made from a detubularized segment of bowel, with implantation of ureters and urethra. The most common indication for this operation is bladder replacement after cystectomy following bladder cancer in elderly or cervical cancer Stage IV patients. However, nowadays indications are expanded to many benign diseases (interstitial cystitis (IC), neurogenic bladder, chronic pelvic pain) in reproductive age. Pregnancy in women with neobladder is a rare condition, hence published experience is limited. Most of the published cases were delivered by caesarean, due to the concern for possible complications. The authors report a case of a 36-year-old woman who underwent a vesico ileocystoplasty for IC, became pregnant six years after the operation, and delivered a healthy baby vaginally. Her obstetric and urologic outcomes were assessed, during, and after pregnancy. Careful antenatal monitoring by both an obstetrician and a urologist, awareness of potential complications, and their prompt treatment, can result in a successful pregnancy and vaginal delivery where neither fetus or mother nor neobladder are endangered.

ARE MAST CELLS STILL GOOD BIOMARKERS FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS?

Gamper M, Regauer S, Welter J, Eberhard J, Viereck V. J Urol. 2015 Jan 14. pii: S0022-5347(15)00057-9. doi: 10.1016/j.juro.2015.01.036. [Epub ahead of print]. PMID: 25596361

Guidelines by the International Society for the Study of BPS/IC (ESSIC) identify mast cell infiltrates of detrusor muscle as a diagnostic criterion for bladder pain syndrome/interstitial cystitis, but elevated mast cells are also characteristic for overactive bladder syndrome. The lack of uniformity in mast cell detection methods hampers comparison of data. Using state-of-the-art techniques, Gamper and colleagues from Switzerland investigated if mast cells differ among bladder conditions. Bladder biopsies from 56 patients (31 bladder pain syndrome/interstitial cystitis with (12) and without (19) Hunner lesions, 13 overactive bladder syndrome, and 12 without bladder symptoms) were analyzed for quantity, location, distribution and activation of mast cells using immunohistochemistry with anti-mast cell tryptase. Patients were allocated to study groups by key bladder symptoms commonly used to define conditions (pain, major urgency). Subepithelial mast cell localization and elevated detrusor mast cells were characteristic for bladder pain syndrome/interstitial cystitis with Hunner's lesion. The optimal cutoff of 32 detrusor mast cells/mm² reached an accuracy level of only 68% (38% positive predictive value). No difference between bladder pain syndrome/interstitial cystitis without Hunner lesion and overactive bladder syndrome was observed. Differences between the patient groups were found in lymphocytic infiltration, nodular lymphocyte aggregates, and urothelial integrity. Subepithelial mast cell distribution was characteristic for bladder pain syndrome/interstitial cystitis with Hunner lesions. Detrusor mastocytosis had a poor predictive value for bladder pain syndrome/interstitial cystitis, and mast cell assessment did not distinguish bladder pain syndrome/interstitial cystitis without Hunner lesion from overactive bladder syndrome.

EFFICIENT AND COST-EFFECTIVE ALTERNATIVE TREATMENT FOR RECURRENT URINARY TRACT INFECTIONS AND INTERSTITIAL CYSTITIS IN WOMEN: A TWO-CASE REPORT.

Mansour A, Hariri E, Shelh S, Irani R, Mroueh M. Case Rep Med. 2014;2014:698758. doi: 10.1155/2014/698758. Epub 2014 Dec 21. PMID: 25587284

Urinary tract infections (UTIs) are among the most common bacterial infections affecting women. UTIs are primarily caused by *Escherichia coli*, which increases the likelihood of a recurrent infection. Mansour and colleagues from the Lebanon encountered two cases of recurrent UTIs (rUTIs) with a positive *E. coli* culture, not improving with antibiotics due to the development of antibiotic resistance. An alternative therapeutic regimen based on parsley and garlic, L-arginine, probiotics, and cranberry tablets has been given. This regimen showed a significant health improvement and symptoms relief without recurrence for more than 12 months. In conclusion, the case supports the concept of using alternative medicine in treating rUTI and as a prophylaxis or in patients who had developed antibiotic resistance.

EVALUATION OF PROSTAGLANDIN E2 AND E-SERIES PROSTAGLANDIN RECEPTOR IN PATIENTS WITH INTERSTITIAL CYSTITIS.

Wada N, Ameda K, Furuno T, Okada H, Date I, Kakizaki H. J Urol. 2015 Jan 13. pii: S0022-5347(15)00031-2. doi: 10.1016/j.juro.2015.01.010. [Epub ahead of print] PMID: 25595860

This study from Japan by Wada and colleagues evaluated prostaglandin E2 (PGE2) and E-series prostaglandin (EP) receptor in patients with interstitial cystitis (IC). Twenty female patients with IC (11 with and 9 without Hunner lesions), 9 female controls with other urological diseases who needed cystoscopic procedure and 10 normal volunteers were enrolled. O'Leary-Sant Score (OSS) for symptoms and problems and voluntary urine for PGE2 analysis were obtained from all subjects. Under anesthesia, the bladder was distended by saline in a stepwise fashion (from 100ml to maximum capacity) in patients with IC, and the infused saline was retrieved each time for PGE2 analysis. They also measured PGE2 and expression of EP receptors mRNA in bladder biopsy tissue in patients with IC. Symptoms and problems index in IC patients with Hunner lesions was significantly higher than IC patients without Hunner lesions. Urinary PGE2 in IC patients with Hunner lesions was significantly higher than IC patients without Hunner lesions, controls and normal volunteers. PGE2 level in retrieved saline in IC patients with Hunner lesions increased depending on infusion volume, but not in IC patients without Hunner lesions. PGE2 content in bladder biopsy tissue was significantly higher in IC patients with Hunner lesions than controls. In IC patients with Hunner lesions, expression of EP1 and EP2 mRNA was significantly higher than controls. The authors conclude that their study showed an increase in PGE2 production and mRNA expression of EP1 and EP2 receptors in the bladder in IC patients with Hunner lesions and that further studies are warranted to explore its pathophysiological and therapeutic implication.

ABNORMALITIES IN EXPRESSION OF STRUCTURAL, BARRIER, AND DIFFERENTIATION RELATED PROTEINS AND CHONDROITIN SULFATE IN THE UROTHELIUM OF CATS WITH FELINE INTERSTITIAL CYSTITIS MIMIC THOSE SEEN IN HUMAN INTERSTITIAL CYSTITIS.

Hauser PJ, VanGordon SB, Seavey J, Sofinowski TM, Ramadan M, Abdullah S, Buffington CA, Hurst RE. *J Urol.* 2015 Jan 27. pii: S0022-5347(15)00180-9. doi: 10.1016/j.juro.2015.01.090. [Epub ahead of print] PMID: 25636658

In this study from Oklahoma, the urothelium of cats diagnosed with feline interstitial cystitis (FIC) was analyzed to determine if abnormalities in protein expression patterns could be detected, and whether the pattern of expression was similar to that observed in human Interstitial Cystitis/Bladder Pain Syndrome patients. The proteins that were analyzed are involved in cell adhesion, barrier function, comprise the glycosaminoglycan (GAG) layer, or are markers of differentiation. Formalin-fixed biopsies from 8 cats with FIC and 7 healthy controls were labeled using immunohistochemistry and scored using a modified version of a system previously used for human samples. Cluster analysis was performed to investigate relationships between the markers and samples. The results showed that 89% of the FIC bladders displayed abnormal protein expression and chondroitin sulfate (CS) patterns, whereas only 27% of the normal tissues exhibited slight abnormalities. Abnormalities were found in most of the FIC samples, biglycan (87.5%), CS (100%), decorin (100%), E-cadherin (100%), keratin-20 (K20, 100%), uroplakin (50%), ZO-1 (87.5%). In the FIC bladders, about 75% of the CS, biglycan, and decorin samples displayed absence of luminal staining or no staining. Results from the cluster analysis revealed that the FIC and normal samples fell into two clearly separate groups, demonstrating that the urothelium of cats with FIC is altered from normal. FIC produces similar changes in luminal GAG and several proteins as is seen in human patients, suggesting some commonality in mechanism and supporting the use of FIC as a model for human IC.

PODOPLANIN (D2-40) IS A RELIABLE MARKER OF URINARY BLADDER MYOFIBROBLASTS (TELOCYTES).

Povýšil C, Kaňa M, Zámečník L, Vařová Z, Hanuš T. *Folia Biol (Praha).* 2014;60(6):286-9. PMID: 25629270

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Podoplanin, D2-40, has been described in a variety of normal and neoplastic tissues. It is often used for highlighting lymphatics. Povýšil and colleagues from Prague evaluated the expression of podoplanin in α -smooth muscle actin positive myofibroblasts producing the suburothelial layer in tunica propria of the urinary bladder that have some similar features with telocytes. Their results showed that these cells demonstrate distinct D2-40 immunoreactivity from telocytes occurring in the renal pelvis and ureter. They observed positive reaction not only in bioptic specimens from women with interstitial cystitis, but also in a control group of women and men treated for pathological bladder lesion different from interstitial cystitis. It is interesting that identical staining reaction was observed in the ureters only exceptionally. In addition, they examined samples from myofibroblastic tumoriform lesions of soft tissue such as nodular fasciitis and fibromatosis (desmoid) and obtained negative results. It means that the so-called myofibroblasts of urinary bladder tunica propria have a unique immunophenotype that has probably not been described until now. Their findings suggest that D2-40 can be used as a complementary immunostainer to α -smooth muscle actin on urinary bladder biopsies from patients with interstitial cystitis. The role of D2-40 as an immunohistochemical marker is still being investigated.

EXTRACORPOREAL SHOCK WAVE THERAPY AMELIORATES CYCLOPHOSPHAMIDE-INDUCED RAT ACUTE INTERSTITIAL CYSTITIS THROUGH INHIBITING INFLAMMATION AND OXIDATIVE STRESS-IN VITRO AND IN VIVO EXPERIMENT STUDIES.

Chen YT, Yang CC, Sun CK, Chiang HJ, Chen YL, Sung PH, Zhen YY, Huang TH, Chang CL, Chen HH, Chang HW, Yip HK. *Am J Transl Res.* 2014 Nov 22;6(6):631-48. eCollection 2014. PMID: 25628776

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Chen and colleagues from Taiwan investigated whether extracorporeal shock wave (ECSW) therapy can attenuate cyclophosphamide (CYP)-induced acute interstitial cystitis (AIC) in rats. They found that ECSW therapy markedly attenuated CYP-induced AIC through inhibitions of the inflammation and oxidative stress.

STATUS OF UROLOGICAL KAMPO MEDICINE: A NARRATIVE REVIEW AND FUTURE VISION.

International Painful Bladder Foundation

Minagawa T, Ishizuka O. *Int J Urol*. 2015 Jan 18. doi: 10.1111/iju.12685. [Epub ahead of print] PMID: 25597936
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In our previous Newsletter, we mentioned an article on traditional Kampo medicine in general. We are now happy to be able to present to you this free access paper from Japan on Kampo medicine in urology. Clinical evidence for traditional Japanese Kampo medicine has been provided by modern scientific methodologies. Indeed, more than 150 Kampo formulations have been approved for use as prescription drugs by the Ministry of Health, Labor and Welfare of Japan, and are widely used in daily medical practice. More than 10 of these formulations can be used for urological problems, especially in cases of lower urinary tract dysfunction. However, there are few opportunities to introduce urological Kampo medicines for worldwide use, and the status of urological Kampo medicine has not been reviewed yet. Here, the authors present a narrative review to introduce the current status of urological Kampo medicine in Japan. First, they introduce the essence of general Kampo medicine, including its history and current status in Japan. They focus on Sou-Sei-Sou-Koku, "promotion and inhibition network among the Five Elements," which is the central dogma of Kampo medicine. To present Kampo medicine as scientific medicine, neural cross-talk among pelvic organs is compared with Sou-Sei-Sou-Koku. Secondly, they list representative urological Kampo formulations used for lower urinary tract symptoms. Furthermore, they also discuss their roles in the urological field, including their position in Japanese clinical guidelines. Thirdly, the authors propose the multi-organ targeting strategy using Kampo formulations as a future vision. Dai-Ken-Chu-Tou (a common Kampo formulation for gastrointestinal problems and hypersensitivity to cold) is one candidate, and present the results of a preliminary study using this Kampo medicine formulation.

BRAIN/BLADDER

[BRAIN-BLADDER CONTROL NETWORK: THE UNSOLVED 21ST CENTURY UROLOGICAL MYSTERY.](#)

Kitta T, Mitsui T, Kanno Y, Chiba H, Moriya K, Shinohara N. *Int J Urol*. 2015 Apr;22(4):342-8. doi: 10.1111/iju.12721. Epub 2015 Feb 17. PMID: 25693685

A review from Hokkaido, Japan of functional brain imaging studies of bladder control in participants with normal control and pathological conditions. In the normal condition, bladder and urethral afferents received in the periaqueductal gray relay the information to the insula, the anterior cingulate cortex and the prefrontal cortex. During the storage phase, these superior regions control the pontine micturition center to inhibit voiding. In overactive bladder patients, brain responses are different. Cortical responses become exaggerated, especially in the anterior cingulate cortex and the supplementary motor area. That is what presumably evokes the "urgency". The supplementary motor area is activated during contraction of the pelvic floor muscles, and provides protection against incontinence. Kitta and colleagues believe that functional brain imaging studies are promising not only for the understanding of bladder dysfunction, but also as an aid to the development of therapeutic options for chronic disorders.

SELF MANAGEMENT ISSUES

[SELF-MANAGEMENT SUPPORT FROM THE PERSPECTIVE OF PATIENTS WITH A CHRONIC CONDITION: A THEMATIC SYNTHESIS OF QUALITATIVE STUDIES.](#)

Dwarswaard J, Bakker EJ, van Staa A, Boeije HR. *Health Expect*. 2015 Jan 26. doi: 10.1111/hex.12346. [Epub ahead of print] PMID: 25619975

Receiving adequate support seems to be crucial to the success of self-management. Although different empirical studies separately examined patients' preferences for self-management support (SMS), an overview is lacking. The aim of this qualitative review from the Netherlands was to identify patients' needs with respect to SMS and to explore by whom this support is preferably provided. 37 studies were included. The authors found that chronic patients need instrumental support, psychosocial support and relational support from health-care professionals, family/friends and fellow patients to manage the chronic condition. Relational support is at the centre of the support needs and fuels all other types of support. Patients do not self-manage on their own. Patients expect health-care professionals to fulfil a comprehensive role. Support needs can be

knitted together only when patients and professionals work together on the basis of collaborative partnership. Dynamics in support needs make it important to regularly assess patient needs.

FIBROMYALGIA

COMMON QUESTIONS ABOUT THE DIAGNOSIS AND MANAGEMENT OF FIBROMYALGIA.

Kodner C. Am Fam Physician. 2015 Apr 1;91(7):472-8. PMID: 25884747

Fibromyalgia has a distinct pathophysiology involving central amplification of peripheral sensory signals. Core symptoms are chronic widespread pain, fatigue, and sleep disturbance. Most patients with fibromyalgia have muscle pain and tenderness, forgetfulness or problems concentrating, and significant functional limitations. Fibromyalgia is diagnosed using an updated set of clinical criteria that no longer depend on tender point examination; laboratory testing may rule out other disorders that commonly present with fatigue, such as anemia and thyroid disease. Patients with fibromyalgia should be evaluated for comorbid functional pain syndromes and mood disorders. Management of fibromyalgia should include patient education, symptom relief, and regular aerobic physical activity. Serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptics, and muscle relaxants have the strongest evidence of benefit for improving pain, fatigue, sleep symptoms, and quality of life. Multiple complementary and alternative medicine therapies have been used but have limited evidence of effectiveness. Opioids should be used to relieve pain in carefully selected patients only if alternative therapies are ineffective.

WHAT HAS FUNCTIONAL CONNECTIVITY AND CHEMICAL NEUROIMAGING IN FIBROMYALGIA TAUGHT US ABOUT THE MECHANISMS AND MANAGEMENT OF 'CENTRALIZED' PAIN?

Napadow V, Harris RE. Arthritis Res Ther. 2014;16(5):425. PMID: 25606591

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Research suggests that fibromyalgia is a central, widespread pain syndrome supported by a generalized disturbance in central nervous system pain processing. Over the past decades, multiple lines of research have identified the locus for many functional, chronic pain disorders to the central nervous system, and the brain. In recent years, brain neuroimaging techniques have heralded a revolution in our understanding of chronic pain, as they have allowed researchers to non-invasively (or minimally invasively) evaluate human patients suffering from various pain disorders. While many neuroimaging techniques have been developed, growing interest in two specific imaging modalities has led to significant contributions to chronic pain research. For instance, resting functional connectivity magnetic resonance imaging (fcMRI) is a recent adaptation of fMRI that examines intrinsic brain connectivity - defined as synchronous oscillations of the fMRI signal that occurs in the resting basal state. Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive magnetic resonance imaging technique that can quantify the concentration of multiple metabolites within the human brain. This review outlines recent applications of the complementary imaging techniques - fcMRI and 1H-MRS - to improve our understanding of fibromyalgia pathophysiology and how pharmacological and non-pharmacological therapies contribute to analgesia in these patients. A better understanding of the brain in chronic pain, with specific linkage as to which neural processes relate to spontaneous pain perception and hyperalgesia, will greatly improve our ability to develop novel therapeutics. Neuroimaging will play a growing role in the translational research approaches needed to make this a reality.

DAYTIME NAPPING ASSOCIATED WITH INCREASED SYMPTOM SEVERITY IN FIBROMYALGIA SYNDROME.

Theadom A, Copley M, Kantermann T. BMC Musculoskelet Disord. 2015 Feb 7;16(1):13. PMID: 25888479

Previous qualitative research has revealed that people with fibromyalgia use daytime napping as a coping strategy for managing symptoms against clinical advice. Yet there is no evidence to suggest whether daytime napping is beneficial or detrimental for people with fibromyalgia. The purpose of this multi-centre study was to explore how people use daytime naps and to determine the links between daytime napping and symptom severity in fibromyalgia syndrome. A community based sample of 1044 adults who had been diagnosed with fibromyalgia syndrome by a clinician completed an online questionnaire. Associations between napping behavior, sleep quality and fibromyalgia symptoms were explored using Spearman correlations, with possible predictors of napping behaviour entered into a logistic regression model. Differences between participants who napped on a daily basis and those who napped less regularly, as well as nap duration were explored.

Daytime napping was significantly associated with increased pain, depression, anxiety, fatigue, memory difficulties and sleep problems. Sleep problems and fatigue explained the greatest amount of variance in napping behaviour. Those who engaged in daytime naps for >30 minutes had higher memory difficulties ($t = -3.45$) and levels of depression than those who napped for shorter periods (<30mins). Frequent use and longer duration of daytime napping was linked with greater symptom severity in people with fibromyalgia. Given the common use of daytime napping in people with fibromyalgia evidence based guidelines on the use of daytime napping in people with chronic pain are urgently needed.

SJÖGREN'S SYNDROME

SJÖGREN'S SYNDROME COMPLICATED BY INTERSTITIAL CYSTITIS: A CASE SERIES AND LITERATURE REVIEW.

Darrietort-Laffite C, André V, Hayem G, Saraux A, Le Guern V, Le Jeunne C, Puéchal X. Joint Bone Spine. 2015 Feb 10. pii: S1297-319X(14)00281-4. doi: 10.1016/j.jbspin.2014.12.007. [Epub ahead of print] PMID: 25680227

The purpose of this study from France was to characterize the interstitial cystitis (IC) associated with Sjögren's syndrome (SS). Only cases fulfilling the American-European consensus criteria for SS and the European Society for the Study of Interstitial Cystitis criteria with positive histological findings for IC were included. Thirteen cases of SS and IC have been reported in women, including the three reported here, with a mean age of 54 years. SS appeared first in 77% (n=10) of cases, a mean of 6.6 years before IC. The symptoms of IC included pollakiuria (n=11), lower abdominal pain (n=8), urinary urgency (n=5), painful micturition (n=6), hematuria (n=3) and dysuria (n=3). Urinary dilatation occurred in three cases, leading to acute renal failure in two patients. The diagnosis of IC was confirmed by anatomical evidence of cystitis inflammation on bladder biopsy in all (n=13) patients. Treatment was reported for nine patients, seven of whom (78%) received corticosteroid treatment, which was partially or completely effective in six cases. Immunosuppressive treatment was added in three cases (cyclosporine, n=2; azathioprine, n=1; cyclophosphamide, n=1). Local bladder treatments were performed, with hydraulic distension in five cases and DMSO instillation in one patient. A urinary catheter was inserted in the two cases of acute obstructive renal failure. It was concluded by the authors that urinary symptoms without infection should lead the physician to consider a diagnosis of IC in SS patients. Urinary dilatation may occur, leading to acute obstructive renal failure. Corticosteroid treatment may be effective and local treatments have been tried.

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

GASTRO-INTESTINAL DISORDERS

DIET IN IRRITABLE BOWEL SYNDROME.

El-Salhy M, Gundersen D. Nutr J. 2015 Apr 14;14(1):36. [Epub ahead of print] PMID: 25880820

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

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal disorder that is characterized by intermittent abdominal pain/discomfort, altered bowel habits and abdominal bloating/distension. The aim of this review from Norway was to present recent developments concerning the role of diet in the pathophysiology and management of IBS. The authors report that there is no convincing evidence that IBS patients suffer from food allergy/intolerance, and there is no evidence that gluten causes the debated new diagnosis of non-coeliac gluten sensitivity (NCGS). IBS symptoms are triggered by the consumption of the poorly absorbed fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) and insoluble fibre. On reaching the distal small intestine and colon, FODMAPs and insoluble fibre increase the osmotic pressure in the large-intestine lumen and provide a substrate for bacterial fermentation, with consequent gas production, abdominal distension and abdominal pain or discomfort. Poor FODMAPs and insoluble fibres diet reduces the symptoms and improve the quality of life in IBS patients. Moreover, it changes favourably the intestinal microbiota and restores the abnormalities in the gastrointestinal endocrine cells. Five gastrointestinal endocrine cell types that produce hormones regulating appetite and food intake are abnormal in IBS patients. Based on these hormonal abnormalities, one would expect IBS patients to have increased food intake and body weight gain. However, the link between obesity and IBS is not fully studied. Individual dietary guidance for

intake of poor FODMAPs and insoluble fibres diet in combination with probiotics intake and regular exercise is to be recommended for IBS patients.

TEMPOROMANDIBULAR DISORDERS

TMD AND CHRONIC PAIN: A CURRENT VIEW.

Furquim BD, Flamengui LM, Conti PC. Dental Press J Orthod. 2015 Jan-Feb;20(1):127-33. doi: 10.1590/2176-9451.20.1.127-133.sar. PMID: 25741834

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This review from Brazil aims at presenting a current view on the physiopathologic mechanisms associated with temporomandibular disorders (TMDs). While joint pain is characterized by a well-defined inflammatory process mediated by tumor necrosis factor- α and interleukin, chronic muscle pain presents with enigmatic physiopathologic mechanisms, being considered a functional pain syndrome similar to fibromyalgia, irritable bowel syndrome, interstitial cystitis and chronic fatigue syndrome. Central sensitization is the common factor unifying these conditions, and may be influenced by the autonomic nervous system and genetic polymorphisms. The authors believe TMDs symptoms should be understood as a complex response which might get worse or improve depending on an individual's adaptation.

CHRONIC (PELVIC) PAIN

NEW CONCEPTS ON FUNCTIONAL CHRONIC PELVIC AND PERINEAL PAIN: PATHOPHYSIOLOGY AND MULTIDISCIPLINARY MANAGEMENT.

Ploteau S, Labat JJ, Riant T, Levesque A, Robert R, Nizard J. Discov Med. 2015 Mar;19(104):185-92. PMID: 25828522

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In this interesting paper from Nantes, France, Ploteau and colleagues notes that the management of chronic pelvic and perineal pain has been improved by a better understanding of the mechanisms of this pain and an optimized integrated multidisciplinary approach to the patient. The concept of organic lesions responsible for a persistent nociceptive factor has gradually been replaced by that of dysregulation of nociceptive messages derived from the pelvis and perineum. In this setting, painful diseases identified by organ specialists are usually also involved and share several common denominators (triggering factors, predisposing clinical context). These diseases include painful bladder syndrome, irritable bowel syndrome, vulvodynia, and chronic pelvic pain syndrome. The painful symptoms vary from one individual to another and according to his or her capacity to activate pain inhibition/control processes. Although the patient often attributes chronic pain to a particular organ (with the corollary that pain will persist until the organ has been treated), this pain is generally no longer derived from the organ but is expressed via this organ. Several types of clinical presentation of complex pelvic pain have therefore been pragmatically identified to facilitate the management of treatment failures resulting from a purely organ-based approach, which can also reinforce the patient's impression of incurability. These subtypes correspond to neuropathic pain, central sensitization (fibromyalgia), complex regional pain syndrome, and emotional components similar to those observed in post-traumatic stress disorder. These various components are also often associated and self-perpetuating. Consequently, when pelvic pain cannot be explained by an organ disease, this model, using each of these four components associated with their specific mechanisms, can be used to propose personalized treatment options and also to identify patients at high risk of postoperative pelvic pain (multi-operated patients, central sensitization, post-traumatic stress disorder, etc.), which constitutes a major challenge for prevention of these types of pain that have major implications for patients and society.

IMAGING BRAIN MECHANISMS IN CHRONIC VISCERAL PAIN.

Mayer EA, Gupta A, Kilpatrick LA, Hong JY. Pain. 2015 Apr;156 Suppl 1:S50-63. doi: 10.1097/j.pain.000000000000106. PMID: 25789437

Chronic visceral pain syndromes are important clinical problems with largely unmet medical needs. Based on the common overlap with other chronic disorders of visceral or somatic pain, mood and affect, and their responsiveness to centrally targeted treatments, an important role of central nervous system in their pathophysiology is likely. A growing number of brain imaging studies in irritable bowel syndrome, functional dyspepsia, and bladder pain syndrome/interstitial cystitis has identified abnormalities in evoked brain

responses, resting state activity, and connectivity, as well as in gray and white matter properties. Structural and functional alterations in brain regions of the salience, emotional arousal, and sensorimotor networks, as well as in prefrontal regions, are the most consistently reported findings. Some of these changes show moderate correlations with behavioral and clinical measures. Most recently, data-driven machine-learning approaches to larger data sets have been able to classify visceral pain syndromes from healthy control subjects. Future studies need to identify the mechanisms underlying the altered brain signatures of chronic visceral pain and identify targets for therapeutic interventions.

STRESS AND CHRONIC PELVIC PAIN.

Pierce AN, Christianson JA. Prog Mol Biol Transl Sci. 2015;131:509-35. doi: 10.1016/bs.pmbts.2014.11.009. Epub 2015 Feb 2. PMID: 25744684

According to Pierce and colleagues from the USA, chronic pelvic pain is the number one reason that patients suffering from irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, vulvodynia, or chronic prostatitis/chronic pelvic pain syndrome seek medical attention. These syndromes generally have no associated pathology or identified underlying etiology, although dysfunction within the immune system, central nervous system, and peripheral nervous system has been identified. Due to the lack of pathology, chronic pelvic pain syndromes are often diagnosed by exclusion, and the high degree of comorbid symptomology among these and other functional pain disorders complicate identifying appropriate treatment strategies. Chronic stress exposure early in life has been shown to increase the likelihood of pelvic pain later in life, and acute stress exposure can induce or increase symptom severity. In this chapter, the authors describe the individual chronic pelvic pain syndromes and how stress influences the likelihood of diagnosis and the severity of symptoms experienced by patients.

NEUROIMAGING CHRONIC PAIN: WHAT HAVE WE LEARNED AND WHERE ARE WE GOING?

Martucci KT, Ng P, Mackey S. Future Neurology. 2014;9(6):615-626.

Advances in neuroimaging have helped illuminate our understanding of how the brain works in the presence of chronic pain, which often persists with unknown etiology or after the painful stimulus has been removed and any wounds have healed. Neuroimaging has enabled us to make great progress in identifying many of the neural mechanisms that contribute to chronic pain, and to pinpoint the specific regions of the brain that are activated in the presence of chronic pain. It has provided us with a new perception of the nature of chronic pain in general, leading researchers to move toward a whole-brain approach to the study and treatment of chronic pain, and to develop novel technologies and analysis techniques, with real potential for developing new diagnostics and more effective therapies. Martucci and colleagues review the use of neuroimaging in the study of chronic pain, with particular emphasis on magnetic resonance imaging.

URINARY TRACT INFECTION IN INFANCY IS A RISK FACTOR FOR CHRONIC ABDOMINAL PAIN IN CHILDHOOD.

Rosen JM, Kriegermeier A, Adams PN, Klumpp DJ, Saps M. J Pediatr Gastroenterol Nutr. 2015 Feb;60(2):214-6. doi: 10.1097/MPG.0000000000000599. PMID: 25625577

Adverse early life events are key factors for development of functional gastrointestinal disorders (FGIDs). Urinary tract infection (UTI) is associated with chronic pelvic pain in adults, a finding that has been recapitulated in murine models, but the relation between UTI and chronic pelvic and abdominal pain has not been studied in children. Rosen and colleagues hypothesized that UTI in infancy increases the risk of FGIDs and chronic abdominal pain (CAP) in childhood. This study included children, ages 4 to 18 years, with a single UTI in the first year of life and their siblings with no history of UTI. Parents completed the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version (QPGS-III) by telephone. Children meeting QPGS-III criteria for FGIDs but with pain less than once weekly were considered to have CAP. A total of 57 patients with UTI and 58 sibling controls were identified. Mean age at UTI was 4.8 months, and mean time since UTI was 9.3 years. At the time of survey, mean age of patients was 9.7 years (5-16 years, 40% boys) and that of controls was 9.6 years (range 4-17 years, 57% boys). FGIDs were diagnosed in 6 of 57 (11%) patients, and 1 of 58 (2%) controls. CAP was identified in 10 of 57 (18%) patients and 2 of 58 (3%) controls ($P=0.02$). Predominant sex (female), infecting organism (*E coli*), and treatment (third-generation cephalosporin) were similar in patients with UTI with and without CAP. The authors show for the first time that UTI is associated with CAP in childhood. They speculate that pelvic organ sensory convergence explains their findings.

VULVODYNIA/VULVAL PAIN SYNDROME

VULVODYNIA.

Edwards L. *Clin Obstet Gynecol.* 2015 Mar;58(1):143-52. doi: 10.1097/GRF.000000000000093. PMID: 25608256

Vulvodynia – also known as vulval pain syndrome - is a genital pain syndrome occurring in 7% to 8% of women. Although common, most practitioners are uncomfortable with the diagnosis and management of these women's pain, and many unfortunately believe this is psychologically based. Multifactorial in origin, ubiquitous factors include pelvic floor muscle abnormalities, neuropathic pain, anxiety, and primary or secondary sexual dysfunction. Although there are many published studies on vulvodynia, quality trials that evaluate therapy are lacking. However, experience suggests that most patients are significantly improved with pelvic floor physical therapy, medication for neuropathic pain, psychological support, and attention to sexual function.

VULVODYNIA-AN EVIDENCE-BASED LITERATURE REVIEW AND PROPOSED TREATMENT ALGORITHM.

De Andres J, Sanchis-Lopez N, Asensio-Samper JM, Fabregat-Cid G, Villanueva-Perez VL, Monsalve Dolz V, Minguez A. *Pain Pract.* 2015 Jan 12. doi: 10.1111/papr.12274. [Epub ahead of print] PMID: 25581081

De Andres and colleagues from Valencia, Spain searched the medical literature from the last 15 years (1998 to 2013) relating to the etiology, diagnosis, and treatment of vulvodynia. The evidence was reviewed supporting the therapeutic proposals currently in use and propose the incorporation of novel, minimally invasive, interventional therapies, within the context of a multidisciplinary approach. This was a systematic review of all relevant studies with no language restrictions. A total of 391 papers were assessed. Of these, 215 were analyzed and 175 were excluded, as they pertained to areas not directly related to the disease under review. The optimal therapy for vulvar pain syndrome remains elusive, with low percentages of therapeutic success, using either local or systemic pharmacological approaches. Surgery involving invasive and often irreversible therapeutic procedures has resulted in success for certain subtypes of vulvodynia. The authors present a multidisciplinary approach whereby pain treatment units may provide an intermediate level of care between standard medical and surgical treatments.

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