

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 47, January 2018

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

The International Painful Bladder Foundation (IPBF) would like to wish all its readers a Happy, Healthy and Successful New Year 2018!

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

- Two International IC/BPS meetings in 2018
 - Joint Meeting of the 4th International Consultation on Interstitial Cystitis Japan (ICICJ) and the Annual Meeting of the Society of Interstitial Cystitis of Japan (SICJ)
 - ESSIC Annual International Meeting 2018
- Treatment effectiveness in IC/BPS: do patient perceptions align with efficacy based guidelines?
- IASP new definitions of terms for multimodal pain treatment
- European Patients Forum: the added value of patient organisations
- Publications
- Calendar of Upcoming Events
- Research Update
- Donations & Sponsoring

TWO INTERNATIONAL IC/BPS MEETINGS IN 2018: 4th ICICJ IN JAPAN AND ESSIC IN ITALY

The coming year promises to be a very interesting and active year where interstitial cystitis, bladder pain syndrome and hypersensitive bladder are concerned. And we can only hope that international discussions will finally lead to concrete decisions to help end the confusion experienced by patients, healthcare professionals, researchers, the pharma industry, government and health insurance authorities worldwide due to multiple names with different definitions, different diagnostic criteria and all their consequences with regard to treatment and the development, registration and reimbursement of new treatments as well as the lack of reliable study documentation needed for this purpose. This year has to mark a turning point, for the sake of the patients. Brainstorming is now a matter of urgency if we are to achieve a breakthrough.

- JOINT MEETING OF THE 4TH INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS JAPAN (ICICJ) AND THE ANNUAL MEETING OF THE SOCIETY OF INTERSTITIAL CYSTITIS OF JAPAN (SICJ)

The first of these international meetings and consultations will be held in Kyoto, Japan on 17th and 18th April, prior to the 106th Annual Meeting of the Japanese Urological Association (JUA), and is a joint meeting of the International Consultation on Interstitial Cystitis Japan (ICICJ) and the Society of Interstitial Cystitis of Japan (SICJ). This special occasion will be the 4th international ICICJ conference and can be expected to attract IC/BPS experts from around the world, including patient advocates. According to Dr Tomohiro Ueda, President of ICICJ, more than fifty top international urologists and researchers, and a hundred eminent Japanese urologists and scientists will be invited to Kyoto for this international brainstorming meeting. This two-day meeting will discuss the state-of-the-art progress of interstitial cystitis (IC), and particularly Hunner lesions.

The deadline for abstract submission is 28 February 2018. Details about submission are available on the meeting website.

Meeting website: www.icicj.jp/en/meeting/2018/. Meeting secretariat email: info@hainyo-net.org

- ESSIC ANNUAL INTERNATIONAL MEETING 2018

The date has not yet been finally fixed for this meeting, but it is likely to be held in December in Italy. Further information will be made available on the meeting website: <https://www.essicmeeting.eu/>

TREATMENT EFFECTIVENESS IN IC/BPS: DO PATIENT PERCEPTIONS ALIGN WITH EFFICACY BASED GUIDELINES?

In our Research Update, we include an interesting paper by Lusty and colleagues from Canada who ask whether patient perceptions align with efficacy based guidelines and conclude that there is a disconnect between real-world patient perceived effectiveness of IC/BPS treatments compared to the efficacy reported from clinical trial data and subsequent guidelines developed from this efficacy data. The authors are of the opinion that while optimal therapy must include the best evidence from clinical research, it should also include real-life clinical practice implementation and effectiveness.

Let us hope that this year's brainstorming conferences also include this aspect.

IASP NEW DEFINITIONS OF TERMS FOR MULTIMODAL PAIN TREATMENT

Standard definitions of terms used in healthcare and research are important to ensure that everyone knows exactly what everyone else is talking about. In October last year, the International Association for the Study of Pain (IASP) approved definitions for the terms: unimodal, multimodal, multidisciplinary and interdisciplinary treatment as a response to existing confusion.

These terms have been defined by the IASP task force on multicomponent pain care as follows:

[Unimodal treatment](#) is defined as a single therapeutic intervention directed at a specific pain mechanism or pain diagnosis. For example: the application of exercise treatment by a physiotherapist.

[Multimodal treatment](#) is defined as the concurrent use of separate therapeutic interventions with different mechanisms of action within one discipline aimed at different pain mechanisms. For example: the use of pregabalin and opioids for pain control by a physician; the use of NSAID and orthosis for pain control by a physician.

[Multidisciplinary treatment](#) is defined as multimodal treatment provided by practitioners from different disciplines. For example: the prescription of an anti-depressant by a physician alongside exercise treatment from a physiotherapist, and cognitive behavioural treatment by a psychologist, all the professions working separately with their own therapeutic aim for the patient and not necessarily communicating with each other.

[Interdisciplinary treatment](#) is defined as multimodal treatment provided by a multidisciplinary team collaborating in assessment and treatment using a shared biopsychosocial model and goals. For example: the prescription of an anti-depressant by a physician alongside exercise treatment from a physiotherapist, and cognitive behavioural treatment by a psychologist, all working closely together with regular team meetings (face to face or online), agreement on diagnosis, therapeutic aims and plans for treatment and review.

Further information can be found at: <https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=6981>

PUBLICATIONS

BLADDER PAIN SYNDROME – AN EVOLUTION

Editors: Hanno, P.M., Nordling, J., Staskin, D.R., Wein, A.J., Wyndaele, J.J.

Published by: Springer; 2018. 175 pages.

eBook ISBN 978-3-319-61449-6

Hardcover ISBN 978-3-319-61448-9

Further information: <http://www.springer.com/gp/book/9783319614489>

While this book has a completely new title, it is in fact a second edition or update of the earlier book "Interstitial Cystitis" (eds Hanno, Staskin, Krane and Wein) published by Springer in 1990 which was perhaps best known for being the only place where you could find the 1988 revised version of the original NIDDK 1887 interstitial cystitis consensus criteria intended for scientific studies. This second edition provides reflections on the original book: where it got it right and where with the benefit of hindsight it got it wrong. It highlights developments since 1990 and covers epidemiology, etiology, diagnosis and management with chapters by well-known experts from around the world, including three chapters by patient advocates.

EUROPEAN PATIENTS FORUM (EPF) ISSUES REPORT ON THE ADDED VALUE OF PATIENT ORGANISATIONS

The European Patients Forum (EPF) commissioned this report to give an overview of the role of patient organisations in Europe, to highlight their value as legitimate stakeholders in civil dialogue in health-related policies and to draw attention to the challenges patient organisations are facing. The objective of the report is to emphasise the contribution of patient organisations in representing and voicing the situation of a specific population that would otherwise not be represented. The main activities of patient organisations are set out in four different areas: policy, capacity building and education, peer support and research & development (both health and pharmaceutical).

http://www.eu-patient.eu/globalassets/library/publications/epf_added_value_report_final.pdf

CALENDAR OF UPCOMING EVENTS

SOCIETY OF URODYNAMICS, FEMALE PELVIC MEDICINE AND UROGENITAL RECONSTRUCTION (SUFU)

2018 WINTER MEETING

February 27 - March 3, 2018, Hilton Austin, Austin, Texas, USA

<https://sufu.org.com/meetings.aspx>

EUROPEAN ASSOCIATION OF UROLOGY (EAU) 2018

16-20 March 2018, Copenhagen, Denmark

<http://eau18.uroweb.org/>

JOINT MEETING OF THE 4TH INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS, JAPAN (ICICJ) AND THE ANNUAL MEETING OF THE SOCIETY OF INTERSTITIAL CYSTITIS OF JAPAN (SICJ)

17-18 April, 2018, Kyoto, Japan. Abstract submission by 28 February 2018.

www.icicj.jp/en/meeting/2018/

info@hainyo-net.org

14th INTERNATIONAL SYMPOSIUM ON SJOGREN'S SYNDROME

18-21 April, 2018

The Capital Hilton, Washington DC, USA

<https://hopkinscme.cloud-cme.com/aph.aspx?P=5&EID=7139>

5TH MIPS ANNUAL MEETING

3-5 May, 2018. Rome, Italy

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

THE EUROPEAN CONFERENCE ON RARE DISEASES & ORPHAN PRODUCTS 2018

10 - 12 May, 2018, Vienna, Austria.

"Rare Diseases 360° – collaborative strategies to leave no one behind"

<https://www.eurordis.org/news/european-conference-rare-diseases-orphan-products-2018-vienna>

INTERNATIONAL ALLIANCE OF PATIENTS' ORGANIZATIONS (IAPO)

8TH GLOBAL PATIENTS CONGRESS (invitation only)

23 - 26 May 2018 at the Marriott Dadeland, Miami, Florida USA.

Theme: Globally Empowered Patients. Building on the momentum

<https://www.iapo.org.uk/global-patients-congress>

AMERICAN UROLOGICAL ASSOCIATION (AUA) 2018

18-22 May 2018, San Francisco, CA, USA

www.aua2018.org

INTERNATIONAL UROGYNECOLOGICAL ASSOCIATION (IUGA)

26-30 June 2018, Vienna, Austria

<https://iugameeting.org/>

INTERNATIONAL CONTINENCE SOCIETY ANNUAL SCIENTIFIC MEETING 2018

28-31 August 2018, Philadelphia, USA

www.ics.org/2018

IASP 17th WORLD CONGRESS ON PAIN

12-16 September 2018, Boston, USA

<https://www.iaspworldcongressonpain.org/>

ESSIC ANNUAL MEETING 2018

Planned for December in Italy.

<https://www.essicmeeting.eu/>

RESEARCH HIGHLIGHTS

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

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

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

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

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

[A CASE-CROSSOVER STUDY OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME FLARE TRIGGERS IN THE MAPP RESEARCH NETWORK.](#)

Sutcliffe S, Jemielita T, Lai HH, Andriole GL, Bradley CS, Clemens JQ, Gallop R, Hooton TM, Kreder KJ, Krieger JN, Kusek JW, Labus J, Lucia MS, Mackey S, Naliboff BD, Robinson NA, Rodriguez LV, Stephens-Shields A, van Bokhoven A, Wolin KY, Yan Y, Yang CC, Landis JR, Colditz GA; [MAPP Research Network](#). *J Urol*. 2017 Dec 27. pii: S0022-5347(17)78185-2. doi: 10.1016/j.juro.2017.12.050. [Epub ahead of print] PMID: 29288643

Although many factors have been proposed to trigger symptom exacerbations ("flares") in patients with interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, few studies have investigated these factors empirically. In this MAPP Research Network study, Sutcliffe and colleagues embedded a case-crossover study in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain longitudinal study to evaluate a range of patient-reported triggers. Exposure to proposed triggers (diet, physical activities, sedentary behaviors, stress, sexual activities, infection-like symptoms, and allergies) was assessed by questionnaire a maximum of three times when participants reported flares and at three randomly-selected times. Participants' pre-flare to non-flare exposures were compared by conditional logistic regression. In their full analytic sample (292 participants), only two factors, recent sexual activity and symptoms of a urinary tract infection, which may overlap with those of flares, were associated with flare onset. In sub-analyses restricted to flares with specific, suspected triggers, additional positive associations were observed for some (certain dietary factors, abdominal muscle exercises, and vaginal infection-like symptoms and fever), but not other (e.g., stress) factors. With the exception of sexual activity, the authors believe that their findings suggest that patient-reported triggers may be either individual/group-specific or may not contribute to flares. These findings suggest caution in following rigid, global flare prevention strategies and support additional research to develop evidence-based strategies.

[CORRELATES OF HEALTH-CARE SEEKING ACTIVITIES IN PATIENTS WITH UROLOGICAL CHRONIC PELVIC PAIN SYNDROMES: FINDINGS FROM THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN \(MAPP\) COHORT.](#)

Clemens JQ, Stephens-Shields A, Naliboff BD, Lai HH, Rodriguez L, Krieger JN, Williams DA, Kusek JW, Landis JR; [MAPP Research Network](#). *J Urol*. 2018 Jan 4. pii: S0022-5347(18)30004-1. doi: 10.1016/j.juro.2017.12.055. [Epub ahead of print] PMID: 29307682

Clemens and colleagues examined health-care seeking activities over a 12-month period in a cohort of men and women with urological chronic pelvic pain syndromes (UCPPS). A total of 191 men and 233 women with UCPPS were followed with biweekly internet-based questionnaires about their symptoms and health-care seeking (HCS) activities, including a) healthcare provider contacts; b) office visits; c) emergency room/urgent care visits; d) medication changes; and e) medical procedures. Multivariable modelling was used to determine the association

of demographic and clinical variables with HCS. HCS 'super-users' were defined as individuals who reported HCS activity at least 11 times during the 23 biweekly assessments. Mean values for HCS activities were 2.4 office contacts, 2.5 office visits, 1.9 medication changes, 0.9 medical procedures, and 0.3 ER/urgent care visits. There were 31 HCS 'super-users' who accounted for 26% of the HCS activities. Worse baseline pain severity and female sex were associated with a higher rate of all HCS activities except ER/urgent care visits. The presence of a non-urologic chronic pain condition was associated with more provider contacts, office visits, and medical procedures. Greater baseline depression symptoms were associated with more provider contacts, office visits, and medication changes. Other examined variables (age, symptom duration, catastrophizing, anxiety, urinary symptom severity, symptom variability) had minimal association with HCS. HCS activities were strongly influenced by UCPPS pain severity, but not urinary symptom severity. Women and those with non-urologic overlapping pain conditions were more likely to be seen and treated for their symptoms.

RELATIONSHIPS BETWEEN BRAIN METABOLITE LEVELS, FUNCTIONAL CONNECTIVITY, AND NEGATIVE MOOD IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME PATIENTS COMPARED TO CONTROLS: A MAPP RESEARCH NETWORK STUDY.

Harper DE, Ichesco E, Schrepf A, Halvorson M, Puiu T, Clauw DJ, Harris RE, Harte SE; [MAPP Research Network](#). *Neuroimage Clin.* 2017 Nov 15;17:570-578. doi: 10.1016/j.nicl.2017.11.014. eCollection 2018. PMID: 29201643 [Free full article, click on title](#)

Until recently, the predominant pathology of chronic pelvic pain conditions was thought to reside in the peripheral tissues. However, mounting evidence from neuroimaging studies suggests an important role of the central nervous system in the pathogenesis of these conditions. In the present cross-sectional study, proton magnetic resonance spectroscopy (1H-MRS) of the brain was conducted in female patients with urologic chronic pelvic pain syndrome (UCPPS) to determine if they exhibit abnormal concentrations of brain metabolites (e.g. those indicative of heightened excitatory tone) in regions involved in the processing and modulation of pain, including the anterior cingulate cortex (ACC) and the anterior and posterior insular cortices. Compared to a group of age-matched healthy subjects, there were significantly higher levels of choline in the ACC of UCPPS patients. ACC choline levels were therefore compared with the region's resting functional connectivity to the rest of the brain. Higher choline was associated with greater ACC-to-limbic system connectivity in UCPPS patients, contrasted with lower connectivity in controls (i.e. an interaction). In patients, ACC choline levels were also positively correlated with negative mood. ACC γ -aminobutyric acid (GABA) levels were lower in UCPPS patients compared with controls, but this did not meet statistical correction for the 4 separate regional comparisons of metabolites. These results are the first to uncover abnormal GABA and choline levels in the brain of UCPPS patients compared to controls. Low GABA levels have been identified in other pain syndromes and might contribute to CNS hyper-excitability in these conditions. The relationships between increased ACC choline levels, ACC-to-limbic connectivity, and negative mood in UCPPS patients suggest that this metabolite could be related to the affective symptomatology of this syndrome.

IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT

TREATMENT EFFECTIVENESS IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: DO PATIENT PERCEPTIONS ALIGN WITH EFFICACY BASED GUIDELINES?

Lusty A, Kavalier E, Zakariasen K, Tolls V, Nickel JC. *Can Urol Assoc J.* 2017 Dec 1. doi: 10.5489/cuaj.4505. [Epub ahead of print] PMID: 29173267

Lusty and colleagues from Canada sought to determine if patients' perceptions of success or failure of interstitial cystitis/bladder pain syndrome (IC/BPS) therapies proposed in treatment guidelines align with the evidence from available clinical trial treatment data. A total of 1628 adult females with a self-reported diagnosis of IC completed a web-based survey in which patients described their perceived outcomes with the therapies they were exposed to. Previously published literature used in part to develop IC/BPS guidelines provided the clinical trial data outcomes. Patient-reported outcomes were compared to available clinical trial outcomes and published treatment guidelines. Based on patient perceived outcomes (benefit:risk ratio), the most effective treatments were opioids, phenazopyridine, and alkalizing agents, with amitriptyline and antihistamines reported as moderately effective. The only surgical procedure with any effectiveness was electrocautery of Hunner's lesions. In order of efficacy reported in the literature, the therapies for IC/BPS with predicted superior outcomes should be: cyclosporine A, amitriptyline, hyperbaric oxygen, pentosan polysulfate plus subcutaneous heparin, botulinum toxin A plus hydrodistension, and L-arginine. While some of the guideline recommendations aligned with patient-reported effectiveness data, there was a general disconnect between guidelines and effectiveness reported in clinical practice.

The authors concluded that there is a disconnect between real-world patient perceived effectiveness of IC/BPS treatments compared to the efficacy reported from clinical trial data and subsequent guidelines developed from this efficacy data. Optimal therapy must include the best evidence from clinical research, but should also include real-life clinical practice implementation and effectiveness.

CURRENT PHARMACOLOGIC APPROACHES IN PAINFUL BLADDER RESEARCH: AN UPDATE.

Andersson KE, Birder L. *Int Neurourol J.* 2017 Dec;21(4):235-242. doi: 10.5213/inj.1735022.511. Epub 2017 Dec 31. PMID: 29298474

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The symptoms of interstitial cystitis (IC)/bladder pain syndrome (BPS) may have multiple causes and involve many contributing factors. Traditional treatments (intravesical instillations) have had a primary focus on the bladder as origin of symptoms without adequately considering the potential influence of other local (pelvic) or systemic factors. Systemic pharmacological treatments have had modest success. A contributing factor to the low efficacy is the lack of phenotyping the patients. Individualized treatment based on is desirable, but further phenotype categorization is needed. There seems to be general agreement that IC is a unique disease and that BPS is a syndrome with multiple pathophysiologies, but this has so far not been well reflected in preclinical research with the aim of finding new pharmacological treatments. Current research approaches, including anti-nerve growth factor treatment, anti-tumor necrosis factor- α treatment, activation of SHIP1 (AQX-1125), and P2X3 receptor antagonists, and α_1 -adrenoceptor antagonists are potential systemic treatments, implying that not only the bladder is exposed to the administered drug, which may be beneficial if the IC/BPS is a bladder manifestation of a systemic disease, or negative (adverse effects) if it is a local bladder condition. Local treatment approaches such as the antagonism of Toll-like receptors (which still is only experimental) and intravesical liposomes (with positive proof-of-concept), may have the advantages of a low number of systemic adverse effects, but cannot be expected to have effects on symptoms generated outside the bladder. Assessment of which of the treatment approaches discussed in this review that can be developed into useful therapies requires further studies.

DIGITAL QUANTITATIVE ANALYSIS OF MAST CELL INFILTRATION IN INTERSTITIAL CYSTITIS.

Akiyama Y, Maeda D, Morikawa T, Niimi A, Nomiya A, Yamada Y, Igawa Y, Goto A, Fukayama M, Homma Y. *Neurourol Urodyn.* 2017 Oct 24. doi: 10.1002/nau.23365. [Epub ahead of print] PMID: 29065222

The purpose of this study from Japan was to evaluate the significance of mast cell infiltration in interstitial cystitis (IC) by comparison with equally inflamed controls using a digital quantification technique. Bladder biopsy specimens from 31 patients with Hunner type IC and 38 patients with non-Hunner type IC were analyzed. Bladder biopsy specimens from 37 patients without IC, including 19 non-specific chronic cystitis ("non-IC cystitis") specimens and 18 non-inflamed bladder ("normal bladder") specimens, were used as controls. Mast cell tryptase-, CD3-, CD20-, and CD138-immunoreactive cells were quantified using digital image analysis software to evaluate both mast cell and lymphoplasmacytic cell densities. Mast cell and lymphoplasmacytic cell densities were counted independently in the entire lamina propria and detrusor areas and compared among the four groups. In the lamina propria, there were no significant differences in mast cell and lymphoplasmacytic cell densities between Hunner type IC and non-IC cystitis or between non-Hunner type IC and normal bladder specimens. In the detrusor, the mast cell densities were not significantly different among the four groups. Mast cell density was correlated with lymphoplasmacytic cell density, but not with clinical parameters. The authors report that mast cell density is not significantly different between IC specimens and non-IC control specimens with a similar degree of background inflammation. The intensity of mast cell infiltration generally correlated with that of lymphoplasmacytic cells. They conclude that mast cell count is of no value in the differential diagnosis between IC and other etiologies.

OPTOGENETIC SILENCING OF NOCICEPTIVE PRIMARY AFFERENTS REDUCES EVOKED AND ONGOING BLADDER PAIN.

Samineni VK, Mickle AD, Yoon J, Grajales-Reyes JG, Pullen MY, Crawford KE, Noh KN, Gereau GB, Vogt SK, Lai HH, Rogers JA, Gereau RW 4th. *Sci Rep.* 2017 Nov 20;7(1):15865. doi: 10.1038/s41598-017-16129-3. PMID: 29158567

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Patients with IC/BPS suffer from chronic pain that severely affects quality of life. Although the underlying pathophysiology is not well understood, inhibition of bladder sensory afferents temporarily relieves pain. Here, the authors explored the possibility that optogenetic inhibition of nociceptive sensory afferents could be used to modulate bladder pain. The light-activated inhibitory proton pump Archaeorhodopsin (Arch) was expressed

under control of the sensory neuron-specific sodium channel (SNS) gene to selectively silence these neurons. Optically silencing nociceptive sensory afferents significantly blunted the evoked visceromotor response to bladder distension and led to small but significant changes in bladder function. To study the role of nociceptive sensory afferents in freely behaving mice, Samineni and colleagues from the USA developed a fully implantable, flexible, wirelessly powered optoelectronic system for the long-term manipulation of bladder afferent expressed opsins. They found that optogenetic inhibition of nociceptive sensory afferents reduced both ongoing pain and evoked cutaneous hypersensitivity in the context of cystitis, but had no effect in uninjured, naïve mice. These results suggest that selective optogenetic silencing of nociceptive bladder afferents may represent a potential future therapeutic strategy for the treatment of bladder pain.

IMPACT OF CYSTECTOMY WITH URINARY DIVERSION UPON TRACKED RECEIPT OF OPIOID PRESCRIPTIONS AMONG PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Koslov DS, Vilson F, Colaco M, Terlecki RP, Evans RJ. Urology. 2017 Nov 17. pii: S0090-4295(17)31201-3. doi: 10.1016/j.urology.2017.11.009. [Epub ahead of print] PMID: 29158174

The purpose of this study was to compare opioid requirements before and after cystectomy for end stage Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) using a state-wide tracking system. Narcotic prescriptions were captured using the North Carolina Controlled Substance Reporting System for patients at a single institute undergoing cystectomy with urinary diversion (CWUD) for refractory, end stage IC/BPS between 2010-2017. Values were documented for the year before and the year after surgery (excluding 30 days postoperatively to account for surgical pain) and converted to Morphine Equivalents (ME). Values were compared using the Student's T-test. Following CWUD, there was a mean decrease in opioid receipt per patient of 6,535 ME/year ($p = 0.321$). 8/26 (31%) had not filled any opiate prescriptions for the preceding 3 months at time of manuscript. In certain patients with end stage, refractory IC/BPS, CWUD can help reduce opioid requirements.

THE ROLE OF TSG-6 AND UROPLAKIN III IN BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS IN RATS AND HUMANS.

Lv YS, Gao R, Lin QM, Jiang T, Chen Q, Tang SX, Mao HP, Zhou HL, Cao LS. Iran J Basic Med Sci. 2017 Nov;20(11):1242-1249. doi: 10.22038/IJBMS.2017.9540. PMID: 29299202

Lv and colleagues from China investigated the relationship between the expression of tumor necrosis factor-inducible gene 6 (TSG-6) with inflammation and integrity of the bladder epithelium in the bladder tissues of patients with bladder pain syndrome/interstitial cystitis (BPS/IC) and the mechanism of action using a rat model of BPS/IC. Expression of TSG-6 and uroplakin III was determined by immuno- histochemistry of bladder biopsy samples from control human subjects and patients with verified BPS/IC. Their rat model of BPS/IC was employed to measure the perfusion of bladders with hyaluronidase, and assessment of the effect of TSG-6 administration on disease progression. Treatment effects were assessed by measurement of metabolic characteristics, RT-PCR of TGR-6 and interleukin-6, bladder histomorphology, and immunohistochemistry of TGR-6 and uroplakin III. The bladders of patients with BPS/IC had lower expression of uroplakin III and higher expression of TSG-6 than controls. Rats treated with hyaluronidase for 1 week developed the typical signs and symptoms of BPS/IC, and rats treated with hyaluronidase for 4 weeks had more serious disease. Administration of TSG-6 reversed the effects of hyaluronidase and protected against disease progression. The authors are of the opinion that their results indicate that TSG-6 plays an important role in maintaining the integrity of the bladder epithelial barrier.

MIRABEGRON AS ADJUVANT TREATMENT FOR PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Di Lena M, Tolls V, Kelly KL, Nickel JC. Can Urol Assoc J. 2017 Dec 22. doi: 10.5489/cuaj.4325. [Epub ahead of print] Can Urol Assoc J. 2017 Dec 22. doi: 10.5489/cuaj.4325. [Epub ahead of print]

Interstitial cystitis/bladder pain syndrome (IC/BPS) patients represent a heterogeneous group with pain and urinary storage symptoms and varying responses to current treatment options. The novel beta-3 agonist, mirabegron, has been shown to improve storage symptoms of patients with bladder overactivity; however, its effect on symptoms in the IC/BPS population has yet to be studied. Patients diagnosed at a single IC centre with IC/BPS undergoing standard therapy were treated with additional daily mirabegron 25 mg and seen in follow-up post-treatment. Patients completed the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI), and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF) prior to and following mirabegron treatment. Global (NRS) and symptom-specific outcomes were assessed by comparing the pre- and post-treatment mean scores using tailed-t test. A total of 23 patients were available for review pre- and post-mirabegron treatment. There was no significant difference in ICSI, ICPI, or PUF pre- and post-treatment. Analysis of symptom-specific outcomes show statistically significant improvements in urgency; however, no statistically

significant improvements in frequency or pain were observed with mirabegron therapy. The authors concluded that IC/BPS patients treated with mirabegron had improvement of urinary urgency, but no significant benefit in terms of pain or urinary frequency. This data suggests that mirabegron's role in the IC/BPS patient should be that of adjuvant treatment to ameliorate urgency.

EXPRESSION OF PROGRAMMED DEATH LIGAND-1 ON BLADDER TISSUES IS DETECTED IN A CLINICALLY AND HISTOLOGICALLY WELL-DEFINED INTERSTITIAL CYSTITIS COHORT.

Chen Y, Yu W, Yang Y, Xiao Y, Cui Y, Duan J, He Q, Jin J, Wu S. NeuroUrol Urodyn. 2017 Dec 26. doi: 10.1002/nau.23459. [Epub ahead of print] PMID: 29277923

The purpose of this study from Beijing, China was to investigate the expression of programmed death ligand-1 (PD-L1) in interstitial cystitis (IC). Chen and colleagues reviewed the data of IC patients who underwent hydrodistension plus bladder biopsy. Follow-ups were performed. They assessed the degree of inflammation of the bladder wall on slides stained with hematoxylin and eosin (H&E). They performed immunohistochemistry for PD-L1 expression detection and for counting T lymphocytes and B lymphocytes. The present study included eight men and 32 women. With H&E staining, they detected 13, 15, and 12 patients with mild, moderate, and severe inflammation. The degree of inflammation was negatively correlated with disease course and positively correlated with bladder pain. Hydrodistension was found effective at postoperative 3-month for 19 patients. Overall, 17, 15, 7, and 1 subject had no, mild, moderate, and high PD-L1 expression, that correlated positively with the degree of inflammation. Compared with patients with no and mild PD-L1 expression, patients with moderate and high PD-L1 expression tended to have more effective hydrodistension outcomes (12 of 32 vs 7 of 8). In the subset of 12 patients with severe inflammation, there were five of six patients (83.3%) with moderate or high PD-L1 expression and one of six patients (16.7%) with no and mild PD-L1 expression with an effective hydrodistension outcome. The authors found that expression of PD-L1 on bladder was detected in a cohort of IC patients presenting with diffuse global glomerulation or Hunner ulcer and concluded that PD-L1 expression is more common in IC patients with severe bladder inflammation.

A SYSTEMATIC REVIEW OF MYCOPLASMA AND UREAPLASMA IN UROGYNAECOLOGY.

Combaz-Söhnchen N, Kuhn A. Geburtshilfe Frauenheilkd. 2017 Dec;77(12):1299-1303. doi: 10.1055/s-0043-119687. Epub 2017 Dec 18. PMID: 29269957

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Mycoplasma species relevant to the urogenital tract include mycoplasma hominis, mycoplasma genitalia and ureaplasma urealyticum. Their occurrence in the context of urogynaecological disease has been demonstrated in urethritis, cystitis and upper renal tract infections. Their role in hyperactive bladder and interstitial cystitis/painful bladder syndrome is controversial. All the above-mentioned microorganisms can occur as commensals or as potential pathogens. In most cases their role in any particular pathology cannot be proven, only presumed. The aim of this systematic review from Switzerland was to summarise current knowledge on the influence of mycoplasma and ureaplasma in urogynaecological pathology and to provide clinical guidance on diagnosis (when and how is pathogen detection indicated?) and treatment. 377 relevant articles were analysed. In summary: a urethral swab for PCR analysis of the three bacteria should be performed in the context of symptomatic sterile leukocyturia, chronic urethritis and suspected hyperactive bladder or interstitial cystitis/painful bladder syndrome. Symptomatic women should be treated strictly according to results of the antibiogram.

REPEATED INTRAVESICAL INJECTIONS OF PLATELET-RICH PLASMA ARE EFFECTIVE IN THE TREATMENT OF INTERSTITIAL CYSTITIS: A CASE CONTROL PILOT STUDY.

Jhang JF, Wu SY, Lin TY, Kuo HC. Low Urin Tract Symptoms. 2017 Dec 19. doi: 10.1111/luts.12212. [Epub ahead of print] PMID: 29265766

Interstitial cystitis (IC), also known as bladder pain syndrome (BPS), is a debilitating chronic disease. There are few treatment options for IC/BPS refractory to current medical therapy. This study from Taiwan investigated the clinical efficacy of intravesical injections of platelet-rich plasma (PRP) in IC/BPS. Fifteen patients with IC/BPS received 4 intravesical injections, at 1-monthly intervals, of 12 mL PRP extracted from 50 mL of the patient's whole blood, followed by cystoscopic hydrodistention. The primary endpoint was the change in O'Leary-Sant symptom (OSS) index from baseline to 1 month after the 4th PRP injection. Secondary endpoints were changes in pain (measured using a visual analog scale [VAS]), daily frequency, nocturia, functional bladder capacity (FBC), maximum flow rate, voided volume, post-void residual (PVR) volume, and global response assessment (GRA). Urinary cytokine levels were measured at baseline and 1 month after the 1st PRP treatment. Of the 15 women in the study, 13 completed the 4 injections and follow-up visits. The OSS index and VAS pain score decreased

significantly and FBC and GRA increased after the 1st PRP injection and lasted until the final endpoint. There was no change in PVR after repeated PRP injections, and all patients were free of urinary tract infections and difficulty urinating. Urinary interleukin (IL)-2 and IL-8 concentrations increased significantly after the 1st PRP injection. In patients with reductions in the VAS pain score ≥ 1 , urinary IL-8 and vascular endothelial growth factor increased. In patients without reductions in the VAS pain score, IL-6 concentrations increased after PRP injection. According to the authors, repeated intravesical PRP injections are well tolerated and appear to be safe and effective in medically refractive IC/BPS, providing significant symptom improvement.

[PATHOPHYSIOLOGICAL ROLE OF TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 IN A MOUSE LONG-LASTING CYSTITIS MODEL INDUCED BY AN INTRAVESICAL INJECTION OF HYDROGEN PEROXIDE.](#)

Oyama S, Dogishi K, Kadera M, Kakae M, Nagayasu K, Shirakawa H, Nakagawa T, Kaneko S. *Front Physiol.* 2017 Nov 7;8:877. doi: 10.3389/fphys.2017.00877. eCollection 2017. PMID: 29249972

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Chronic inflammatory bladder disorders, such as interstitial cystitis/bladder pain syndrome, are associated with poor quality of life. The exact pathological processes remain unclear, but accumulating evidence suggests that reactive oxidative species (ROS) are involved in urinary bladder disorders. Transient receptor potential ankyrin 1 (TRPA1), the most sensitive TRP channel to ROS, was shown to be responsible for urinary bladder abnormalities and hyperalgesia in an acute cystitis model. However, the roles of TRPA1 in chronic inflammatory bladder are not fully understood. Oyama and colleagues from Japan previously established a novel mouse cystitis model induced by intravesical injection of hydrogen peroxide (H_2O_2), resulting in long-lasting frequent urination, bladder inflammation, pain-related behavior, and histopathological changes. In the present study, they investigated the pathophysiological role of TRPA1 in the H_2O_2 -induced long-lasting cystitis mouse model. Under anesthesia, 1.5% H_2O_2 solution was introduced transurethraly into the bladder of female wild-type (WT) and TRPA1-knockout mice and maintained for 30 min. This increased the number of voids in WT mice at 1 and 7 days after injection, but reduced the number in TRPA1-knockout mice at 1 day but not 7 days after injection. Spontaneous locomotor activities (increase in freezing time and decrease in distance moved) were reduced at 3 h after injection in WT mice, whereas the spontaneous visceral pain-related behaviors were attenuated in TRPA1-knockout mice. Furthermore, upregulation of *c-fos* mRNA in the spinal cord at 1 day after injection was observed in WT but not TRPA1-knockout mice. However, there was no difference in histopathological changes in the urinary bladder, such as edematous thickening in the submucosa, between WT and TRPA1-knockout mice at 1 or 7 days after injection. Finally, *Trpa1* mRNA levels in the L5-S1 dorsal root ganglion were not altered, but levels in the urinary bladder were drastically increased at 1 and 7 days after injection. Taken together, these results suggest that TRPA1 contributes to acute bladder hyperactivity such as frequent urination and bladder pain, but does not appear to play a major role in the pathological processes of long-lasting cystitis.

[SAFETY AND FEASIBILITY OF INTRAVESICAL INSTILLATION OF BOTULINUM TOXIN-A IN HYDROGEL-BASED SLOW RELEASE DELIVERY SYSTEM IN INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME PATIENTS: A PILOT STUDY.](#)

Rappaport YH, Zisman A, Jeshurun-Gutshat M, Gerassi T, Hakim G, Vinshtok Y, Stav K. *Urology.* 2018 Jan 4. pii: S0090-4295(18)30004-9. doi: 10.1016/j.urology.2017.12.028. [Epub ahead of print] PMID: 29307733

The purpose of this study from Israel was to assess feasibility and safety of a mixture instillation of TC-3 Gel, a novel reverse-thermal gelation hydrogel, and botulinum toxin-A (BTX-A) for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). TC-3 Gel/BTX-A mix is instilled into the bladder as liquid, solidifies due to body heat and gradually dissolves to release BTX-A for several hours. A single intravesical instillation of 200U BTX-A premixed with 40ml TC-3 Gel was delivered to the bladder. Adverse events (AE's) and preliminary efficacy outcome measures were assessed: bladder diary, visual analogue scale (VAS) for pain and IC symptom and problem index (ICSI, ICPI) at baseline, 2, 6 and 12 weeks. 15 severely symptomatic IC/BPS patients (ICSI and ICPI range 12-19 and 12-16, respectively; median VAS=7) were enrolled. M/F=4/11, age 24-76. No increase in VAS score was noted at instillation. All AE's were transient and mild, the most common being temporary mild constipation. Mean VAS at baseline vs. week 12 was 6.6 ± 2.7 vs. 5.3 ± 2.8 . Mean ICSI and ICPI scores were reduced at week 12 compared to baseline. Mean number of voids per night at baseline decreased for 6 weeks and then returned to baseline level at week 12. Intravesical instillation of a TC-3 Gel/BTX-A mixture is safe and tolerable. Preliminary results suggest temporary efficacy lasting for a few weeks.

[CROWDSOURCING DISEASE BIOMARKER DISCOVERY RESEARCH; THE IP4IC STUDY.](#)

Chancellor MB, Bartolone SN, Veerecke A, Lamb LE. *J Urol.* 2017 Dec 7. pii: S0022-5347(17)78037-8. doi: 10.1016/j.juro.2017.09.167. [Epub ahead of print] PMID: 29225061

Biomarker discovery is limited by readily assessable, cost efficient, human samples available in large numbers that represent the entire heterogeneity of the disease. Chancellor and colleagues developed a novel active participation crowdsourcing method to develop a Bladder Permeability Defect Risk Score (BP-RS) based on non-invasive urinary cytokines to discriminate Interstitial cystitis/bladder pain syndrome (IC/BPS) with Hunner's lesion (UIC) patients from controls and IC patients without Hunner's lesions. A national crowdsourcing study was done in cooperation with the Interstitial Cystitis Association. Patients answered demographic, symptom severity, and urinary frequency questionnaires on a HIPAA compliant website. Urine samples were collected at home, stabilized with a preservative and sent to Beaumont for analysis. Expression of three urinary cytokines was used in a machine learning algorithm to develop the BP-RS. IP4IC study collected 448 urine samples consisting of 153 IC patients (147 female, 6 male), of which 54 were UIC patients (50 females, 4 male), 159 female controls and 136 male controls. Controls were age-matched. A defined BP-RS was calculated to predict UIC, or a bladder permeability defect etiology, with 89% validity. This novel participation crowdsourcing study collected a large number of urine samples from 46 states collected at home, shipped, and stored at room temperature. Using a machine learning algorithm, they developed the BP-RS to quantify UIC risk, indicative of a bladder permeability defect etiology. The BP-RS is the first validated urine biomarker assay for IC/BPS and one of the first biomarker assays to be developed using crowdsourcing.

MICRORNA-139-5P INHIBITS EPITHELIAL-MESENCHYMAL TRANSITION AND FIBROSIS IN POST-MENOPAUSAL WOMEN WITH INTERSTITIAL CYSTITIS BY TARGETING LPAR4 VIA THE PI3K/AKT SIGNALING PATHWAY.

Jiang C, Tong Z, Fang WL, Fu QB, Gu YJ, Lv TT, Liu DM, Xue W, Lv JW. J Cell Biochem. 2017 Dec 14. doi: 10.1002/jcb.26610. [Epub ahead of print] PMID: 29240250

This study from Shanghai, China explores whether miR-139-5p targeting LPAR4 affects epithelial-mesenchymal transition (EMT) and fibrosis in post-menopausal women with interstitial cystitis (IC) via the PI3K/Akt signaling pathway. Bladder tissues of IC and normal bladder tissues were collected. The pathology of bladder tissues was observed by HE, Masson and Picrosirius red staining. LPAR4 positive expression rate were determined by IHC. ELISA was performed to detect the levels of IL-6, IL-8, IL-10 and TNF- α . Rat IC models were randomized into seven different groups. miR-139-5p, LPAR1, LPAR2, LPAR3, LPAR4, LPAR5, P13K, Akt, E-cadherin, N-cadherin, Vimentin, TGF- β 1 and CTGF expression were determined by RT-qPCR and Western blotting. Dual luciferase reporter gene assay verified that LPAR4 is a target gene of miR-139-5p. Fibrosis was a pathological manifestation of IC. The IC group showed higher LPAR4, PI3K, Akt, p-PI3K, p-Akt, N-cadherin, Vimentin, TGF- β 1 and CTGF expression but lower miR-139-5p and E-cadherin expression than the normal group. The levels of IL-6, IL-8, IL-10 and TNF- α expression decreased while HB-EGF increased in the IC group in comparison of the normal group. Compared with the blank and NC groups, E-cadherin expression was increased in the miR-139-5p mimic and siRNA-LPAR4 groups, while LPAR4, PI3K, Akt, p-P13K, p-Akt, N-cadherin, Vimentin, TGF- β 1 and CTGF expression were decreased. An opposite trend was found in the miR-139-5p inhibitor group. The miR-139-5p decreased in the miR-139-5p inhibitor + siRNA-LPAR4 and miR-139-5p inhibitor + wortmannin groups. Conclusively, miR-139-5p targeting LPAR4 inhibits EMT and fibrosis in post-menopausal IC women through the PI3K/Akt signalling pathway.

UMBILICAL CORD-DERIVED MESENCHYMAL STEM CELLS ALLEVIATED INFLAMMATION AND INHIBITED APOPTOSIS IN INTERSTITIAL CYSTITIS VIA AKT/MTOR SIGNALING PATHWAY.

Xie J1, Liu B1, Chen J1, Xu Y1, Zhan H1, Yang F1, Li W1, Zhou X2. Biochem Biophys Res Commun. 2018 Jan 1;495(1):546-552. doi: 10.1016/j.bbrc.2017.11.072. Epub 2017 Nov 11. PMID: 29137981

Interstitial cystitis (IC) is a bladder syndrome characterized by pelvic pain and urinary frequency without infection or other identifiable pathology. There are no effective treatments to cure IC. This study from Guangzhou, China investigated the effects of human umbilical cord-derived mesenchymal stem cells (UC-MSCs) injection on IC rat model. The authors used a coculture system to find the possible molecular mechanism on the human uroepithelial cells (SV-HUC-1), which was the cell model of IC. A rat model of IC was established via systemic injection with cyclophosphamide (CYP) and a cell model of IC was induced by being exposed to tumor necrosis factor (TNF)- α (10 ng/ml). After one week, UC-MSCs injection significantly ameliorated the bladder voiding function in IC rat model. And the Histo- and immunohistochemical analyses showed that UC-MSCs can repair impaired bladder, reduce mast cell infiltration and inhibit apoptosis of urothelium. ELISA results showed that UC-MSCs can decrease IL-1 β , IL-6 and TNF- α in bladder. In the coculture system, UC-MSCs can promote proliferation of impaired SV-HUC-1 cells, and inhibit apoptosis. However, while knocked down EGF secreted by UC-MSCs with siRNA, the effects would be weakened. Western blot showed that UC-MSCs increase protein expression levels of p-AKT and p-mTOR in SV-HUC-1 cells, and decrease the levels of cleaved caspase-3. Taken together, the authors suggest that there is evidence that UC-MSCs therapy can successfully alleviate IC in a

preclinical animal Model and cell model by alleviating inflammation, promoting proliferation and inhibiting apoptosis. In addition, they demonstrate that the AKT/mTOR signalling pathway was activated.

[APOPTOTIC EFFECT AS BIOMARKER OF DISEASE, SEVERITY AND FOLLOW-UP IN INTERSTITIAL CYSTITIS.](#)

Di Capua-Sacoto C, Sanchez-Llopis A, Oconnor JE, Martinez-Romero A, Ruiz-Cerdá JL. Actas Urol Esp. 2017 Nov 10. pii: S0210-4806(17)30195-X. doi: 10.1016/j.acuro.2017.09.007. [Epub ahead of print] PMID: 29132932 [Article in English, Spanish]

The purpose of this study from Spain was to determine whether the apoptotic effect test could serve as a biomarker of severity in bladder pain syndrome/interstitial cystitis. A prospective study was conducted between January 2010 and January 2015, which included 57 patients diagnosed with interstitial cystitis and 49 diagnosed with chronic pelvic pain of gynaecological origin. The urine was exposed to cell cultures, and the urine's capacity for inducing apoptosis in the cultures was analysed. A statistical analysis was then conducted to assess whether the apoptotic effect was associated with the symptoms. After performing an analysis of the association between the degree of apoptotic effect and the symptoms of patients with interstitial cystitis, the authors observed a significant increase in the mean percentages of apoptosis as the degree of symptom severity increased. After analysing the association between the apoptotic effect and symptoms, they obtained a positive correlation in the patients with interstitial cystitis and a lack of correlation in the patients with chronic pelvic pain of gynaecological origin. The rates of apoptosis increased progressively in the patients with interstitial cystitis as the symptoms increased, while the patients with chronic pelvic pain of gynaecological origin remained stable. It was concluded that the apoptotic effect of the urine of patients with interstitial cystitis could be a marker of disease, thus differentiating patients with interstitial cystitis from patients with chronic pelvic pain. The effect could also provide an objective measure of symptom severity.

[ACYLOXYACYL HYDROLASE MODULATES PELVIC PAIN SEVERITY.](#)

Yang W, Yaggie RE, Jiang MC, Rudick CN, Done JD, Heckman CJ, Rosen JM, Schaeffer AJ, Klumpp DJ. Am J Physiol Regul Integr Comp Physiol. 2017 Nov 8:ajpregu.00239.2017. doi: 10.1152/ajpregu.00239.2017. [Epub ahead of print] PMID: 29118019

Chronic pelvic pain causes significant patient morbidity and is a bane to clinicians. Using a murine neurogenic cystitis model that recapitulates key aspects of interstitial cystitis/bladder pain syndrome (IC), Yang and colleagues recently showed that pseudorabies virus (PRV) induces severe pelvic allodynia in BALB/c mice, relative to C57BL/6 mice. Here, they report that a quantitative trait locus (QTL) analysis of PRV-induced allodynia in F2CxB progeny identified a polymorphism on chromosome 13, rs6314295, significantly associated with allodynia (LOD=3.11). The nearby gene encoding acyloxyacyl hydrolase, (AoaH), was induced in the sacral spinal cord of PRV-infected mice. AOA-H-deficient mice exhibited increased vesicomotor reflex in response to bladder distension, consistent with spontaneous bladder hypersensitivity, and increased pelvic allodynia in neurogenic cystitis and post-bacterial chronic pain models. AOA-H deficiency resulted in greater bladder pathology and TNF production in PRV neurogenic cystitis, markers of increased bladder mast cell activation. AOA-H immunoreactivity was detectable along the bladder-brain axis, including in brain sites previously correlated with human chronic pelvic pain. Finally, AOA-H-deficient mice had significantly higher levels of bladder VEGF, an emerging marker of chronic pelvic pain in humans. These findings indicate that AOA-H modulates pelvic pain severity, suggesting that allelic variation in AoaH influences pelvic pain in IC.

[TRANSDERMAL LIGHT NEUROMODULATION: OPTOGENETICS IN THE MURINE URINARY TRACT.](#)

Wallace SL, Kelley RS, Mehta S, Descalzi G, Fantl JA, Ascher-Walsh C. NeuroUrol Urodyn. 2017 Nov 23. doi: 10.1002/nau.23458. [Epub ahead of print] PMID: 29168214

Optogenetics is a biologic technique that uses light to control living neurons, which have been genetically modified to express light-sensitive ion-channels. Using an adenovirus to modify the sciatic nerves of mice, Wallace and colleagues from the USA aimed to demonstrate peripheral neuromodulation of bladder pain using transdermal light. This pilot study is divided into: A) Confirmation and Application and B) Behavioral Step. A) Six mice were injected with AAV6-hSyn-ChR2(H134R)-eYFP virus into their sciatic nerves. This encoded an excitatory opsin, enabling light-inducible stimulation. At 4-6 weeks after injection, the authors induced foot pain responses with an activating blue 475 nm wavelength of light. B) Two optogenetically primed mice and two control mice underwent anesthesia and capsaicin was instilled into their bladders via catheter. The catheters were removed and the mice awoke in a chamber that exposed them to either blue 475 nm light or no light. Groin licking was scored in a binary fashion by two blinded observers. A) All six mice exhibited pain response to 475 nm blue light either by licking of foot or avoidance of light. B) The optogenetically primed mice had a 48% reduction in bladder pain behavior when exposed to blue 475 nm light whereas the control mice had a 18% reduction. The authors

report that to their knowledge this is the first demonstration of the application of optogenetics to modulate sensation in the lower urinary tract. It suggests that the process of priming peripheral nerves for optogenetic modulation is possible and can be used to study bladder pain response in mice.

DEVELOPMENT OF AN INTERSTITIAL CYSTITIS RISK SCORE FOR BLADDER PERMEABILITY.

Lamb LE, Janicki JJ, Bartolone SN, Peters KM, Chancellor MB. *PLoS One*. 2017 Oct 31;12(10):e0185686. doi: 10.1371/journal.pone.0185686. eCollection 2017. PMID: 29088231

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Interstitial cystitis/bladder pain syndrome (IC) is a multifactorial syndrome of severe pelvic and genitalia pain and compromised urinary function; a subset of IC patients with Hunner's lesions or ulcers on their bladder walls (UIC). UIC is diagnosed by cystoscopy, which may be quite painful. The objective of this study was to determine if a calculated Bladder Permeability Defect Risk Score (BP-RS) based on non-invasive urinary cytokines could discriminate UIC patients from controls and IC patients without Hunner's ulcers. A national crowdsourcing effort targeted IC patients and age-matched controls to provide urine samples. Urinary cytokine levels for GRO, IL-6, and IL-8 were determined using a Luminex assay. Lamb and colleagues collected 448 urine samples from 46 states consisting of 153 IC patients (147 female, 6 male), of which 54 UIC patients (50 females, 4 male), 159 female controls, and 136 male controls. A defined BP-RS was calculated to classify UIC, or a bladder permeability defect etiology, with 89% validity. The BP-RS Score quantifies UIC risk, indicative of a bladder permeability defect etiology in a subset of IC patients. The Bladder Permeability Defect Risk Score is the first validated urine biomarker assay for interstitial cystitis/bladder pain syndrome.

COMPARATIVE STUDY OF EFFICACY AND SAFETY BETWEEN BLADDER BODY AND TRIGONAL INTRAVESICAL ONABOTULINUMTOXINA INJECTION IN THE TREATMENT OF INTERSTITIAL CYSTITIS REFRACTORY TO CONVENTIONAL TREATMENT-A PROSPECTIVE, RANDOMIZED, CLINICAL TRIAL.

Jiang YH, Jhang JF, Lee CL, Kuo HC. *Neurourol Urodyn*. 2018 Jan 13. doi: 10.1002/nau.23475. [Epub ahead of print] PMID: 29331031

Intravesical onabotulinumtoxinA (BoNT-A) injection can relieve symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). However, the therapeutic efficacy of different injection sites is not well known. This study from Taiwan compared therapeutic efficacy and safety between bladder body and trigonal BoNT-A injection. Patients were randomly treated with 100U of BoNT-A in 10 mL saline injected into 20 bladder body sites or 10 trigonal sites. The primary endpoint was changes of Visual Analog Scale (VAS) for Pain at 8th week after injection. Secondary endpoint included changes of Global Response Assessment (GRA), urinary frequency episodes, O'Leary-Sant score (OSS), and urodynamic study. Thirty-nine patients (bladder body, N = 20; trigone, N = 19) completed the study visits. Patients in both groups had significant improvement in VAS, OSS, and functional bladder capacity after treatment. There was no significant difference in changes of urinary frequency, voided volume, post-void residual volume, and bladder capacity from baseline to 8 weeks between groups. Thirteen (65.0%) patients in bladder body group and 10 (52.6%) patients in trigone group had decrease of VAS more than 2 points after treatment. Excellent symptom improvement was noted in 9 (45%) patients with bladder body injection and 10 (52.6%) patients with trigonal injection. Nine (45.0%) patients in bladder body group and 10 (52.6%) in trigonal group experienced dysuria after treatment. No significant difference in the improvement of IC symptoms and urodynamic parameters after intravesical BoNT-A injection in the bladder body or trigone. The rate of adverse events was similar between groups.

HUNNER LESIONS

EXTENT OF HUNNER LESIONS: THE RELATIONSHIPS WITH SYMPTOM SEVERITY AND CLINICAL PARAMETERS IN HUNNER TYPE INTERSTITIAL CYSTITIS PATIENTS.

Akiyama Y, Niimi A, Nomiya A, Yamada Y, Nakagawa T, Fujimura T, Fukuhara H, Kume H, Igawa Y, Homma Y. *Neurourol Urodyn*. 2018 Jan 9. doi: 10.1002/nau.23467. [Epub ahead of print] PMID: 29315774

The purpose of this study from Japan was to assess the clinical impact of Hunner lesions in patients with Hunner type interstitial cystitis (HIC). The clinical records of 94 HIC patients who underwent their first hydrodistension (with lesion fulguration) were retrospectively reviewed. At surgery, the extent of each lesion was classified in terms of the relative involvement for the whole-bladder luminal surface; the authors defined four grades of involvement: <10%, 10-24%, 25-49%, and ≥50%; and two grades of severity: <25% (focal) and ≥25% (extensive). They examined the relationships between the extent of the lesions and all demographic characteristics, symptom scores, voiding symptoms, and bladder capacity. Factors predictive of the need for repeat hydrodistension were also explored. Symptom severity worsened as the lesional extent rose. Those with extensive lesions scored higher on the O'Leary and Sant Symptom and Problem Index scales, the pain visual

analog scale, the International Prostate Symptom Score scale, and a quality-of-life index; and exhibited greater daytime urinary frequency, more nocturia, and a smaller bladder capacity than the focal group. No symptomatic or clinical parameters predicted the need for repeat hydrodistension. The extent of Hunner lesions was associated with both symptom severity and bladder capacity but not with other clinical parameters, including the need for repeat hydrodistension, in patients with HIC.

[THERAPEUTIC EFFECTS OF ENDOSCOPIC ABLATION IN HUNNER TYPE INTERSTITIAL CYSTITIS PATIENTS.](#)

Ko KJ, Chung H, Suh YS, Lee SW, Kim TH, Lee KS. BJU Int. 2017 Dec 12. doi: 10.1111/bju.14097. [Epub ahead of print] PMID: 29232035

The aim of this study from South Korea was to investigate the efficacy of endoscopic ablation of Hunner lesions (HLs) in patients with interstitial cystitis (IC) and to find predictors of early recurrence of HLs. A prospective study was performed for Hunner type IC who underwent transurethral ablation. Ko and colleagues repeated endoscopic ablation when symptoms and HLs recurred during the follow-up period. The primary endpoint was recurrence-free time. Secondary endpoints were a change of number of frequency, nocturia, and urgency episodes and changes in visual analogue scale for pain and other symptom indices at follow-up visits. A total of 72 patients were analyzed. The median follow-up period was 29.5 (range, 12.0-50.0) months. After primary ablation treatment, HLs recurred in 75.0% (54/72) of subjects, and the median recurrence-free time was 12.0 ± 1.6 months. Among the 54 patients with recurrence, 50 underwent a second ablation treatment. HLs occurred in 44.0% (22/50) of individuals after the second operation, and the median recurrence-free time was 18.0 ± 5.1 months. Lower maximal cystometric capacity was the predictive factor for early recurrence. There were significant improvements in the visual analogue scale for pain, O'Leary-Sant interstitial cystitis symptom index and problem index, pelvic pain and urgency/frequency patient symptom scale after treatment. The authors concluded that endoscopic ablation is an effective treatment option for HLs and significantly reduces pain and improves voiding symptoms. Repeat ablation upon recurrence could help symptom control and bladder preservation only if the bladder capacity is maintained.

IC/BPS/HSB AND QUALITY OF LIFE

[ADDRESSING QUALITY OF LIFE IN THE PATIENT WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Vasudevan V, Moldwin R. Asian J Urol. 2017 Jan;4(1):50-54. doi: 10.1016/j.ajur.2016.08.014. Epub 2016 Dec 2. PMID: 29264207

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating, chronic condition characterized by chronic pelvic pain, urinary urgency, and frequency and is well-known to be associated with a decrease in work productivity, emotional changes, sleep, sexual dysfunction, and mobility. Many metrics of quality of life (QoL) in this patient population have been developed; however, a unified, standardized approach to QoL in these patients has not been determined. The effects of IC/BPS and co-morbid conditions on QoL are described using current validated metrics. Next, data regarding successful treatment of IC/BPS in terms of QoL improvement are reviewed. While QoL is the single most important clinical measure of success in the treatment of patients suffering from IC/BPS, addressing QoL in this patient population remains a significant challenge, as its effects on QoL are highly variable and unable to be differentiated from the effects of comorbid conditions on QoL, including depression, poor sleep, and inability to work. Future studies will need to address treatment efficacy on the basis of IC/BPS specific QoL metrics, and multi-modal assessment and therapy to address comorbid disease will also play an important role in the future to ensure comprehensive management of these patients.

URINARY TRACT INFECTIONS

[FIRST EXPERIENCE IN THE UK OF TREATING WOMEN WITH RECURRENT URINARY TRACT INFECTIONS WITH THE BACTERIAL VACCINE UROMUNE®](#)

Yang B, Foley S. BJU Int. 2017 Nov 23. doi: 10.1111/bju.14067. [Epub ahead of print] PMID: 29171130

The purpose of this study from Reading, UK was to determine the effectiveness of Uromune® in preventing recurrent urinary tract infections (UTIs) in women. A total of 77 women with microbiology-proven recurrent UTIs were given Uromune sublingual vaccine for a period of 3 months. Time to first UTI recurrence since treatment and adverse events were prospectively recorded in a follow-up period of up to 12 months. Of the 77 women, 75 completed the treatment. Of the 75 women who completed treatment, 59 (78%) had no subsequent UTIs in the follow-up period. Prior to treatment, all women had experienced a minimum of three or more episodes of UTI during the preceding 12 months. Proportionally, the majority of

recurrences occurred in postmenopausal women. One patient had to stop treatment because of an adverse event (rash over face and neck). This prospective study suggests that Uromune is safe and effective at preventing UTIs in women. Further research is required in larger groups of patients for longer treatment times. An international double-blind randomized control trial comparing Uromune with placebo is currently underway.

LOWER URINARY TRACT SYMPTOMS THAT PREDICT MICROSCOPIC PYURIA.

Khasriya R, Barcella W, De Iorio M, Swamy S, Gill K, Kupelian A, Malone-Lee J. Int Urogynecol J. 2017 Oct 2. doi: 10.1007/s00192-017-3472-7. [Epub ahead of print] PMID: 28971220

Urinary dipsticks and culture analyses of a mid-stream urine specimen (MSU) at 10^5 cfu ml⁻¹ of a known urinary pathogen are considered the gold standard investigations for diagnosing urinary tract infection (UTI). However, the reliability of these tests has been much criticised and they may mislead. It is now widely accepted that pyuria (≥ 1 WBC μl^{-1}) detected by microscopy of a fresh unspun, unstained specimen of urine is the best biological indicator of UTI available. Khasriya and colleagues from the UK aimed to scrutinise the greater potential of symptoms analysis in detecting pyuria and UTI. Lower urinary tract symptom (LUTS) descriptions were collected from patients with chronic lower urinary tract symptoms referred to a tertiary referral unit. The symptoms informed a 39-question inventory, grouped into storage, voiding, stress incontinence and pain symptoms. All questions sought a binary yes or no response. A bespoke software package was developed to collect the data. The study was powered to a sample of at least 1,990 patients, with sufficient power to analyse 39 symptoms in a linear model with an effect size of Cohen's $f^2 = 0.02$, type 1 error probability = 0.05; and power $(1-\beta)$; 95% where β is the probability of type 2 error). The inventory was administered to 2,050 female patients between August 2004 and November 2011. The data were collated and the following properties assessed: internal consistency, test-retest reliability, inter-observer reliability, internal responsiveness, external responsiveness, construct validity analysis and a comparison with the International Consultation on Incontinence Modular Questionnaire for female lower urinary tract symptoms (ICIQ-FLUTS). The dependent variable used as a surrogate marker of UTI was microscopic pyuria. An MSU sample was sent for routine culture. The symptoms proved reliable predictors of microscopic pyuria. In particular, voiding symptoms correlated well with microscopic pyuria. The symptom inventory has significant psychometric characteristics as below: test-retest reliability: Cronbach's alpha was 0.981; inter-observer reliability, Cronbach's alpha was 0.995, internal responsiveness $F = 221$, $p < 0.001$, external responsiveness $F = 359$, $df = 5$, $p < 0.001$. The correlation coefficients for the domains of the ICIQ-FLUTS were around $R = 0.5$, $p < 0.001$. This symptoms score performed well on the standard, psychometric validation. The score changed in response to treatment and in a direction appropriate to the changes in microscopic pyuria. It correlated with measures of quality of life. It would seem to make a good candidate for monitoring treatment progress in ordinary clinical practice.

THE USE OF INTRAVESICAL GENTAMICIN TO TREAT RECURRENT URINARY TRACT INFECTIONS IN LOWER URINARY TRACT DYSFUNCTION.

Abrams P, Hashim H, Tomson C, Macgowan A, Skews R, Warren K. Neurourol Urodyn. 2017 Nov;36(8):2109-2116. doi: 10.1002/nau.23250. Epub 2017 May 15. PMID: 28503891

The purpose of this study by Abrams et al was to assess the use of intravesical gentamicin to treat intractable recurrent urinary tract infections in lower urinary tract dysfunction. A two-center retrospective cohort study of 27 patients treated with intravesical gentamicin was performed over a 2-year period. A treatment protocol was developed, reviewed, and accepted by the clinical effectiveness committee of both hospitals. Patients were taught to instill the gentamicin into the bladder on a nightly basis. Inclusion criteria included failure to respond to standard therapy, having six or more cultured confirmed UTIs over a 12-month period, or at least one hospital admission with sepsis. Serum gentamicin levels were taken after 7 days and the treatment was discontinued if the level was >1 mg/L. Patients were counselled about the limited evidence base for this treatment. 27 patients were treated with intravesical gentamicin for an average of 26 months. 17 were performing ISC, 5 had suprapubic catheters, 3 were voiding, and 2 had ileal conduits at the time of instituting treatment. All patients started on daily 80 mg gentamicin. 22 patients had less frequent infections after starting intravesical gentamicin treatment. 6 stopped the treatment and none had side effects as a result of the instillations. This study has shown that in a small group of adult patients who have multiple symptomatic UTIs refractory to conventional treatment, intravesical gentamicin is effective in reducing the frequency of infections. The treatment is well tolerated with no evidence of systemic absorption.

AN EVIDENCE-BASED PROTOCOL FOR ANTIBIOTIC USE PRIOR TO CYSTOSCOPY DECREASES ANTIBIOTIC USE WITHOUT IMPACTING POST-PROCEDURAL SYMPTOMATIC URINARY TRACT INFECTION RATES

Gregg JR, Bhalla RG, Cook JP, Lai C, Dmochowski R, Talbot TR, Barocas DA. *J Urol.* 2017 Nov 3. pii: S0022-5347(17)77806-8. doi: 10.1016/j.juro.2017.10.038. [Epub ahead of print]

Symptomatic urinary tract infection is a complication of office based cystourethroscopy. Studies are mixed regarding the efficacy of antibiotic prophylaxis to prevent urinary tract infections. The aim of this study was to develop and evaluate an evidence-based protocol that reduces unnecessary antibiotic use while avoiding an increase in urinary tract infections. Gregg and colleagues created a clinic antibiogram based on all urology office visits performed during a 2-year period. Bacterial resistance rates, institutional risk related data and clinical guidelines were applied to create a protocol for antibiotic administration before cystourethroscopy. They then analyzed 1,245 consecutive patients without a renal transplant who underwent outpatient cystourethroscopy, including 610 after protocol initiation. Urinary tract infection rates and antibiotic use were analyzed for an association with the protocol change using the Fisher exact test. Cultures had an overall 20% rate of resistance to fluoroquinolones, representing 40% of the cultures that grew *Escherichia coli*. Before the protocol change 602 of 635 patients (94.8%) received a preprocedural antibiotic compared to 426 of 610 (69.9%) after protocol initiation. A total of 19 patients (3.0%) had a symptomatic urinary tract infection prior to the protocol change while 16 (2.6%) had a urinary tract infection after the change. Regarding resistance, fluoroquinolone resistant organisms grew in the cultures of 12 of 19 patients (63.2%) with a urinary tract infection before the protocol change compared to 5 of 16 (31.3%) with a urinary tract infection after the change. Recent antibiotic administration, hospitalization and chronic catheterization were associated with urinary tract infection in the entire cohort. The authors concluded that a local antibiogram with infection related risk data effectively risk stratifies patients before cystourethroscopy, decreasing the use of antibiotics without increasing the rate of symptomatic urinary tract infection.

CHRONIC PROSTATITIS

CHRONIC PROSTATITIS AND COMORBID NON-UROLOGICAL OVERLAPPING PAIN CONDITIONS: A CO-TWIN CONTROL STUDY.

Gasperi M, Krieger JN, Forsberg C, Goldberg J, Buchwald D, Afari N. *J Psychosom Res.* 2017 Nov;102:29-33. doi: 10.1016/j.jpsychores.2017.09.005. Epub 2017 Sep 6. PMID: 28992894

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by pain and voiding symptoms in the absence of an obvious infection or other cause. CP/CPPS frequently occurs with non-urological chronic overlapping pain conditions (COPCs) of unknown etiology. Gasperi and colleagues from the USA conducted a co-twin control study in men discordant for chronic prostatitis (CP), an overarching diagnosis of which approximately 90% is CP/CPPS. The primary aim was to investigate the contribution of familial factors, including shared genetic and common environmental factors, to the comorbidity of CP and COPCs. Data from 6824 male twins in the Vietnam Era Twin Registry were examined to evaluate the association between self-reported lifetime physician diagnosis of CP with COPCs including fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorder, tension headaches, and migraine headaches. Random effects logistic regression models were used and within-pair analyses evaluated confounding effects of familial factors on the associations. There were significant associations between CP and all 6 examined COPCs. After adjusting for shared familial influences in within twin pair analyses, the associations for all COPCs diminished but remained significant. Familial confounding was strongest for the association of CP with fibromyalgia and temporomandibular disorder and smallest for irritable bowel syndrome. CP and COPCs are highly comorbid. These associations can be partially explained by familial factors. The mechanisms underlying these relationships are likely diverse and multifactorial. Future longitudinal research can help to further elucidate specific genetic and environmental mechanisms and determine potentially causal relationships between CP and its comorbidities.

URINARY MICROBIOME, MICROBIOTA

THE URINARY MICROBIOME AND ITS CONTRIBUTION TO LOWER URINARY TRACT SYMPTOMS; ICI-RS 2015.

Drake MJ, Morris N, Apostolidis A, Rahnama'i MS, Marchesi JR. *Neurourol Urodyn.* 2017 Apr;36(4):850-853. doi: 10.1002/nau.23006. PMID: 28444712

The microbiome is the term used for the symbiotic microbial colonisation of healthy organs. Studies have found bacterial identifiers within voided urine which is apparently sterile on conventional laboratory culture, and accordingly there may be health and disease implications. The International Consultation on Incontinence Research Society (ICI-RS) established a literature review and expert consensus discussion focussed on the increasing awareness of the urinary microbiome, and potential research priorities. The consensus considered

the discrepancy between findings of conventional clinical microbiology methods, which generally rely on culture parameters predisposed towards certain "expected" organisms. Discrepancy between selective culture and RNA sequencing to study species-specific 16S ribosomal RNA is increasingly clear, and highlights the possibility that protective or harmful bacteria may be overlooked where microbiological methods are selective. There are now strong signals of the existence of a "core" urinary microbiome for the human urinary tract, particularly emerging with ageing. The consensus reviewed the potential relationship between a patient's microbiome and lower urinary tract dysfunction, whether low-count bacteriuria may be clinically significant and mechanisms which could associate micro-organisms with lower urinary tract symptoms. Key research priorities identified include the need to establish the scope of microbiome across the range of normality and clinical presentations, and gain consensus on testing protocols. Proteomics to study enzymatic and other functions may be necessary, since different bacteria may have overlapping phenotype. Longitudinal studies into risk factors for exposure, cumulative risk, and emergence of disease need to be undertaken.

GUIDELINES AND DIAGNOSTIC CRITERIA

SYSTEMATIC REVIEW OF ORAL THERAPY FOR THE TREATMENT OF SYMPTOMS OF BLADDER PAIN SYNDROME: THE BRAZILIAN GUIDELINES.

Santos TGD, Miranda IAS, Nygaard CC, Schreiner L, Castro RA, Haddad JM. Rev Bras Ginecol Obstet. 2017 Dec 14. doi: 10.1055/s-0037-1609049. [Epub ahead of print] PMID: 29241263

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Interstitial cystitis (IC), including bladder pain syndrome (BPS), is a chronic and debilitating disease that mainly affects women. It is characterized by pelvic pain associated with urinary urgency, frequency, nocturia and negative urine culture, with normal cytology. In 2009, the Society for Urodynamics and Female Urology (SUFU) defined the term IC/BPS as "an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than 6 weeks duration, in the absence of infection or other identifiable causes." This is the definition used by the American Urological Association (AUA) in the most recent guidelines on IC/BPS. Interstitial cystitis may be sufficiently severe to have a devastating effect on the quality of life, but it may also be associated with moderate symptoms whose effects are less debilitating. Although there are several clinical trials to assess oral and intravesical therapies, the treatment for IC remains far from ideal. This systematic assessment evaluates published randomized clinical trials on oral medications used to treat symptoms of BPS. This study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) method. Two independent reviewers screened the studies to determine their inclusion or exclusion and to perform the methodological analysis. The inclusion criteria included randomized studies published between April of 1988 and April of 2016 that used oral medications to treat symptoms of BPS or IC. According to the systematic review performed, we should consider pentosan polysulfate as one of the best options of oral drugs for the treatment of BPS symptoms. However, this drug is not an available option in Brazil. Orally administered amitriptyline is an efficacious medical treatment for BPS, and it should be the first treatment offered.

KETAMINE CYSTITIS

THE IMMUNOMODULATORY IMBALANCE IN PATIENTS WITH KETAMINE CYSTITIS.

Fan GY, Cherng JH, Chang SJ, Poongodi R, Chang A, Wu ST, Meng E. Biomed Res Int. 2017;2017:2329868. doi: 10.1155/2017/2329868. Epub 2017 Oct 24. PMID: 29204439

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The pathogenesis of ketamine cystitis (KC) has been recently linked with immune response to patients but the same has not yet been established. This study from Taiwan aims to propose a possible immune mechanism of irreversible bladder damage caused by KC. A total of 53 KC patients and 21 healthy volunteers as controls have been retrospectively assessed. The levels of serum immunoglobulin E (IgE), IL-6, and IFN- γ of KC patients were significantly higher than those of controls, whereas the TGF- β levels of KC patients substantially reduced but the IL-2 and IL-4 levels of KC patients were comparable to those of controls. Moreover, the KC patients had significantly higher counts of T_H1, T_H2, and T_H17 cells than those of controls. The immune response of KC users may begin with the IL-6 production and differentiation of T_H17 and may be followed by alternating between high expressions of T_H1 and T_H2. The IL-6 may further suppress the T_{REG} cells which can aggravate chronic inflammation in KC patients and the imbalance in T_H17 and T_{REG} cells may involve the pathogenesis of KC. Further investigation is needed to define the role of IL-6 in T_H1/T_H2/T_H17-regulated signalling pathway in ketamine-induced cystitis.

CHANGES TO THE BLADDER EPITHELIAL BARRIER ARE ASSOCIATED WITH KETAMINE-INDUCED CYSTITIS.

Duan Q, Wu T, Yi X, Liu L2, Yan J, Lu Z. *Exp Ther Med.* 2017 Oct;14(4):2757-2762. doi: 10.3892/etm.2017.4913. Epub 2017 Aug 9. PMID: 28966667

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The aim of the present study was to investigate the changes of the bladder epithelial barrier in the pathogenesis of ketamine-induced cystitis(KIC). A total of 60 female mice were randomly allocated into control and ketamine groups, which received daily intraperitoneal injections of saline and ketamine, respectively. Micturition behavior was recorded in 2-h intervals at the end of 4, 8 and 12 weeks, and bladders were harvested for subsequent analyses. Routine hematoxylin and eosin staining was performed on the bladders and histopathological changes were analyzed using light microscopy. The distribution of zonula occludens-1 (ZO-1) protein was determined by immunohistochemical analysis. The ultrastructure of umbrella cells was observed using a transmission electron microscope (TEM). Ketamine-addicted mice exhibited a significantly increased frequency of micturitions following 8 and 12 weeks of ketamine treatment ($P<0.05$ and $P<0.01$, respectively). Suburothelial congestion and infiltration of mononuclear cells was observed in ketamine-addicted mice following 8 and 12 weeks of treatment. Immunohistochemical examination demonstrated that there was an increased abnormal distribution of ZO-1 in the bladders of ketamine-treated mice compared with control mice. TEM analysis demonstrated that the surface of bladder urothelium became flattened, the tight junctions between umbrella cells became thinner and the endothelial cells exhibited cell body shrinkage, chromatin condensation and layer denudation in mice treated with ketamine. The present study indicated that the structural and functional changes to the bladder epithelial barrier caused by long-term use of ketamine may be key mechanisms in the development of KIC.

THE EFFECTS OF RECREATIONAL KETAMINE CYSTITIS ON URINARY TRACT RECONSTRUCTION - A SURGICAL CHALLENGE.

Sihra N, Ockrim J, Wood D. *BJU Int.* 2017 Dec 12. doi: 10.1111/bju.14094. [Epub ahead of print] PMID: 29230940

The aim of this study from London was to identify the rate of post-operative complications in patients who require surgical reconstruction for ketamine-induced urinary tract dysfunction and to identify any predictors for poor post-operative outcome with subsequent management strategies. A retrospective review of data collected between 2007 and 2017 was performed. Evaluation included CT urogram, cystoscopy and biopsy. Indications and outcomes for surgical intervention were assessed. 44 patients were identified. 68% were male and mean age at presentation was 31 years (range 23-55). All bladder biopsies confirmed an eosinophilic inflammatory infiltrate. A significant proportion of patients (81.8%) were found to have reduced cystoscopic bladder capacity of <300mls. 29 patients were treated conservatively with a view to symptom resolution. 2 patients underwent dilatation for urethral strictures. 4 patients underwent repeated intra-detrusor onabotulinum toxin injection with minimal subjective symptom relief. 2 of these patients proceeded to have major reconstruction. Indications for urinary tract reconstruction included intractable symptoms, high pressure compliance loss with renal compromise and ureteric obstruction. Patients were advised to abstain from ketamine use for a minimum of six months prior to consideration of surgical intervention. 14 patients underwent major reconstruction. Surgical intervention included ileal conduit urinary diversion, augmentation cystoplasty with or without mitrofanoff channels, ureteric re-implantation and cystectomy with neobladders. Complications included anastomotic leaks, ureteric strictures, adhesional small bowel obstruction, renal failure and sepsis. In total complications occurred in 10/14 patients. It was concluded that in a tertiary high volume reconstructive unit, ketamine patients were at high risk of significant peri-operative complications. There did not appear to be any other common factor apart from their use of ketamine, and the significant inflammatory change associated with this. The authors recommend meticulous pre-operative evaluation and multidisciplinary consultation for all patients to determine optimal treatment strategies.

CHRONIC PELVIC PAIN

TREATMENT OF CHRONIC REFRACTORY NEUROPATHIC PELVIC PAIN WITH HIGH FREQUENCY 10 KILOHERTZ SPINAL CORD STIMULATION.

Simopoulos T, Yong J, Gill JS. *Pain Pract.* 2017 Nov 6. doi: 10.1111/papr.12656. [Epub ahead of print] PMID: 29106051

Chronic non-malignant pain perceived in the pelvic region commonly presents as a diagnostic challenge and is often difficult to manage. Treatment options are delayed as well as limited. The prevalence in the United States and the United Kingdom has been estimated to range from 14.7 % to 24% respectively. Common chronic pelvic

pain syndromes include interstitial cystitis, chronic prostatitis, coccygodynia, vulvodynia, chronic proctalgia, and pudendal neuralgia.

CHRONIC PELVIC PAIN IN AN INTERDISCIPLINARY SETTING: 1-YEAR PROSPECTIVE COHORT.

Allaire C, Williams C, Bodmer-Roy S, Zhu S, Arion K, Ambacher K, Wu J, Yosef A, Wong F, Noga H, Britnell S, Yager H, Bedaiwy MA, Albert AY, Lisonkova S, Yong PJ. *Am J Obstet Gynecol.* 2018 Jan;218(1):114.e1-114.e12. doi: 10.1016/j.ajog.2017.10.002. Epub 2017 Oct 12. PMID: 29031895

Allaire and colleagues from Canada note that chronic pelvic pain affects some 15% of women, and presents a challenging problem for gynecologists due to its complex etiology involving multiple comorbidities. An interdisciplinary approach has therefore been proposed for chronic pelvic pain, where these multifactorial comorbidities can be addressed by different interventions at a single integrated centre. While cross-sectional studies can provide some insight into the association between these comorbidities and chronic pelvic pain severity, prospective longitudinal cohorts can identify comorbidities associated with changes in chronic pelvic pain severity over time. The authors sought to describe trends and factors associated with chronic pelvic pain severity over a 1-year prospective cohort at an interdisciplinary centre, with a focus on the role of comorbidities and controlling for baseline pain, demographic factors, and treatment effects. This was a prospective 1-year cohort study at an interdisciplinary tertiary referral centre for pelvic pain and endometriosis, which provides minimally invasive surgery, medical management, pain education, physiotherapy, and psychological therapies. Exclusion criteria included menopause or age >50 years. Sample size was 296 (57% response rate at 1 year; 296/525). Primary outcome was chronic pelvic pain severity at 1 year on an 11-point numeric rating scale (0-10), which was categorized for ordinal regression (none-mild 0-3, moderate 4-6, severe 7-10). Secondary outcomes included functional quality of life and health utilization. Baseline comorbidities were endometriosis, irritable bowel syndrome, painful bladder syndrome, abdominal wall pain, pelvic floor myalgia, and validated questionnaires for depression, anxiety, and catastrophizing. Multivariable ordinal regression was used to identify baseline comorbidities associated with the primary outcome at 1 year. Improvements in chronic pelvic pain severity, quality of life, and health care utilization were observed in a 1-year cohort in an interdisciplinary setting. Higher pain catastrophizing at baseline was associated with greater chronic pelvic pain severity at 1 year. Consideration should be given to stratifying pelvic pain patients by catastrophizing level (rumination, magnification, helplessness) in research studies and in clinical practice.

IRRITABLE BOWEL SYNDROME

THE GUT-BRAIN AXIS AND THE MICROBIOME: CLUES TO PATHOPHYSIOLOGY AND OPPORTUNITIES FOR NOVEL MANAGEMENT STRATEGIES IN IRRITABLE BOWEL SYNDROME (IBS).

Quigley EMM. *J Clin Med.* 2018 Jan 3;7(1). pii: E6. doi: 10.3390/jcm7010006. PMID: 29301380

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Irritable bowel syndrome (IBS) is one of the most common of all medical disorders worldwide and, while for some it represents no more than a nuisance, for others it imposes significant negative impacts on daily life and activities. IBS is a heterogeneous disorder and may well have a number of causes which may lie anywhere from the external environment to the contents of the gut lumen and from the enteric neuromuscular apparatus and the gut immune system to the central nervous system. Consequently, the paradigm of the gut-brain axis, which includes the participation of these various factors, has proven a useful model to assist clinicians and patients alike in understanding the genesis of symptoms in IBS. Now, given the widespread interest in the gut microbiome in health and disease, in general, reports of disordered enteric bacterial communities in IBS, and experimental data to indicate that components of the gut microbiota can influence brain morphology and function, as well as behavior and cognition, this concept has been extended to encompass the microbiota-gut-brain axis. The implications of this novel concept to the assessment and management of IBS are explored in this review.

AAPT DIAGNOSTIC CRITERIA FOR CHRONIC ABDOMINAL, PELVIC, AND UROGENITAL PAIN: IRRITABLE BOWEL SYNDROME.

Zhou Q, Wesselmann U, Walker L, Lee L, Zeltzer L, Verne GN. *J Pain.* 2017 Oct 24. pii: S1526-5900(17)30737-X. doi: 10.1016/j.jpain.2017.10.002. [Epub ahead of print] PMID: 29079542

In conjunction with the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the US Food and Drug Administration and the American Pain Society (APS), the ACTTION-APS Pain Taxonomy (AAPT) initiative strove to develop the characteristics of a diagnostic system useful for clinical and research purposes across disciplines and types of chronic pain conditions. Following the establishment of these characteristics, a working group of clinicians and

clinical and basic scientists with expertise in abdominal, pelvic, and urogenital pain began generating core diagnostic criteria and defining the related extraintestinal somatic pain and other symptoms experienced by patients. Systematic diagnostic criteria for several common abdominal, pelvic, and urogenital pain conditions are in development. Here, they present the proposed AAPT criteria for irritable bowel syndrome (IBS), the most common chronic, non-cancer abdominal pain condition. A systematic review and synthesis was conducted to complement the Rome IV Diagnostic Criteria for IBS. Future efforts will subject these proposed AAPT criteria to systematic empirical evaluation of their feasibility, reliability, and validity. The AAPT IBS criteria are part of an evidence-based classification system that provides a consistent vocabulary regarding diagnostic criteria, common features, co-morbidities, consequences, and putative mechanisms of the disorder. A similar approach is being applied to other chronic and often debilitating abdominal, pelvic, and urogenital pain conditions.

CROSS-ORGAN SENSITISATION

CROSS-ORGAN SENSITISATION BETWEEN THE COLON AND BLADDER: TO PEE, OR NOT TO PEE?

Grundy L, Brierley SM. *Am J Physiol Gastrointest Liver Physiol.* 2017 Nov 16;ajpgi.00272.2017. doi: 10.1152/ajpgi.00272.2017. [Epub ahead of print] PMID: 29146678

Chronic abdominal and pelvic pain are common, debilitating clinical conditions experienced by millions of patients around the globe. The origin of such pain commonly arises from the intestine and bladder, which share common primary roles; the collection, storage and expulsion of waste. These visceral organs are located in close proximity to one another, and also share common innervation from spinal afferent pathways. Chronic abdominal pain, constipation or diarrhoea are primary symptoms for patients with Irritable Bowel Syndrome (IBS) or Inflammatory Bowel Disease (IBD). Chronic pelvic pain, urinary urgency and frequency are primary symptoms experienced by patients with lower urinary tract disorders such as interstitial cystitis/painful bladder syndrome (IC/PBS). It is becoming clear that these symptoms and clinical entities do not occur in isolation, with considerable overlap in symptom profiles across patient cohorts. Here Grundy and Brierley from Australia review recent clinical and experimental evidence documenting the existence of 'cross-organ sensitisation' between the colon and bladder. In such circumstances, colonic inflammation may result in profound changes to the sensory pathways innervating the bladder, resulting in severe bladder dysfunction.

ENDOMETRIOSIS

DIAGNOSTIC AND TREATMENT GUIDELINES FOR GASTROINTESTINAL AND GENITOURINARY ENDOMETRIOSIS.

Young S, Burns MK, DiFrancesco L, Nezhat A, Nezhat C. *J Turk Ger Gynecol Assoc.* 2017 Dec 15;18(4):200-209. doi: 10.4274/jtgga.2017.0143. PMID: 29278234

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Endometriosis is commonly misdiagnosed, even among many experienced gynecologists. Gastrointestinal and genitourinary endometriosis is particularly difficult to diagnose, and is commonly mistaken for other pathologies, such as irritable bowel syndrome, interstitial cystitis, and even psychological disturbances. This leads to delays in diagnosis, mismanagement, and unnecessary testing. In this review, Young and colleagues discuss the diagnosis and management of genitourinary and gastrointestinal endometriosis. Medical management may be tried first, but often fails in cases of urinary tract endometriosis. This is particularly important in cases of ureteral endometriosis because silent obstruction can lead to eventual kidney failure. The authors therefore recommend complete surgical treatment in these cases. Bladder endometriosis may be managed more conservatively, and only if symptomatic, because these rarely lead to significant morbidity. In cases of bowel endometriosis, they recommend medical management first in all cases, and the least invasive surgical management only if medical treatment fails. This is due to the extensive nervous and vasculature supply to the lower rectum. Injury to these nerves and vessels can cause significant complications and postoperative morbidity.

ENDOMETRIOSIS INCREASED THE RISK OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A POPULATION-BASED STUDY.

Wu CC, Chung SD, Lin HC. *Neurourol Urodyn.* 2018 Jan 10. doi: 10.1002/nau.23462. [Epub ahead of print] PMID: 29318645

Previous studies have suggested an association between bladder pain syndrome/interstitial cystitis (BPS/IC) and endometriosis. However, no nation-wide population study has yet reported an association between them. In this study from Taiwan, Wu and colleagues examined the risk of BPS/IC among subjects with endometriosis during a 3-year follow-up in Taiwan using a population-based dataset. This study comprised 9191 subjects with

endometriosis, and 27 573 subjects randomly selected as controls. The authors individually followed-up each subject (n = 36 764) for a 3-year period to identify subjects subsequently diagnosed with BPS/IC. A Cox proportional hazards regression model was employed to estimate the risk of subsequent BPS/IC following a diagnosis of endometriosis. Incidences of BPS/IC during the 3-year follow-up period was 0.2% and 0.05% for subjects with and without endometriosis, respectively. The hazard ratio for developing BPS/IC over a 3-year period for subjects with endometriosis compared to subjects without endometriosis was 4.43 (95% CI: 2.13-9.23). After adjusting for co-morbidities like diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraines, sicca syndrome, allergies, endometriosis, asthma, tobacco use, and alcohol abuse, the Cox proportional hazards regressions revealed that the hazard ratio for BPS/IC among subjects with endometriosis was 3.74 compared to that in controls. The authors are of the opinions that this study provides epidemiological evidence of an association between endometriosis and a subsequent diagnosis of BPS/IC.

VULVODYNIA/VULVAL PAIN SYNDROME

THE VULVAR PAIN ASSESSMENT QUESTIONNAIRE: FACTOR STRUCTURE, PRELIMINARY NORMS, INTERNAL CONSISTENCY, AND TEST-RETEST RELIABILITY.

Dargie E, Holden RR, Pukall CF. J Sex Med. 2017 Dec;14(12):1585-1596. doi: 10.1016/j.jsxm.2017.10.072. PMID: 29198513

The Vulvar Pain Assessment Questionnaire (VPAQ) was developed to assist in the assessment and diagnosis of chronic vulvar pain (vulvodynia). The purpose of this study from Canada was to further establish the psychometric properties of the VPAQ by examining factor structure, test-retest reliability, internal consistency, and scale normative data, and to gather feedback from those with vulvar pain about the usefulness and accessibility of the questionnaire. 182 participants completed a confidential online study and 70 participated again at time 2 (4 weeks later). Participants were asked to complete the full VPAQ, which assesses pain characteristics, effects on various parts of their lives, coping strategies used, and romantic partner factors. Additional questions captured sociodemographics and feedback about the instrument. Approximately half the participants reported an increase in their comfort level in discussing a range of topics after completing the VPAQ. Most participants reported that the length, readability, and range of VPAQ questions were "good" or "excellent." This study established the psychometric properties of the VPAQ scales using multiple methods at 2 time points and gathered feedback from participants. However, data were collected online so diagnoses could not be confirmed and more than half the initial sample did not complete the survey at time 2. The results of this study suggest that most VPAQ subscales (except the coping subscale) have moderate to strong psychometric properties and that the VPAQ is user friendly.

FIBROMYALGIA

DELAYED-TYPE HYPERSENSITIVITY TO METALS IN CONNECTIVE TISSUE DISEASES AND FIBROMYALGIA.

Bjørklund G, Dadar M, Aaseth J. Environ Res. 2018 Feb;161:573-579. doi: 10.1016/j.envres.2017.12.004. PMID: 29245125

Rheumatic diseases include a group of autoimmune disorders with environmental and genetic etiology that are characterized as a subgroup of connective tissue diseases (CTD). Rheumatoid arthritis (RA) often involves the small joints of the hands in a symmetrical fashion that can lead to loss of joint function, and RA, as well as Sjögren's syndrome (SS) and other rheumatic diseases, are often accompanied by sensitivity to metals. Numerous investigations on metal sensitivity were evaluated in this review. A detailed metal exposure history was collected by different evaluation of studies. In all subjects, the main source of metal exposure was nickel, mercury, gold, palladium, titanium, and chromium. All of SLE (systemic lupus erythematosus), RA and SS patients appeared to have an increased frequency of metal delayed-type hypersensitivity (DTH) (Type IV allergy). As dental restorative materials release minor amounts of their metals (including mercury, gold, and nickel), many adults are commonly exposed to these metal ions by vapor or corrosion into saliva. Metal-related DTH in these patients will induce an inflammatory response. Such inflammations are important factors in CTD progress. It is hypothesized that metal-specific T cell reactivity can act as an etiological agent in the propagation and chronification of rheumatic inflammation. The key responses of metal delayed-type hypersensitivity in autoimmunity are precipitating as an appealing challenge for further investigations.

SLEEP PROBLEMS

CHRONIC EXPOSURE TO INSUFFICIENT SLEEP ALTERS PROCESSES OF PAIN HABITUATION AND SENSITIZATION

Simpson NS, Scott-Sutherland J, Gautam S, Sethna N, Haack M. Pain. 2017 Sep 1. doi: 10.1097/j.pain.0000000000001053. [Epub ahead of print] PMID: 28891869

Simpson and colleagues from the USA report that chronic pain conditions are highly co-morbid with insufficient sleep. While the mechanistic relationships between the two are not understood, chronic insufficient sleep may be one pathway through which central pain-modulatory circuits deteriorate, thereby contributing to chronic pain vulnerability over time. To test this hypothesis, an in-laboratory model of three weeks of restricted sleep with limited recovery (five nights of 4-hour sleep/night followed by two nights of 8-hour sleep/night) was compared to three weeks of 8-hour sleep/night (control protocol). Seventeen healthy adults participated, with fourteen completing both three-week protocols. Measures of spontaneous pain, heat-pain thresholds, cold-pain tolerance (measuring habituation to cold over several weeks), and temporal summation of pain (examining the slope of pain ratings during cold water immersion) were assessed at multiple points during each protocol. Compared to the control protocol, participants in the sleep-restriction/recovery protocol experienced mild increases in spontaneous pain. Heat-pain thresholds decreased following the first week of sleep restriction, but normalized with longer exposure to sleep restriction. In contrast, chronic exposure to restricted sleep was associated with decreased habituation to, and increased temporal summation in response to cold pain, although only in the last two weeks of the sleep restriction protocol. These changes may reflect abnormalities in central pain-modulatory processes. Limited recovery sleep did not completely resolve these alterations in pain-modulatory processes, indicating that more extensive recovery sleep is required. Results suggest that exposure to chronic insufficient sleep may increase vulnerability to chronic pain by altering processes of pain habituation and sensitization.

SJOGREN'S SYNDROME

VITAMIN D AND SJÖGREN SYNDROME.

García-Carrasco M, Jiménez-Herrera EA, Gálvez-Romero JL, de Lara LV, Mendoza-Pinto C, Etchegaray-Morales I, Munguía-Realpozo P, Ruíz-Argüelles A, Jose R, Vera-Recabarren M, Cervera R. Autoimmun Rev. 2017 Jun;16(6):587-593. doi: 10.1016/j.autrev.2017.04.004. Epub 2017 Apr 12. PMID: 28411165

The immunomodulatory effects of vitamin D have been extensively studied in the context of autoimmunity. Multiple studies have demonstrated a high prevalence of vitamin D deficiency in autoimmune diseases. Recently, a possible protective role of vitamin D in autoimmunity has been described; however, this function remains controversial. Few studies have investigated the role of vitamin D in patients with Sjögren syndrome (SS). In this review, García-Carrasco and colleagues compiled the main features of SS pathogenesis, the vitamin D immunomodulatory effects and the possible interaction between both. Data suggests that vitamin D may play a role in the SS pathogenesis. In addition, vitamin D low levels have been found in SS patients, which are associated with extra-glandular manifestations, such as lymphoma or neuropathy, suggesting a possible benefit effect of vitamin D in SS.

A QUALITATIVE EXPLORATION OF PHYSICAL, MENTAL AND OCULAR FATIGUE IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME.

Stack RJ, Southworth S, Fisher BA, Barone F, Buckley CD, Rauz S, Bowman SJ. PLoS One. 2017 Oct 31;12(10):e0187272. doi: 10.1371/journal.pone.0187272. eCollection 2017. PMID: 29088284

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Primary Sjögren's Syndrome (pSS) affects exocrine glands such as those producing the tear film, leading to dry and painful eyes, but is also associated with fatigue. The experience of fatigue in pSS, and its relationship with sicca symptoms, is poorly understood. Twenty people diagnosed with pSS were recruited to participate in a semi-structured qualitative interview about their symptoms experience. Interviews were audio-recorded, transcribed verbatim and analysed using thematic analysis. People with pSS described physical tiredness, mental fatigue and ocular fatigue. Mental fatigue was characterised by difficulties in attention, particularly, the ability to follow conversations and short-term memory problems. Participants linked their experience of fatigue to feeling of depression, frustration, irritation and anxiety, and therefore, fatigue was suggested to have had a large impact on their psychological well-being. People with pSS also described a range of ocular symptoms including pain, dryness, and itching, which were compounded by fatigue. For some, eye fatigue was pervasive, and daily activities involving the eyes such as reading, using the computer and driving were impaired. In some cases, the level of ocular discomfort was so severe it prevented sleep, which in turn impacted on general fatigue levels. People with pSS experience fatigue in a range of ways; physical, mental and ocular fatigue were described.

Fatigue was suggested to exacerbate other ocular symptoms, posed serious physical limitations and caused psychological distress. Further research into the nature of fatigue and ocular symptoms in pSS is required.

E-HEALTH

[DESIGNING A MOBILE HEALTH APPLICATION PROTOTYPE FOR THE MANAGEMENT OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.](#)

Griffith J. Stud Health Technol Inform. 2017;245:94-97. PMID: 29295059

The design of an early mobile health application (app) prototype to manage interstitial cystitis/painful bladder syndrome, a chronic condition characterized by recurrent pain/discomfort in the bladder and pelvic floor, is described. The purpose of this app prototype is to help people who have IC/PBS manage and learn what triggers their symptoms. Another aim of this research was to provide an example of how sex and gender could be included into the design of a health information system. Based on a literature search of common symptoms and challenges faced by people living with IC/PBS, the researcher created an app prototype design including many features: resources for relaxation, mental health, intimacy, pregnancy, and daily life; reminders for appointments, and medication; logs for diet, activity, sleep, pain, menstruation; and a link to a public washroom locator. This prototype will later undergo usability and content evaluation.

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