

International Painful Bladder Foundation

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

IPBF e-Newsletter and Research Update

Issue 30, July 2012

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

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

- Review of Convergences PP
- Review of SIP 2012
- Pain Alliance Europe
- Review of ESSIC Annual Meeting 2012
- Review of Sensory Bladder Meeting
- Upcoming Meetings: 14th World Congress on Pain/PUGO Meeting on Treating Chronic Pelvic Pain, International Continence Society, ESSIC 2013, 1st World Congress on Pelvic Pain 2013
- Useful Websites
- Update on therapies in the experimental pipeline
- Research Highlights
- Donations & Sponsoring

MEETING REVIEWS

CONVERGENCES PP - CONVERGENCES IN PELVIPERINEAL PAIN

The Convergences PP meeting was held this year 26-28 April in the historic town of Nîmes in France, with its remarkable ancient Roman arena, aqueduct and the remains of baths and temples with beautiful mosaics. Since this meeting coincided with the Nîmes "Roman Games" festival, delegates were treated to the amazing sight of battalions of Roman soldiers marching past the windows of the conference venue!! Delegates came from around the world, including the USA, Canada, Australia, Brazil, Chile as well as Europe. A number of patient advocates representing different organisations from Europe in the field of pelvic pain also attended, including many IC patient support groups, and a patient workshop was held on the role of patient associations. Convergences PP is a federative meeting on pelviperineal pain with expert speakers in this field from around the world. The concept was launched in Nantes a few years ago and the term "pelviperineal" originated here. For detailed information about the 2012 Convergences PP programme, go to: <http://www.convergencespp.com/CPPbrochureBD.pdf>.

Webcasts can be found at:

<http://www.sifud-pp.org/congres/convergences-pp/2012/index.phtml> on the website of SIFUD PP (Société Interdisciplinaire Francophone d'UroDynamique et de Pelvi Péritéologie). Some of these webcast presentations are spoken in French with English slides, some entirely in French and some entirely in English. This year, many of the presentations revolved around central sensitisation and aspects of hypersensitivity, particularly pelvic and bladder hypersensitivity, with and without pain, including presentations on myofascial pain syndromes, triggerpoints, vulval pain, gastrointestinal pain and an interesting presentation by Dr J.J. Labat (Nantes) on how to define a **consensus on clinical criteria** to identify hypersensitisation in chronic pelviperineal pain syndromes. He also explained the French proposals regarding bladder and pelvic hypersensitivity. This interesting presentation was entirely in French. However, the concepts were presented at the Sensory Bladder Meeting in English and are detailed in our review of the Annecy meeting ([click here](#)). The French hypersensitivity proposal distinguishes between: non-painful visceral hypersensitivity, painful visceral hypersensitivity, painful pelvic hypersensitivity. A team of experts is currently working on definitions and criteria.

SIP 2012, 3RD SOCIETAL IMPACT OF PAIN SYMPOSIUM

Over four hundred people from more than 30 countries attended the SIP 2012, 3rd Societal Impact of Pain Symposium at the ultra-modern, twin tower Bella Sky hotel and conference centre in Copenhagen, 29-31 May 2012. It was a truly multi-stakeholder meeting, with doctors from many disciplines dealing with chronic pain patients, health authorities, European Parliament, EU Commission DG Sanco, pharmaceutical industry and last but certainly not least representatives from many patient organisations focused on pain or diseases and conditions causing chronic pain, all with the aim of raising awareness on the societal impact of pain, exchanging national best practices and fostering European and national pain care policy projects. Jane Meijlink (IPBF) and Francoise Watel (AFCI France) were there to represent the IC patients.

The Societal Impact of Pain (SIP) is an international, multi-stakeholder platform created in 2010 and aims to:

- Raise awareness of the relevance of the impact that pain has on our societies, health and economic systems
- Exchange information and share best practices across all member states of the European Union
- Develop and foster European-wide policy strategies and activities for an improved pain care in Europe.

The platform provides opportunities for discussion for healthcare professionals, pain advocacy groups, politicians, insurance companies, representatives of health authorities, regulators and budget holders. Further information can be found at <http://www.sip-platform.eu/announcement-kopie.html>

The new Pain Alliance Europe (President: Joop van Griensven, website: <http://www.pae-eu.eu>) took advantage of the opportunity to hold a general assembly of its members immediately prior to the start of the symposium in Denmark. The PAE enjoyed a high profile at this SIP symposium, with Joop van Griensven playing a leading role on many session panels. He and other PAE members, together with representatives from other patient organisations including the Danish FAKS, gave presentations on the patient perspective.

A review of this meeting by the IPBF is available at:

http://www.painful-bladder.org/pdf/2012_SIP_Copenhagen.pdf

PAIN ALLIANCE EUROPE (PAE)

Pain Alliance Europe (PAE), President Joop van Griensven, is a relatively new European patient umbrella organisation, launched at the European Parliament on 29 November 2011, which was set up to improve the quality of life of people living with chronic pain in Europe and with the aim of promoting awareness of chronic pain, promoting European policy on chronic pain and reducing the impact of chronic pain on European society. It aims to achieve this by working closely with all other stakeholders, by gathering and distributing information on chronic pain from the patient point of view and by promoting or initiating research into chronic pain.

Contact information: info@pae-eu.eu, <http://www.pae-eu.eu>

ESSIC ANNUAL MEETING 2012

This year, the ESSIC Annual Meeting was held 10-12 May at the HF Ipanema Park Hotel in the beautiful old city of Porto in Portugal and many congratulations are due to Dr Paulo Dinis Oliveira for the excellent organisation of this international meeting. Delegates (who included several patient advocates representing the IPBF, the Italian AICI and the Portuguese ADDB) came not only from European countries, but also from further afield including the USA, India and Japan. The meeting followed the standard ESSIC format of two days of conference followed by an educational course day devoted to diagnosis and treatment. Plenty of time was allowed for discussion and many different viewpoints were raised. The focus of this year's meeting was "pain" which was particularly appropriate since Portugal was in fact the first country to hold a National Pain Day in 1999.

Another area of attention was the issue of international harmonisation of terminology and definitions for which plenty of time was allowed for discussion. This aspect is reviewed in detail in the IPBF report on this meeting: http://www.painful-bladder.org/pdf/2012_ESSIC_Porto.pdf

The meeting also included a patient session comprising presentations by two patient advocates. Jane Meijlink from the Netherlands (IPBF) looked at pain from a patient perspective, noting that our perception of pain and how we interpret it evolves from birth and may depend on many different factors: our country and culture, social background, family environment, upbringing, character, temperament, experiences in early life, and even religious upbringing. Loredana Nasta from Italy (Italian IC Patient Association AICI and the Italian Rare Disease Foundation UNIAMO) presented an excellent overview of the results of a 2 year study conducted from 2009 to

2012 aimed at quantifying the socio-economic costs and healthcare needs of people affected by IC/BPS, including the families, analysing the services and assessing the impact of the disease on society in terms of costs and quality of life.

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SENSORY BLADDER MEETING

Around 95 expert speakers and participants from 13 different countries gathered in the breathtakingly beautiful setting of Les Pensières on the bank of Lake Annecy in France, against a picturesque backdrop of snow-capped Alps, to discuss many different aspects of the Sensory Bladder during a multidisciplinary meeting organised by Professors G. Amarenco and E. Chartier-Kastler. Honorary President of this special meeting was Professor Clare Fowler. The meeting with 25 speakers focused on sensory disorders and the urinary bladder, from anatomy to therapeutic strategies, including the latest information on imaging of the brain and generated a huge amount of information. The organisers are to be congratulated for this welcome and useful initiative which enabled all participants to obtain a more complete picture of the sensory bladder.

Since the meeting language was English only, this international event provided a unique opportunity for particularly French research and ideas to reach a wider audience, instead of being published exclusively in the French language as is so often the case. Our review gives a brief look at aspects of particular interest in our field: http://www.painful-bladder.org/pdf/2012_SBM_Veyrier%20du%20Lac.pdf

The presentations on the first day will be available as webcasts on the SIFUD PP website: <http://www.sifud-pp.org> and hopefully an official review will also be published in due course.
The programme and abstracts book of this meeting are still available on: <http://sbm2012.jimdo.com>.

UPCOMING MEETINGS

Reminder - Registration fees are often too high for patient volunteers

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

14TH WORLD CONGRESS ON PAIN, MILAN CONVENTION CENTRE, MILAN, ITALY, 27-31 AUGUST, 2012 WITH SYMPOSIUM ON TAKING CARE OF THE PATIENT WITH CHRONIC PELVIC PAIN, SUNDAY 26 AUGUST.

"Taking Care of the Patient with Chronic Pelvic Pain" is an official satellite symposium of the 14th World Congress on Pain, organised by the International Association for the Study of Pain www.iasp-pain.org, to be held in Milan Convention Centre, 27-31 August. This symposium is organised by Pain of UroGenital Origin (PUGO), a special interest group of the IASP

42ND ANNUAL SCIENTIFIC MEETING OF THE INTERNATIONAL CONTINENCE SOCIETY (ICS)

15-19 OCTOBER 2012 BEIJING, CHINA

This year, the annual scientific meeting of the ICS will be held at the China National Convention Center in Beijing. The meeting website with all information is at: www.ics-meeting.com. The scientific programme can be found at: <http://www.icsoffice.org/Abstracts/Publish/134/ScientificProgramme.pdf> and this includes the workshops with several related to IC. The meeting this year also includes a state of the art lecture on Sexual Implications of Chronic Pelvic Pain by Professor Kristene E Whitmore (United States) which promises to be very interesting.

ESSIC ANNUAL MEETING 21-23 MARCH 2013, KYOTO, JAPAN

The ESSIC Annual Meeting 2013 will be held in Kyoto, Japan, 21-23 March 2013. The meeting will be a joint meeting with the Japanese ICICJ. Further information will be made available on the ESSIC website www.essic.eu in due course.

1ST WORLD CONGRESS ON PELVIC PAIN, 30 MAY-1 JUNE 2013 BEURS VAN BERLAGE, AMSTERDAM, THE NETHERLANDS

This 1st World Congress on Pelvic Pain in 2013 will be jointly organised by Pain of UroGenital Origin of the IASP (PUGO), the International Pelvic Pain Society (IPPS) and Convergences Pelviperineal (ConPP). The programme will include: terminology, taxonomy and phenotyping; guidelines on diagnostics and treatment; pain management team; pain after surgery; male chronic pelvic pain; female chronic pelvic pain; myofascial aspects; psychology and sexology; neurology and nerve involvement; new developments in pain research. Apart from sharing high quality information, it is hoped that this multidisciplinary meeting will contribute towards raising further awareness and increase knowledge about all aspects of pelvic pain.

Further information:

www.pelvicpain-meeting.com. Abstract submission starts 1 September 2012, deadline 15 January 2013.

USEFUL WEBSITES

AUA Guideline on OAB

The American Urological Association (AUA) has published a guideline on overactive bladder (OAB). You can find this at: http://www.auanet.org/content/media/OAB_guideline.pdf. It forms a useful companion to the AUA guideline on IC/BPS.

SIFUD PP for French-speakers

SIFUD PP (Société Interdisciplinaire Francophone d'UroDynamique et de Pelvi Périnéologie or Interdisciplinary Society for Urodynamics and Pelvi-Perineology for French speakers) is a scientific society created in 1977 with the objective of promoting pelvi-perineology among the different disciplines involved. There are many webcasts of conferences for French speakers. Also patient information in French on various topics.

If you speak French, useful to keep an eye on this website: <http://www.sifud-pp.org/>

Health Organization for Pudendal Education

<http://www.pudendalhope.info/node/2>

Many patients contact us for information about the pudendal nerve. Run by patients, this website offers a wealth of information in this field with latest literature and research.

The European Federation of IASP Chapters (EFIC)

The European Federation of IASP Chapters (EFIC) is a multidisciplinary professional organisation in the field of pain research and medicine, consisting of the 36 chapters of the International Association for the Study of Pain (IASP), which are the IASP approved official National Pain Societies in each country. Established in 1993, EFIC's constituent chapters represent Pain Societies from 36 European countries and close to 20,000 physicians, basic researchers, nurses, physiotherapists, psychologists and other healthcare professionals across Europe, who are involved in pain management and pain research. <http://www.efic.org>

Works closely with Pain Alliance Europe: <http://www.pae-eu.eu>

Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

<http://www.mappnetwork.org>

A reminder of the website for the NIDDK's Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. This project embraces a systemic—or whole-body—approach in the study of IC/PBS and CP/CPPS. In addition to moving beyond traditional bladder- and prostate-specific research directions, MAPP Network scientists are investigating potential relationships between these two urological syndromes and other chronic conditions that are sometimes seen in IC/PBS and CP/CPPS patients, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. Keep an eye on developments on this website.

UPDATE ON THERAPIES IN THE EXPERIMENTAL PIPELINE

There are a number of potential new therapies for IC currently undergoing trials. We would, however, like to emphasise that the process of trialling a new form of treatment takes many years and goes through many stages. This means that the fact that something is being trialled now does not mean that it will be available next year! It can take many years to develop a new therapy. Furthermore, trials for new therapies are sometimes halted for safety reasons, or because a treatment that appears to be successful in a rat or mouse

proves to be unsuccessful in a human being. We have seen this kind of thing happen to a number of potential therapies for IC in recent years.

Information on trials can be found on the website: <http://clinicaltrials.gov>

In Europe: <http://www.ema.europa.eu/ema/>

Direct link to the European clinical trials register: <https://www.clinicaltrialsregister.eu>

If you would like to know more about how trials are carried out, go to:

<http://www.nih.gov/health/clinicaltrials/basics.htm>

TTI 1612

TTI-1612 is a recombinant soluble form of heparin-binding epidermal growth factor-like growth factor (HB-EGF). It is being developed as a treatment for interstitial cystitis (IC), a chronic bladder disease characterized by low urinary HB-EGF levels and a dysfunctional, "leaky" bladder epithelium. TTI-1612 stimulates the proliferation of bladder epithelial cells and reduces their permeability. TTI-1612 is designed to target the root cause of IC – dysfunction of the bladder urothelium caused by low levels of HB-EGF. TTI-1612 is also being developed for the prevention of necrotizing enterocolitis (NEC), a life-threatening intestinal disorder that occurs predominantly in premature infants. Studies have demonstrated that oral administration of recombinant HB-EGF significantly reduces the incidence and severity of NEC in a rat model. There is clear evidence in this system the HB-EGF restores gut barrier function and promotes the proliferation and migration of intestinal epithelial cells.

Reference: <http://www.trilliumtherapeutics.com/pipeline.html>.

For trial information, go to <http://clinicaltrials.gov/ct2/show/NCT01559961>: A Phase I Dose Escalation Study of the Safety and Pharmacokinetics of Single Intravesical Doses of TTI-1612 in Women with Interstitial Cystitis/Bladder Pain Syndrome.

LiRIS® - Lidocaine-releasing intravesical system

This is a drug delivery system that is inserted into the bladder via cystoscopy, remains in the bladder for up to 2 weeks releasing lidocaine over a 2 week period and is then removed again via cystoscopy. The purpose of this study is to determine if LiRIS® is safe, tolerable and effective in women with Interstitial Cystitis. TARIS has initiated a Phase 1B clinical study to evaluate the safety and tolerability of LiRIS in patients suffering from moderate-to-severe IC.

For trial information go to:

<http://www.clinicaltrials.gov/ct2/show/NCT01475253?term=NCT01475253.&rank=1>

For information from the company: http://www.tarisbiomedical.com/bladder_overview.php

Adalimumab

This study is evaluating the drug adalimumab (Humira®) for improving the symptoms of patients with interstitial cystitis. Humira® is an injectable anti-inflammatory medication that has been available for use since December 31, 2002. Humira® has been FDA approved for the treatment of rheumatoid arthritis, psoriasis, ankylosing spondylitis, and Crohn's disease. These diseases have similar characteristics to interstitial cystitis. This study will evaluate an investigational use of Humira® for the treatment of interstitial cystitis.

Trial information: <http://clinicaltrials.gov/ct2/show/NCT01295814>

Registration for trial: <http://www.icstudy.net/Pages/default.aspx>

Information about Humira: <http://www.humira.com/>

RESEARCH HIGHLIGHTS

A REVIEW OF SELECTED RECENT SCIENTIFIC LITERATURE ON INTERSTITIAL CYSTITIS AND RELATED DISORDERS

A continually updated selection of new scientific literature can be found on our website: <http://www.painful-bladder.org/pubmed.html>. Most of these have a direct link to the PubMed abstract if you click on the title. An increasing number of scientific articles "In Press" or "Early View" are being published early online (on the Journal website) as "Epub ahead of print" sometimes long before they are published in the journals. While abstracts are usually available on PubMed, the pre-publication articles can only be read online if you have

online access to that specific journal. However, in some cases there may be free access to the full article online. Click on the title to go to the PubMed abstract or to the full article in the case of free access.

Terminology: different published articles use different terminology, for example: interstitial cystitis, painful bladder syndrome, bladder pain syndrome, hypersensitive bladder syndrome, chronic pelvic pain (syndrome) or combinations of these. When reviewing the article, we generally use the terminology used by the authors.

IC/BPS/PBS/HBS

CLINICAL CHARACTERISTICS DIFFER CONSIDERABLY BETWEEN PHENOTYPES OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Logadottir Y, Fall M, Kåbjörn-Gustafsson C, Peeker R. Scand J Urol Nephrol. 2012 May 21. [Epub ahead of print]. PMID: 22607036

Logadottir and colleagues from Göteborg, Sweden, note that bladder pain syndrome/interstitial cystitis (BPS/IC) includes a heterogeneous collection of underlying pathological conditions. Compared to the classic IC with a Hunner lesion, now denominated European Society for the Study of Interstitial Cystitis (ESSIC) type 3C, the non-Hunner type of BPS/IC appears to be different with regard to demographic, endoscopic and histological findings, as well as the response to all forms of treatment. The objective of this study was to determine whether there are additional dissimilarities in clinical presentation between the main phenotypes of BPS/IC. In total, 393 BPS/IC patients (210 type 3C and 183 non-Hunner), diagnosed according to NIDDK and ESSIC criteria, were studied by surveying the clinical records including micturition diaries. In this clinical material, BPS/IC ESSIC type 3C accounted for 55% of cases. Patients with non-Hunner disease were on average 20 years younger at the time of diagnosis. Furthermore, there was a marked and significant difference in bladder capacity under general anaesthesia. The authors concluded that the findings in the present series, together with previously published reports by this group and by others, confirm the striking differences between the main forms of BPS/IC and underline the indispensability of adequate subtyping in clinical studies.

BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS ESSIC TYPE 3C: HIGH EXPRESSION OF INDUCIBLE NITRIC OXIDE SYNTHASE IN INFLAMMATORY CELLS.

Logadottir Y, Hallsberg L, Fall M, Peeker R, Delbro D. Scand J Urol Nephrol. 2012 Jul 10. [Epub ahead of print]. PMID: 22775390

Bladder pain syndrome/interstitial cystitis (BPS/IC) includes a heterogeneous collection of underlying pathological conditions. Compared to the classic IC with a Hunner lesion, now denominated ESSIC type 3C, the non-Hunner type of BPS/IC appears different in a number of respects. In a previous study, measuring luminal nitric oxide (NO) in the bladder of patients with BPS/IC, it was reported that all patients with ESSIC type 3C had high levels of NO. The aim of the present study was to investigate the source of inducible nitric oxide synthase (iNOS) and thereby the cellular origin of NO production via iNOS. Immunohistochemistry, with two different anti-iNOS antibodies, was used to study 10 patients with BPS/IC ESSIC type 3C who expressed high levels of intraluminal NO. These results were compared with four patients with non-Hunner BPS/IC. To substantiate further the involvement of iNOS in this condition, the protein expression of nitrotyrosine, a marker for iNOS activation, was also assessed. On routine histopathology, the tissues of type 3C patients exhibited inflammatory infiltrates of varying intensity. Strong immunoreactivity for both iNOS and nitrotyrosine was noted within the urothelium but also within the inflammatory infiltrates in the lamina propria of these subjects. The findings of a clearly detectable protein expression of iNOS in both the urothelium and the inflammatory infiltrates in bladder biopsies from patients with BPS/IC ESSIC type 3C suggest that the production of NO, in this entity, may occur in different tissue compartments.

TRANSIENT RECEPTOR POTENTIAL A1 RECEPTOR-MEDIATED NEURAL CROSS-TALK AND AFFERENT SENSITIZATION INDUCED BY OXIDATIVE STRESS: IMPLICATION FOR THE PATHOGENESIS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Furuta A, Suzuki Y, Hayashi N, Egawa S, Yoshimura N. Int J Urol. 2012 May;19(5):429-36. doi: 10.1111/j.1442-2042.2012.02966.x. Epub 2012 Feb 21. PMID:22353309

Furuta and colleagues from Japan report that although the pathogenesis of interstitial cystitis/bladder pain syndrome remains unknown, there is a significant correlation of IC/BPS with other chronic pain disorders, such as irritable bowel syndrome, endometriosis and fibromyalgia syndrome. In this review, they highlight evidence supporting neural cross-talk in the dorsal root ganglia, spinal cord and brain levels, which might play a role in

the development of chronic pain disorders through central sensitization. In addition, they focus on transient receptor potential V1 and transient receptor potential A1 as the receptor targets for chronic pain conditions, because transient receptor potential V1 and transient receptor potential A1 act as a nocisensor to mediate not only an afferent signal to the dorsal horn of the spinal cord, but also an efferent signal in the periphery through secretion of inflammatory agents, such as substance P and calcitonin gene-related peptide in nociceptive sensory neurons. Furthermore, peripheral inflammation produces multiple inflammatory mediators that act on their cognate receptors to activate intracellular signal transduction pathways and thereby modify the expression and function of transient receptor potential V1 and transient receptor potential A1 (peripheral sensitization). During tissue damage and inflammation, oxidative stress, such as reactive oxygen species or reactive carbonyl species is also generated endogenously. The highly diffusible nature might account for the actions of free radical formation far from the site of injury, thereby producing systemic pain conditions without central sensitization through neural cross-talk. Because oxidative stress is considered to induce activation of transient receptor potential A1, they also discuss exogenous and endogenous oxidative stress to elucidate its role in the pathogenesis of IC/BPS and other chronic pain conditions.

ENHANCED UROTHELIAL EXPRESSION OF HUMAN CHORIONIC GONADOTROPIN BETA (HCGB) IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS (BPS/IC).

Schwalenberg T, Stolzenburg JU, Thi PH, Mallock T, Hartenstein S, Alexander H, Zimmermann G, Hohenfellner R, Denzinger S, Burger M, Horn LC, Neuhaus J. World J Urol. 2012 Jun;30(3):411-7. Epub 2011 Aug 30. PMID: 21877171

The aims of this study by Schwalenberg and colleagues from Leipzig, Germany were to examine the expression of human chorionic gonadotropin (hCG) and luteinizing hormone receptor (LHR) in the urothelium of BPS/IC patients and compare the levels of hCG β with healthy controls. They found constitutive expression of hCG α , hCG β and LHR in healthy controls. HCG β was significantly upregulated in BPS/IC patients in CLSM. PCR analysis revealed higher levels of hCG $\beta 7$ than hCG $\beta 5$ in controls and BPS/IC patients. They concluded that the constitutive expression of hCG and LHR speaks in favour for a functional signalling in urothelial cells without any association with either pregnancy or tumour. They show for the first time that hCG β is upregulated in BPS/IC urothelium and that hCG $\beta 7$ is the dominant splice variant in those cells. Their findings imply a major role of hCG for urothelial integrity and a disturbance of hCG signalling in case of BPS/IC. They concluded that hCG could have relevance for treatment in the future.

MAPPING OF PAIN PHENOTYPES IN FEMALE PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS AND CONTROLS.

Tripp DA, Nickel JC, Wong J, Pontari M, Moldwin R, Mayer R, Carr LK, Doggweiler R, Yang CC, Mishra N, Nordling J. Eur Urol. 2012 May 18. [Epub ahead of print]. PMID: 22633363

Many bladder pain syndrome/interstitial cystitis (BPS/IC) patients report multiple pain locations outside the pelvis. No research has examined pain using a whole-body diagram, pain-associated adjustment factors, or the impact of pain in multiple body areas on patients' quality of life (QoL). The purpose of this study from Canada was to compare and contrast pain in BPS/IC patients and controls using a whole-body diagram (visible body areas) and to examine the association between patient adjustment factors and greater number of body pain areas (pain phenotypes). The authors found that patients reported more pain than controls in all reported body areas. Four pain phenotypes were created based on increasing counts of body locations (BPS/IC only, BPS/IC+plus 1-3 additional locations, BPS/IC plus 4-9, BPS/IC ≥ 10). Patients reported more body pain locations, pain, urinary symptoms, depression, catastrophizing, and diminished QoL than controls. The increased-pain phenotype was associated with poorer psychosocial adjustment and diminished physical QoL, but catastrophizing and low scores for mental QoL remained stable across all patient groups. This study was cross-sectional, relying on correlation-based analyses, thus causality cannot be established. Patients reported numerous systemic pain symptoms outside the areas associated with the bladder/pelvic region, and increased numbers of body pain sites were associated with poorer patient outcomes (ie, pain severity, depression). This study illustrates the significant negative impact of pain on patient adjustment in BPS/IC. The authors are of the opinion that their findings suggest that clinicians should carefully consider pain location distributions and the potential impact of body pain phenotypes during patient evaluation and treatment planning.

PREDICTORS OF RESPONSE TO INTRAVESICAL DIMETHYL-SULFOXIDE COCKTAIL IN PATIENTS WITH INTERSTITIAL CYSTITIS.

Stav K, Beberashvili I, Lindner A, Leibovici D. Urology. 2012 Jul;80(1):61-5. PMID: 22748865

The purpose of this study from Israel was to identify predictors of treatment failure of dimethyl sulfoxide (DMSO) cocktail for patients with interstitial cystitis (IC). Fifty-one IC patients received weekly intravesical instillations of cocktail composed of 50% DMSO (50 mL), 100 mg of hydrocortisone (5 mL), 10,000 U of heparin sulfate (10 mL), and 0.5% bupivacaine (10 mL) for 12 weeks. A reduction from baseline in the O'Leary-Sant questionnaire score of ≥30% was considered as a response. Patients were evaluated every 3 weeks during the treatment course and at 1, 3, 6, 9, and 12 months thereafter. Thirty-one patients (61%) were responders. Intravesical cocktail for IC patients is associated with a 61% response rate. The authors suggest that a small anaesthetic bladder capacity predicts treatment failure.

MEASURING THE SUCCESS OF COMBINED INTRAVESICAL DIMETHYL SULFOXIDE AND TRIAMCINOLONE FOR TREATMENT OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Gafni-Kane A, Botros SM, Du H, Sand RI, Sand PK. *Int Urogynecol J.* 2012 Jun 15. [Epub ahead of print]. PMID: 22699887

The purpose of this study from the USA was to investigate change in bladder capacity as a measure of response to combined intravesical dimethyl sulfoxide (DMSO) and triamcinolone instillations for the treatment of newly diagnosed bladder pain syndrome/interstitial cystitis (BPS/IC). 141 newly diagnosed women were identified retrospectively. 79 were treated with weekly DMSO/triamcinolone instillations. Change in bladder capacity with bladder retrofill, daytime urinary frequency, nocturia episodes per night, and Likert scale symptom scores were reviewed. The authors found that percent change in bladder capacity is a useful objective measure of response to intravesical DMSO/triamcinolone for newly diagnosed BPS/IC and that clinical outcomes do not differ based upon presence of detrusor overactivity.

GAG LAYER REPLENISHMENT THERAPY FOR CHRONIC FORMS OF CYSTITIS WITH INTRAVESICAL GLYCOSAMINOGLYCANs-A REVIEW.

Madersbacher H, van Ophoven A, van Kerrebroeck PE. *Neurourol Urodyn.* 2012 Jul 10. doi: 10.1002/nau.22256. [Epub ahead of print]. PMID: 22782909

Glycosaminoglycan (GAG) layer replenishment is a cornerstone in the therapy of interstitial cystitis (IC). During the last years intravesical GAG layer replenishment has proven to be an effective treatment for overactive bladder (OAB), radiation cystitis, and recurrent urinary tract infections (UTIs). In this review article, Madersbacher and colleagues searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) database for studies on intravesical GAG replenishment. A total of 27 clinical studies remain relevant to this topic, many of them with mixed patient selection and suboptimal definition of symptom improvement/success. Two placebo controlled studies with hyaluronic acid failed to show superiority and have not been published. One active controlled randomized study has been published showing that chondroitin sulphate 0.2% has a clear benefit for OAB patients. Another study with chondroitin sulphate 2.0% failed to show statistically significant evidence, but was underpowered. The authors concluded that a short number of randomized controlled studies confirm efficacy of intravesical GAG layer replenishment therapy. Concluded from the study background (which comprises also uncontrolled studies), so far chondroitin sulphate 0.2% is in favour for intravesical GAG layer replenishment therapy. In general, large-scale trials are urgently needed to underline the benefit of this type of therapy.

INTEGRATION ANALYSIS OF QUANTITATIVE PROTEOMICS AND TRANSCRIPTOMICS DATA IDENTIFIES POTENTIAL TARGETS OF FRIZZLED-8 PROTEIN-RELATED ANTIPIROLIFERATIVE FACTOR IN VIVO.

Yang W, Kim Y, Kim TK, Keay SK, Kim KP, Steen H, Freeman MR, Hwang D, Kim J. *BJU Int.* 2012 Jun 28. doi: 10.1111/j.1464-410X.2012.11299.x. [Epub ahead of print]. PMID: 22738385

Several urinary biomarker candidates have been identified for IC; among the most promising is antiproliferative factor (APF), whose biological activity is detectable in urine specimens from >94% of patients with both ulcerative and non-ulcerative IC. The present study identified several important mediators of the effect of APF on bladder cell physiology, suggesting several candidate drug targets against IC. In an attempt to identify potential proteins and genes regulated by APF in vivo, and to possibly expand the APF-regulated network identified by stable isotope labelling by amino acids in cell culture (SILAC), the authors performed an integration analysis of their own SILAC data and the microarray data of Gamper et al. (2009) BMC Genomics 10: 199. Notably, two of the proteins (i.e. MAPKSP1 and GSPT1) that are down-regulated by APF are involved in the activation of mTORC1, suggesting that the mammalian target of rapamycin (mTOR) pathway is potentially a critical pathway regulated by APF in vivo. Several components of the mTOR pathway are currently being studied as potential therapeutic targets in other diseases. Their analysis suggests that this pathway might also be relevant in the design of diagnostic tools and medications targeting IC. Integration analysis of this

transcriptomics data set with their own quantitative proteomics data set identified 10 genes that are potentially regulated by APF in vivo from 4140 differentially expressed genes identified with a false discovery rate of 1%. Of these, five (i.e. JUP, MAPKSP1, GSPT1, PTGS2/COX-2 and XPOT) were found to be prominent after network modelling of the common genes identified in the proteomics and microarray studies. This molecular signature reflects the biological processes of cell adhesion, cell proliferation and inflammation, which is consistent with the known physiological effects of APF. Lastly, they found the mammalian target of rapamycin pathway was down-regulated in response to APF. The authors concluded that this unbiased integration analysis of in vitro quantitative proteomics data with in vivo quantitative transcriptomics data led to the identification of potential downstream mediators of the APF signal transduction pathway.

A MOUSE MODEL FOR INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME BASED ON APF INHIBITION OF BLADDER EPITHELIAL REPAIR: A PILOT STUDY.

Keay S, Leitzell S, Ochrzin A, Clements G, Zhan M, Johnson D. BMC Urol. 2012 Jun 8;12(1):17. [Epub ahead of print]. PMID: 22682521

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Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic bladder disorder with bladder epithelial thinning or ulceration, pain, urinary frequency and urgency. Bladder epithelial cells from IC/PBS patients make a small glycoprotein antiproliferative factor or "APF" that inhibits proliferation, decreases tight junction protein expression, increases paracellular permeability, and induces changes in gene expression of bladder epithelial cells in vitro that mimic abnormalities in IC/PBS patient biopsy specimens in vivo. Keay and colleagues therefore determined the ability of a synthetic APF derivative to inhibit bladder epithelial repair in mice. On the basis of their results, they believe that this model demonstrates in vivo effects of as-APF which abrogates bladder epithelial repair and expression of UPIII and ZO-1 in CBA/J mice following transurethral acetic acid infusion. As bladder epithelial thinning, decreased UPIII expression, and decreased ZO-1 expression are histopathologic features of IC/PBS patient biopsies, this model may be useful for studying the pathophysiology of IC/PBS and the effect of potential therapies.

DOES PATIENT AGE IMPACT OUTCOMES OF NEUROMODULATION?

Peters KM, Killinger KA, Gilleran J, Boura JA. Neurol Urodyn. 2012 Jun 5. doi: 10.1002/nau.22268. [Epub ahead of print]. PMID: 22674536

Peters and colleagues from Michigan evaluated whether patients stratified by age have the same level of risks/benefits after a staged neuromodulation procedure for refractory voiding symptoms. Urologic diagnosis, complications, and revisions were collected from medical records of adults enrolled in a prospective observational study. Symptoms were assessed over 2 years with diaries, Interstitial Symptom-Problem Indices (ICSI-PI), and the Overactive Bladder Questionnaire-SF (OAB-q SF). 12-item Short-Form Health Survey (SF-12v2®) mental (MCS) and physical (PCS) component summaries evaluated quality of life. Patients (83% female) were grouped by age (years): <40 (46 patients), 40-64 (146 patients), and ≥65 (136 patients). Urge incontinence was predominant in the older groups and more patients <40 had interstitial cystitis/painful bladder syndrome (IC/PBS). In the <40, 40-64, and ≥65 groups, respectively, generator implant (91%, 88%, and 89%) and explant (15%, 12%, and 10%) rates were similar. Complications differed. For the three respective groups, urinary frequency, nocturia, incontinence episodes, urgency, ICSI-PI, and OAB-q scores improved over time. Incontinence severity improved in those >65. SF-12 PCS improved in those 40-64 and MCS scores improved in the <40 and 40-64 age groups. The authors concluded that these data suggest that neuromodulation success is not age dependent, however continued study is needed to confirm findings.

SUICIDAL IDEATION AMONG PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

Hepner KA, Watkins KE, Elliott MN, Clemens JQ, Hilton LG, Berry SH. Urology. 2012 Jun 1. [Epub ahead of print]. PMID: 22658505.

The purpose of this study from the RAND Corporation, Santa Monica, California, was to estimate the prevalence of suicidal ideation (SI) and compare respondents who endorsed SI with respondents who denied SI within a national probability sample of women with bladder pain syndrome or interstitial cystitis (BPS/IC). Data were collected as part of the RAND Interstitial Cystitis Epidemiology (RICE) Study, which screened 146,246 US households to identify adult women who met BPS/IC symptom criteria. In addition to estimating SI prevalence, women with and without recent SI were compared based on demographics, depression symptoms, BPS/IC symptoms, functioning, and treatment. Of 1019 women with BPS/IC symptoms asked about SI, 11.0% reported SI in the past 2 weeks. Those with SI were more likely to be younger, unemployed, unmarried, uninsured, less educated, and of lower income. Women who endorsed SI reported worse mental health functioning, physical

health functioning, and BPS/IC symptoms. Women with SI were more likely to have received mental health treatment, but did not differ on whether they had received BPS/IC treatment. Multivariate logistic regression analyses indicated that severity of BPS/IC symptoms did not independently predict likelihood of endorsing SI. According to Hepner and colleagues, their results suggest that BPS/IC severity may not increase the likelihood of SI except via severity of depression symptoms. They note that additional work is needed to understand how to address the increased needs of women with both BPS/IC and SI.

[Ca₂₊/CALMODULIN-DEPENDENT PROTEIN KINASE II IS ASSOCIATED WITH PELVIC PAIN OF NEUROGENIC CYSTITIS.](#)

Yang W, Rudick CN, Hoxha E, Allsop SA, Dimitrakov JD, Klumpp DJ. Am J Physiol Renal Physiol. 2012 May 30. [Epub ahead of print]. PMID: 22647634

Interstitial cystitis/painful bladder syndrome (IC) is a chronic bladder inflammatory disease of unknown etiology that is often regarded as a neurogenic cystitis. IC is associated with urothelial lesions, voiding dysfunction, and pain in the pelvic/perineal area. In this mouse study, Yang and colleagues used a murine neurogenic cystitis model to identify genes participating in the development of pelvic pain. Neurogenic cystitis was induced by the injection of Bartha's strain of pseudorabies virus (PRV) into the abductor caudalis dorsalis (tail base) muscle of female C57BL/6J mice. Mice infected with PRV developed progressive pelvic pain. The sacral spinal cord was harvested on post infection day (PID) 2 and 4, and gene expression was analyzed by microarrays and confirmed by qRT-PCR. On PID 2 the overall expression profile was similar to that of sham-infected sacral spinal cord; by PID 4 there were substantial differences in expression of multiple functional classes of genes, especially inflammation. Analysis of pain signalling pathways at the dorsal horn suggested that Ca(2+)/Calmodulin-dependent protein kinase II (CaMKII) contributes to neurogenic cystitis pelvic pain. Consistent with this, CaMKII δ expression exhibited a mast cell-dependent increase in the sacral spinal cord at the mRNA level, and phospho-CaMKII immunoreactivity in the dorsal horn was increased on PID 4 during PRV infection. Finally, intrathecal injection of the CaMKII inhibitor KN-93 attenuated the PRV pain response. These data suggest that CaMKII plays a function role in pelvic pain due to neurogenic cystitis.

[INTRAVESICAL ONABOTULINUMTOXINA INJECTIONS FOR REFRACTORY PAINFUL BLADDER SYNDROME.](#)

Chung SD, Kuo YC, Kuo HC. Pain Physician. 2012 May;15(3):197-202. PMID: 22622903

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The aim of this prospective, non-randomized study from Taiwan was to evaluate the efficacy and safety of intravesical BoNT-A injection for treatment of IC/PBS refractory to conventional treatment. Sixty-seven patients with characteristic IC/PBS were enrolled. Intravesical injection of 100U of BoNT-A immediately followed by cystoscopic hydrodistention under intravenous general anesthesia. Changes of the urodynamic parameters, O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), visual analog score (VAS) for pain, functional bladder capacity, and global response assessment (GRA) were evaluated at baseline and 6 months after BoNT-A injection. Adverse events that occurred after this procedure were also assessed. The authors note that this study lacks a placebo control group so the placebo effect cannot be eliminated. This study also does not provide information about the efficacy of this treatment after 6 months. However, they report that intravesical onabotulinumtoxinA injection appears to be a safe and effective therapeutic option for analgesia and increased bladder capacity for patients with IC/PBS.

[AUTONOMIC RESPONSE DURING BLADDER HYDRODISTENTION IN PATIENTS WITH BLADDER PAIN SYNDROME.](#)

Stav K, Lang E, Fanus Z, Leibovici D. J Urol. 2012 Jul;188(1):117-21. Epub 2012 May 12. PMID: 22578723

Stav and colleagues from Israel determined whether patients with bladder pain syndrome who have typical interstitial cystitis endoscopic findings, including glomerulations and/or Hunner ulcer, have a distinct autonomic response during bladder hydrodistention. Included in the study were 50 consecutive patients (40 females and 10 males) who met International Society for the Study of BPS (ESSIC) recommendations. All patients underwent the same clinical evaluation, consisting of medical history, physical examination, urine and blood tests, urine cytology and culture, urinary tract ultrasound and urodynamics. Bladder hydrodistention and biopsies were performed using general anaesthesia. Systolic and diastolic blood pressure and heart rate were recorded after the induction of general anaesthesia and at the end of the filling phase. Patients were divided into 2 groups, including patients with and without typical endoscopic findings, respectively. Clinical, histological and urodynamic variables, and autonomic parameters were compared between the 2 groups. No significant differences in demographics, symptoms, pain severity, comorbidities, previous surgery, urodynamic variables, anaesthetic bladder capacity or histological findings were found between the 2 groups. In patients with endoscopic findings average \pm SD systolic and diastolic blood pressure increased by 25 \pm 19 and 21 \pm 12 mm Hg,

respectively, and average heart rate increased by 12 ± 11 beats per minute. All hemodynamic changes were statistically significant. In patients without endoscopic findings a minor decrease in hemodynamic parameters was observed. Patients with bladder pain syndrome who have typical interstitial cystitis findings on endoscopy show a marked autonomic response during bladder hydrodistention, consisting of an increase in heart rate, and systolic and diastolic blood pressure.

[DISABILITY IN WOMEN SUFFERING FROM INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Katz L, Tripp DA, Nickel JC, Mayer R, Reimann M, van Ophoven A. *BJU Int.* 2012 May 11. doi: 10.1111/j.1464-410X.2012.11238.x. [Epub ahead of print]. PMID: 22578191

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a disease that is associated with significant disability in the areas of self-care, sexual functioning, occupation, family and home responsibilities, and social functions. Compared to age- and cohort-matched controls, patients with IC/BPS reported poorer mental and physical quality of life (QoL), as well as greater pain, depression, anxiety, catastrophizing, sexual dysfunction and less social support. In particular, catastrophizing and depression are suggested to be important for understanding the factors promoting a poorer QoL in IC/BPS. The findings of the present study suggest that psychosocial factors are significant in mediating the relationship between impairments and patient disability, with negative affect (i.e. depression, anxiety) and pain catastrophizing acting as significant mediators. These findings argue that catastrophizing and negative affect may be the mechanisms by which pain and symptoms elevate reports of patient disability. Understanding how pain and pain-associated symptoms may become disabling through cognitive mechanisms represents an importance advance for IC/BPS management. Clinical interventions in women suffering from IC/BPS should target catastrophizing and mood for reduction using cognitive behavioural strategies aiming to decrease pain-related disability. Questionnaires completed by 196 women with IC/BPS provided data for the present study. The measurement model showed good fit to the data. Negative effect and catastrophizing were significant in explaining the relationship between impairments and functional disability, whereas social support did not. It was concluded that disability in patients suffering from IC/BPS is partially explained by the impact of negative effect and catastrophizing. As a result of the refractory nature of IC/BPS, patient management within a biopsychosocial framework represents an essential area of investigation. Decreases in negative effect and catastrophizing will probably lead to improvements in pain-related disability.

[INTRAVESICAL HYALURONIC ACID AND ALKALINIZED LIDOCAINE FOR THE TREATMENT OF SEVERE PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS.](#)

Lv YS, Zhou HL, Mao HP, Gao R, Wang YD, Xue XY. *Int Urogynecol J.* 2012 May 11. [Epub ahead of print]. PMID: 22576327

This study from Fujian, People's Republic of China, looked at the use of intravesical instillation of hyaluronic acid (HA) to restore the integrity of the glycosaminoglycan(GAG) layer in patients with painful bladder syndrome/interstitial cystitis (PBS/IC), and how the benefit may be improved with the addition of alkalinized lidocaine (AL). 48 women with severe PBS/IC who had failed oral medications were enrolled and divided into one trial and two control groups. The trial group received intravesical 40 mg HA, 10 ml of 2 % lidocaine and 5 ml of 8.4 % sodium bicarbonate on a weekly basis for 8 weeks and then monthly for 4 months with a subsequent follow-up of 24 weeks, while the two control groups received 40 mg HA and mixture of 10 ml of 2 % lidocaine and 5 ml of 8.4% sodium bicarbonate respectively following the same procedure. Response to therapy was evaluated by Global Response Assessment, voids per day, Visual Analogue Scale for pain, frequency and urgency, O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index, cystoscopy and bladder capacity. Overall 45 patients finished this study protocol. The HA + AL group and the AL group showed significant improvement at week 2, while the HA group began to show effect at week 4. There was no improvement in the AL group at week 24 and these patients left the study without follow up. On the other hand, the HA + AL and HA group kept on improving until the end of the study without significant difference between the two groups. The authors concluded that intravesical instillation of HA and AL may provide both immediate and sustained relief of symptoms in severe PBS/IC in this preliminary study.

[INTRAVESICAL HYALURONIC ACID AND CHONDROITIN SULPHATE FOR BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: LONG-TERM TREATMENT RESULTS.](#)

Cervigni M, Natale F, Nasta L, Mako A. *Int Urogynecol J.* 2012 May 9. [Epub ahead of print]. PMID: 22569687

Reconstruction of the glycosaminoglycan (GAG) layer is believed to play a role in the successful treatment of bladder pain syndrome/interstitial cystitis (BPS/IC). Intravesical instillations of hyaluronic acid (HA) and chondroitin sulphate (CS) have given results in the short term. Cervigni and colleagues from Italy hypothesise that these benefits continue in the longer term. With the aim of evaluating this therapy over a longer period,

they treated 12 BPS/IC patients refractory to other treatments with a combination of HA 1.6 % and CS 2.0 % over a period of 3 years assessing symptoms and quality of life using a visual analogue scale, 3-day voiding diaries and validated questionnaires. Improvements in bladder function were sustained for 3 years (mean number of daily voids decreased from 17.8 at baseline to 15.5 at 9 months and 11.9 at 3 years, and mean volume per void from 136.8 ml at baseline to 143.9 ml at 9 months and 180.9 ml at 3 years). Quality of life assessments confirmed these improvements. They found that intravesical instillations of HA and CS produced a sustained improvement of symptoms, up to 3 years, in patients with BPS/IC refractory to previous treatments. Further confirmation would be expected from larger controlled trials.

[INTRAVESICAL TREATMENT OF PAINFUL BLADDER SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS.](#)

Matsuoka PK, Haddad JM, Pacetta AM, Baracat EC. *Int Urogynecol J.* 2012 May 9. [Epub ahead of print]. PMID: 22569686

The objective of this study from Brazil was to assess the effectiveness of intravesical treatment for painful bladder syndrome (PBS). A systematic review was performed until December 31, 2010. The selection criteria included only randomized controlled trials of PBS patients who received intravesical treatment. The primary outcomes measures were clinical and urodynamic parameters. Relative risk and mean differences were used for binary and continuous outcomes respectively, with confidence interval of 95%. The search strategy identified 770; however, only 28 eligible trials met methodological requirements for complete analysis. Altogether, the review included four treatment modalities: resiniferatoxin, Bacillus Calmette-Guérin (BCG), oxybutynin, and alkalinized lidocaine. Meta-analysis of BCG therapy showed improvement in symptoms according to the Wisconsin Interstitial Cystitis Symptom Inventory, but no difference in 24-h urinary frequency. Meta-analysis showed an improvement exclusively of the symptoms as measured by the Wisconsin Interstitial Cystitis Inventory, but not in 24-h urinary frequency, with BCG therapy. Further randomized clinical trials, including trials of more recent drugs, are required for evaluation of intravesical therapies for PBS.

[EFFECTS OF INTRAVESICAL DEXPANTHENOL USE ON LIPID PEROXIDATION AND BLADDER HISTOLOGY IN A CHEMICAL CYSTITIS ANIMAL MODEL.](#)

Bayrak O, Seckiner I, Solakhan M, Karakok M, Erturhan SM, Yagci F. *Urology.* 2012 May;79(5):1023-6. PMID: 22546378

In this rabbit study from Turkey, thirty-five New Zealand rabbits were divided into 3 groups. Cystitis was conducted with transurethral intravesical hydrochloric acid instillation on the subjects in groups I and II. Then, Group I subjects were transurethrally administered intravesical dexpantphenol therapy twice a week, Group II subjects were given only intravesical isotonic NaCl instillation, and Group III subjects were administered intravesical isotonic NaCl instillation without conducting chemical cystitis to create the same stress. Treatment schemes of all groups were arranged in the same manner. After 6-week therapy, the rabbits were sacrificed and histopathologic investigations were carried out to demonstrate changes in the urinary bladder. Serum and tissue malondialdehyde (MDA) values were examined to investigate the effect of dexpantphenol on lipid peroxidation. The authors observed that the basal membrane and mucosal integrity were maintained, inflammatory cells were suppressed, and MDA levels decreased in group I, which received dexpantphenol therapy. However, it was also observed that mucosal integrity was spoiled, numerous inflammatory cells were accumulated, and MDA levels were significantly increased in group II, which was administered isotonic NaCl. They concluded that in the light of their findings, intravesical dexpantphenol therapy could be a new therapeutic approach in the treatment of interstitial cystitis because of its low cost and acceptable side effects.

[SECOND MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP EVALUATION OF EFFECTIVENESS AND SAFETY OF INTRAVESICAL SODIUM CHONDROITIN SULFATE COMPARED WITH INACTIVE VEHICLE CONTROL IN SUBJECTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

Nickel JC, Hanno P, Kumar K, Thomas H. *Urology.* 2012 Jun;79(6):1220-5. Epub 2012 Apr 17. PMID: 22516357

The purpose of this study from Canada was to gain additional safety and effectiveness information regarding intravesical 2% chondroitin sulfate in subjects with interstitial cystitis/bladder pain syndrome (IC/BPS) in a controlled clinical trial. Women with IC/BPS were randomized to receive either 8 weekly bladder instillations of 20 mL of 2% chondroitin sulfate or 20 mL of inactive control solution. The primary effectiveness endpoint was the number of positive results using the Global Response Assessment at week 11 (4 weeks after the last instillation). The secondary effectiveness endpoint was a positive response to the Interstitial Cystitis Symptom Index (ICSI) at week 11. Additional effectiveness endpoints were changes from baseline at week 11 in the total ICSI score voiding diary, and visual analog scale for pain. A total of 98 eligible women with a diagnosis of IC/BPS met the inclusion criteria and were the intention to treat population. Of the 98 women, 83% completed the

study. More patients in the chondroitin sulfate group (38.0%) reported moderate or marked improvement (considered responders) compared with the inactive control group (31.3%) at the 11-week endpoint visit. Similarly, more subjects in the active treatment group were classified as ICSI and VAS pain responders and reported a greater decrease in ICSI and VAS pain scores than the control group. None of these differences were statistically significant. The authors concluded that intravesical chondroitin sulfate therapy for IC/BPS might result in minor improvements in IC/BPS-related symptom and pain. However, the magnitude of benefit in our small pilot study does not support its use as monotherapy for this condition. Better strategies for selecting patients with a bladder-specific clinical phenotype might improve the overall response to this type of intravesical therapy.

[THE COMBINATION THERAPY OF PREDNISOLONE AND TACROLIMUS FOR SEVERE PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS.](#)

Kaneko G, Nishimoto K, Ito Y, Uchida A. *Can Urol Assoc J.* 2012 Apr;6(2):E46-9. doi: 10.5489/cuaj.10134. PMID: 22511431

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Kaneko and colleagues from Japan report that a 47-year-old woman visited their hospital with complaints of frequent urination and intensive pelvic pain. Painful bladder syndrome/interstitial cystitis (PBS/IC) was suspected based on her symptoms. Hydrodistention was performed, and crack and petechial hemorrhage were found, and she was treated with tricyclic antidepressants and antihistamine. However, these treatments were ineffective. An allergy or autoimmune reaction was suspected as the pathogenesis due to eosinophilia and elevation of serum IgE levels. The patient was then treated with immunosuppressive agents. Although her symptoms were not sufficiently improved by single-agent therapy with prednisolone or tacrolimus, they were completely improved by their combined administration. This is the first case to report the effectiveness of combination therapy consisting of prednisolone and tacrolimus to treat PBS/IC.

[URINARY CHEMOKINES AS NONINVASIVE PREDICTORS OF ULCERATIVE INTERSTITIAL CYSTITIS.](#)

Tyagi P, Killinger K, Tyagi V, Nirmal J, Chancellor M, Peters KM. *J Urol.* 2012 Jun;187(6):2243-8. Epub 2012 Apr 13. PMID: 22503040

Based on basic research findings an increase in chemokines and cytokines (CXCL-1 and 10, nerve growth factor and interleukin-6) is considered responsible for inflammation and afferent sensitization, according to Tyagi and colleagues from Pittsburgh. In this cross-sectional study, they tested the hypothesis that select chemokines are increased in the urine of patients with ulcerative and nonulcerative interstitial cystitis/painful bladder syndrome. Midstream urinary specimens were collected from 10 patients with ulcerative and nonulcerative interstitial cystitis/painful bladder syndrome, respectively, and from 10 asymptomatic controls. Urinary levels of 7 cytokines were measured by a human cytokine/chemokine assay. Nerve growth factor was measured by enzyme-linked immunosorbent assay. Urinary levels of most chemokines/cytokines were tenfold to 100-fold lower in asymptomatic controls vs patients with ulcerative and nonulcerative interstitial cystitis/painful bladder syndrome. Univariate comparison of 8 tested proteins in the ulcerative vs nonulcerative groups revealed a significant fivefold to twentyfold increase in CXCL-10 and 1, interleukin-6 and nerve growth factor (ANOVA p<0.001). They concluded that differential expression of chemokines in ulcerative and nonulcerative subtypes of interstitial cystitis/painful bladder syndrome suggests differences in paracrine signalling between the 2 entities.

Comment in: [Identifying biomarkers for interstitial cystitis/bladder pain syndrome.](#) [J Urol. 2012]

[Identifying biomarkers for interstitial cystitis/bladder pain syndrome.](#) Erickson DR. *J Urol.* 2012 Jun; 187(6):1958-9. Epub 2012 Apr 11.

[RANDOMIZED MULTICENTER CLINICAL TRIAL OF MYOFASCIAL PHYSICAL THERAPY IN WOMEN WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME AND PELVIC FLOOR TENDERNESS.](#)

FitzGerald MP, Payne CK, Lukacz ES, Yang CC, Peters KM, Chai TC, Nickel JC, Hanno PM, Kreder KJ, Burks DA, Mayer R, Kotarinos R, Fortman C, Allen TM, Fraser L, Mason-Cover M, Furey C, Odabachian L, Sanfield A, Chu J, Huestis K, Tata GE, Dugan N, Sheth H, Bewyer K, Anaeme A, Newton K, Featherstone W, Halle-Podell R, Cen L, Landis JR, Propert KJ, Foster HE jr, Kusek JW, Nyberg LM; Interstitial Cystitis Collaborative Research Network. Collaborators (48): Miller J, Muller CH, Kalhoff J, Bassuk J, Downing S, Bale RF Jr, Shinghal R, Anderson R, Clay D, Ramakrishnan A, Nager C, Chenoweth M, Anton E, Wolfert C, Lampkins L, Keay S, Dinh R, Sangrampurkar R, Morales A, Emerson L, Carr L, Downey J, Clark-Pereira J, Robb S, Brubaker L, Rindels J, Bucher G, Newman DK, Salazar S, Milado J, Moy L, O'Donnell M, Lutgendorf S, Eno M, O'Berry K, Rivers K, Romero S, Peabody M,

Messing E, Smith EB, Rust K, Reeder J, Mickelberg K, Barrell T, Chuai S, Mullins C, Harris M, Ratner V. J Urol. 2012 Jun;187(6):2113-8. Epub 2012 Apr 12. PMID: 22503015

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This team determined the efficacy and safety of pelvic floor myofascial physical therapy compared to global therapeutic massage in women with newly symptomatic interstitial cystitis/painful bladder syndrome. A randomized controlled trial of 10 scheduled treatments of myofascial physical therapy vs global therapeutic massage was performed at 11 clinical centers in North America. They recruited women with interstitial cystitis/painful bladder syndrome with demonstrable pelvic floor tenderness on physical examination and a limitation of no more than 3 years' symptom duration. The primary outcome was the proportion of responders defined as moderately improved or markedly improved in overall symptoms compared to baseline on a 7-point global response assessment scale. Secondary outcomes included ratings for pain, urgency and frequency, the O'Leary-Sant IC Symptom and Problem Index, and reports of adverse events. They compared response rates between treatment arms using the exact conditional version of the Mantel-Haenszel test to control for clustering by clinical centre. For secondary efficacy outcomes cross-sectional descriptive statistics and changes from baseline were calculated. A total of 81 women randomized to the 2 treatment groups had similar symptoms at baseline. The global response assessment response rate was 26% in the global therapeutic massage group and 59% in the myofascial physical therapy group ($p=0.0012$). Pain, urgency and frequency ratings, and O'Leary-Sant IC Symptom and Problem Index decreased in both groups during follow up, and were not significantly different between the groups. Pain was the most common adverse event, occurring at similar rates in both groups. No serious adverse events were reported. They found that a significantly higher proportion of women with interstitial cystitis/painful bladder syndrome responded to treatment with myofascial physical therapy than to global therapeutic massage. Myofascial physical therapy may be a beneficial therapy in women with this syndrome.

EFFECTS OF COMBINATION TREATMENT OF INTRAVESICAL RESINIFERATOXIN INSTILLATION AND HYDRODISTENTION IN PATIENTS WITH REFRACTORY PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS: A PILOT STUDY.

Ham BK, Kim JH, Oh MM, Lee JG, Bae JH. Int Neurorol J. 2012 Mar;16(1):41-6. Epub 2012 Mar 31. PMID: 22500253

This prospective study from Korea investigated the efficacy of intravesical resiniferatoxin (RTX) in PBS/IC refractory to medical treatment. Patients with proven PBS/IC refractory to traditional medical treatment were enrolled. By randomized trial, a total of 18 consecutive patients were divided into two groups: treatment with hydrodistention and intravesical RTX (group 1) or treatment with hydrodistention only (group 2). Ham and colleagues assessed bladder pain by use of a visual analogue pain scale, the maximal urine flow rate, post-void residual urine volume, and a voiding diary before and 3 months after treatment. Frequency, functional bladder capacity, and score on a 5-point pain scale were significantly improved at 3-month after treatment in both groups. Intravesical RTX instillation plus hydrodistention, compared with hydrodistention only, did not have a significant effect on the voiding symptoms or uroflowmetry of the patients but significantly improved scores on the pain scale. They concluded that intravesical RTX instillation plus hydrodistention was effective in relieving pain, but was not effective in improving lower urinary tract symptoms. Further larger studies are needed to clarify the efficacy of combination treatment of intravesical RTX instillation and hydrodistention.

MAST CELLS

MAST CELLS: AN EXPANDING PATHOPHYSIOLOGICAL ROLE FROM ALLERGY TO OTHER DISORDERS.

Anand P, Singh B, Jaggi AS, Singh N. Naunyn Schmiedebergs Arch Pharmacol. 2012 Jul;385(7):657-70. Epub 2012 May 6. PMID: 22562473

Anand and colleagues from Patiala, India, took a look at the role of mast cells in different diseases. They note that mast cells are multi-effector cells with wide distribution in the different body parts and traditionally their role has been well-defined in the development of IgE-mediated hypersensitivity reactions including bronchial asthma. Due to the availability of genetically modified mast cell-deficient mice, the broadened pathophysiological role of mast cells in diverse diseases has been revealed. Mast cells exert different physiological and pathophysiological roles by secreting their granular contents, including vasoactive amines, cytokines and chemokines, and various proteases, including tryptase and chymase. Furthermore, mast cells also synthesize plasma membrane-derived lipid mediators, including prostaglandins and leukotrienes, to produce diverse biological actions. The present review discusses the pathophysiological role of mast cells in different diseases, including atherosclerosis, pulmonary hypertension, ischemia-reperfusion injury, male

infertility, autoimmune disorders such as rheumatoid arthritis and multiple sclerosis, bladder pain syndrome (interstitial cystitis), anxiety, Alzheimer's disease, nociception, obesity and diabetes mellitus.

DIFFERENCES IN MAST CELL INFILTRATION, E-CADHERIN, AND ZONULA OCCLUDENS-1 EXPRESSION BETWEEN PATIENTS WITH OVERACTIVE BLADDER AND INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Liu HT, Shie JH, Chen SH, Wang YS, Kuo HC. Urology. 2012 Jul;80(1):225.e13-8. Epub 2012 Apr 21. PMID: 22521193

In this study from Taiwan, Liu and colleagues investigated the difference of infiltration of mast cells and the distribution of protein involved in the urothelial barrier function between patients with overactive bladder syndrome (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS). Bladder wall biopsies were performed in 27 patients with OAB, 18 patients with IC/BPS, and 19 controls. The expression of junction protein E-cadherin, tight junction protein zonula occludens (ZO-1), and activated mast cells in the bladder wall were evaluated quantitatively using immunofluorescence staining. The numbers of mast cells in the urothelium and suburothelium areas were low in the control group (mean ± standard error 1.77 ± 0.47). A highly significant increase in mast cell infiltration was observed in OAB (4.00 ± 0.55, P = .002) and IC/BPS specimens (4.64 ± 0.72, P = .000). ZO-1 expression was significantly decreased in IC/BPS (7.45 ± 0.99) compared with OAB (13.46 ± 1.32, P = .004) and control bladder samples (14.55 ± 2.08, P = .004). The E-cadherin expression was also significantly decreased in IC/BPS bladder samples (59.05 ± 9.48) compared with the controls (96.30 ± 9.15, P = .001). No significant difference was found in E-cadherin or ZO-1 levels between the OAB and control bladders (P = .170 and P = .763, respectively). Mast cell infiltration was found in both OAB and IC/BPS bladder wall, but E-cadherin and ZO-1 expression was only decreased in IC/BPS, suggesting the urothelial barrier function was not affected in the OAB bladder.

CHRONIC PELVIC/PERINEAL/PUDENDAL PAIN

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

Louppe JM, Nguyen JP, Robert R, Buffenoir K, de Chauvigny E, Riant T, Péron Y, Labat JJ, Nizard J. Neurourol Urodyn. 2012 Jun 5. doi: 10.1002/nau.22269. [Epub ahead of print] PMID: 22674567

A case study from the well-known neuro/uro/pelviperineal centre in Nantes, France in which Louppe and colleagues report that in some patients, with refractory chronic pelvic and perineal pain, pain and quality of life are barely alleviated despite optimal medical treatment, infiltrations and surgical release of the pudendal nerve. The management of these patients is complex, especially after failure of neuromodulation techniques (spinal cord stimulation, S3 nerve root stimulation and direct stimulation of the pudendal nerve). In this article, they report on the first two cases illustrating the value of motor cortex stimulation (MCS), in this new indication. The principle of this technique is chronic stimulation of the motor cortex region corresponding to the painful zone by implanting one or several electrodes into the extradural space. These are then connected to a totally implantable pacemaker type of stimulator. The authors emphasise that identification of the appropriate zone of cortex is a very important phase of this technique and that this zone is usually localized intraoperatively by examining the motor responses obtained by stimulating various cortical zones. The first patient was a 74-year old woman with an 11 year history of left lateral perineal pain. The second patient was a 45-year old woman with a 4 year history of perineal pain following hysterectomy with ovariectomy. After respectively 40 months and 19 months of follow up, both patients reported an improvement of pain ranging from 40-50%. Time to onset of pain on sitting was markedly improved from a few minutes to 90 minutes, and largely contributed to improvement in daily activities and quality of life.

The authors concluded that these two first cases suggest that motor cortex stimulation constitutes a new treatment for refractory pelvic and perineal pain, and should be considered after failure of conventional neuromodulation techniques, especially spinal cord stimulation. They note that prospective randomized studies in a larger population using both rTMS and implanted motor cortex stimulation need to be conducted in order to confirm the good results obtained in these first two cases.

CHRONIC PELVIC PAIN SYNDROME-RELATED DIAGNOSES IN AN OUTPATIENT OFFICE SETTING.

Fenton BW, Brobeck L, Witten E, Von Gruenigen V. Gynecol Obstet Invest. 2012 May 9. [Epub ahead of print]. PMID: 22571935

Chronic pelvic pain (CPP) is a syndrome composed of one or more pain diagnoses arising from pelvic organs. Although the prevalence of many individual diagnoses has been determined in a variety of settings, the concurrent assessment of overlapping pain syndromes in an outpatient gynaecology clinic, which would be

most pertinent to practitioners, has not been reported. Patients waiting to be seen in an outpatient general gynaecology clinic completed a survey composed of validated instruments for different pain diagnoses. Cyclic and constant CPP, irritable bowel syndrome (IBS), interstitial cystitis (IC), and vulvodynia (VVD) were assessed. In the 498 completed surveys, 24% of patients met at least one criterion for CPP, and of these, 23% also met criteria for a second diagnosis. Of all patients, 15% reported symptoms consistent with IBS, 6% with IC, and 5% with VVD. Cyclic CPP was found in 20%, and of these patients, 30% had at least one other CPP-related diagnosis. Although limited by its design as a survey, this study demonstrates that CPP frequently (between 30 and 43%) occurs with other pain syndromes. Clinicians should be prepared to evaluate nongynaecologic causes of pelvic pain.

KETAMINE

SEXUAL DYSFUNCTION IN WOMEN WITH KETAMINE CYSTITIS: A CASE-CONTROL STUDY.

Jang MY, Long CY, Chuang SM, Huang CH, Lin HY, Wu WJ, Juan YS. *BJU Int.* 2012 Aug;110(3):427-431. doi: 10.1111/j.1464-410X.2011.10780.x. Epub 2011 Dec 16. PMID: 22176970

A very interesting study from Taiwan on the topic of ketamine cystitis. Extreme ketamine abuse not only damages the bladder and results in bladder wall fibrosis, but also causes bladder mucosa ulcers [*it is particularly interesting to note that ulceration of the bladder mucosa also occurs with ketamine cystitis as in the classic form of IC. ed.*].

Women with the presence of LUTs and chronic pelvic pain appear to show an impact on sexual functions. Increasing problems of ketamine-associated cystitis are being seen in daily clinical practice. The present case-control study investigated clinical symptom severity and sexual dysfunction in women with KC. The present study showed, with the exception of the sexual desire domain of the female sexual function index, that patients with KC scored lower on all domains compared to controls. The prevalence of sexual dysfunction was high in patients with KC. The purpose of this study was to conduct a case-control study evaluating clinical symptom severity and sexual dysfunction in women with ketamine cystitis. In total, 29 patients with KC and 27 controls completed the symptoms survey. Participants completed a visual pelvic pain analogue scale, an O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index questionnaire, a Female Sexual Function Index, and a short form of the Chinese Health Questionnaire-12. Both the Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index scores were significantly higher in patients with KC compared to controls ($P < 0.001$). The prevalence of sexual dysfunction was high in patients with KC. There was a difference in total adjusted Female Sexual Function Index scores between the patients with KC and controls: mean (sd) total Female Sexual Function Index score 17.65 (6.15) for KC cases vs 25.87 (4.16) for controls. Except for the sexual desire domain of female sexual dysfunction, patients with KC scored lower on all domains compared to controls. There was no significant difference between patients with KC and controls with respect to mental health as evaluated by the Chinese Health Questionnaire-12. It was concluded that sexual dysfunction and KC symptoms severely impacted on quality of life. Mental health had no significant difference between patients with KC and controls.

KETAMINE-ASSOCIATED URINARY TRACT DYSFUNCTION: AN UNDERRECOGNIZED CLINICAL ENTITY.

Lai Y, Wu S, Ni L, Chen Z, Li X, Yang S, Gui Y, Guan Z, Cai Z, Ye J. *J Urol Int.* 2012 Jun 16. [Epub ahead of print]. PMID: 22710265

Lai and colleagues from China report that the use of ketamine as a recreational drug is on the increase among young adults attending clubs and parties. Recreational ketamine users have anecdotally reported increased lower urinary tract symptoms while using the substance. The authors describe the severe lower urinary tract symptoms experienced in 6 patients with chronic recreational ketamine use. They obtained a detailed history and physical examination along with further investigation to identify a relationship between recreational ketamine use and these symptoms. The urine cultures were sterile in all cases. Intravenous urography was performed in 3 patients and demonstrated bilateral upper ureteric narrow, mild bilateral hydronephrosis and contracted bladder urodynamic studies showed detrusor instability with urinary leakage when the bladder was filled to a capacity of 30- 50 ml. Cystoscopy revealed a small capacity bladder with erythematous lesions throughout the bladder. Bladder biopsies were performed in 3 patients and showed up as chronic cystitis. Ketamine cessation along with intravesical sodium hyaluronate solution appeared to provide some symptomatic relief. Ketamine-associated urinary tract dysfunction appears to be a relatively new clinical phenomenon. The pathological mechanism of ketamine-associated urinary tract dysfunction is unknown and current management strategies are ketamine cessation along with intravesical sodium hyaluronate solution.

[KETAMINE-ASSOCIATED UROLOGICAL SYMPTOMS].

[Article in Dutch]

Jansonijs A, Oddens JR. Ned Tijdschr Geneeskd. 2012;156(10):A4176. PMID: 22394445

Jansonijs and Oddens from the Netherlands report on a ketamine case. They note that ketamine is used as an anaesthetic and in third-line pain management. Furthermore, recreational use of the drug is becoming increasingly popular due to its dissociative and hallucinogenic effects. Ketamine can affect the urothelium, possibly with long-term damage to the bladder and kidneys. An otherwise healthy, 22-year-old female smoker was referred to our clinic. Shortly after starting recreational ketamine, she experienced gross haematuria, urgency, frequency and dysuria. There had been no febrile episodes or flank pain. Her urine cultures were sterile. Physical examination, blood tests, urinary cytology and abdominal ultrasound results were normal. A severely inflamed bladder was seen during cystoscopy. Biopsies showed denuded urothelium and inflammation of the submucosa without malignancy.

The precise mechanism of ketamine-associated urological symptoms is currently unknown. Treatment, therefore, is symptom-targeted and cessation of ketamine is imperative. We recommend that ketamine use is considered in patients with otherwise unexplained urological symptoms.

PAIN

FOOD, PAIN, AND DRUGS: DOES IT MATTER WHAT PAIN PATIENTS EAT?

Bell RF, Borzan J, Kalso E, Simonnet G. Pain. 2012 Jun 15. [Epub ahead of print]. PMID: 22704855

In this topical review from Norway, Bell and colleagues write that the importance of nutrition in promoting health and preventing disease is well established. Nutritional strategies may be useful for improving pain management. Such strategies include optimizing the diet to ensure adequate intake of vitamins and essential amino acids, increasing intake of foodstuffs that reduce pain, and restricting foodstuffs that may facilitate pain or reduce the effectiveness of oral analgesics. Adequate nutrition is a basic premise for good health, including pain relief. The authors suggest that the evaluation of diet should be a routine part of the medical work-up for chronic pain, on a par with other lifestyle factors such as exercise and sleep. Future research should focus on pain patients' dietary habits, including intake of polyamines, omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), vitamin D, and caffeine; and the effects of diet on analgesic treatment. Despite an increasing number of preclinical trials demonstrating a role for nutritional factors in pain, epidemiological and clinical trials are lacking. Well designed trials are needed to investigate the antihyperalgesic effects of polyamine-deficient (PD) diet, Mg²⁺, flavonoids, and antioxidants, and to further explore the potential of nutritional therapy in pain patients.

SELF-PERCEIVED BURDEN IN CHRONIC PAIN: RELEVANCE, PREVALENCE, AND PREDICTORS.

Kowal J, Wilson KG, McWilliams LA, Peloquin K, Duong D. Pain. 2012 Jun 13. [Epub ahead of print]. PMID: 22703692

In this article from Ottawa, Kowal and colleagues take a look at the impact of chronic pain on various facets of interpersonal and family functioning. They note that although some studies have examined the extent to which caregivers feel burdened by the provision of emotional and instrumental support to a family member with chronic pain, none have focused on self-perceived burden (SPB) among patients themselves. SPB is defined as "empathic concern engendered from the impact on others of one's illness and care needs, resulting in guilt, distress, feelings of responsibility, and diminished sense of self". It encompasses aspects of self-identity, as well as cognitive, emotional, and interpersonal dimensions. This study examined the prevalence and predictors of self-perceived burden in a tertiary chronic pain sample. Participants were 238 consecutive patients admitted to an outpatient, interdisciplinary, chronic pain management program at a rehabilitation hospital. At admission, participants completed psychometric questionnaires assessing self-perceived burden, as well as a number of clinically relevant constructs. Their significant others (80 people) also completed a measure of caregiver burden. Self-perceived burden was a commonly reported experience among chronic pain patients, with more than 70% of participants endorsing clinically elevated levels. It was significantly correlated with pain intensity ratings, functional limitations, depressive symptoms, attachment anxiety, pain self-efficacy, and caregiver burden. Self-perceived burden was also correlated with an item assessing suicidal thoughts. In a hierarchical regression model, depressive symptoms, pain self-efficacy, and adult attachment significantly predicted self-perceived burden after controlling for demographic and pain-related variables. In conclusion, the study results indicate that SPB is a common and clinically relevant experience among patients with longstanding pain.

PAIN-RELATED CHANGES IN THE BRAIN: DIAGNOSTIC AND THERAPEUTIC POTENTIALS.

Saab CY. *Trends Neurosci.* 2012 Jul 2. [Epub ahead of print]. PMID: 22763295

Emerging evidence suggests that chronic pain is a disease that can alter brain function. Imaging studies have demonstrated structural remapping and functional reorganization of brain circuits under various pain conditions. In parallel, preclinical models have demonstrated that chronic pain causes long-term neuroplasticity. For example, thalamo-cortical oscillations are dysregulated and neurons in the sensory thalamus undergo ectopic firing linked to misexpression of membrane ion channels. In theory, physiological changes at the single-unit, multi-unit, and circuitry levels can be used as predictors of pain, and possibly to guide targeted neuromodulation of specific brain regions for therapeutic purposes. Therefore, multidisciplinary research into the mechanisms of pain-related phenomena in the brain may offer insights into novel approaches for the diagnosis, monitoring, and management of persistent pain.

GASTROINTESTINAL

REFLUX ESOPHAGITIS INCREASED THE RISK OF BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A 3-YEAR FOLLOW-UP STUDY.

Kang JH, Keller JJ, Chen YK, Lin HC. *Neurorol Urodyn.* 2012 Jun 5. doi: 10.1002/nau.22270. [Epub ahead of print]. PMID: 22674619

Those who attended the ESSIC annual meeting in Portugal this year and heard Dr Lori Birder talk about epithelial weakness throughout the body and a possible relationship between IC and gastroesophageal reflux disease (GERD) will be most interested to read this new article from Kang and colleagues from Taipei, Taiwan whose study presented here aimed to explore the association between BPS/IC and reflux esophagitis (RE). They note that inflammatory, neuropathic, allergic, and infectious factors have all been proposed to be involved in the etiology of BPS/IC and that several non-bladder co-morbidities have also been reported to be associated with BPS/IC including fibromyalgia, temporomandibular joint dysfunction, chronic fatigue syndrome (CFS), and systemic autoimmune disease. In this study, they identified 8,962 female patients who had received a diagnosis of RE as the study cohort and randomly selected 44,810 subjects to be included as the comparison cohort. Each patient in this study was individually tracked for a 3-year period to identify those who subsequently received a diagnosis of BPS/IC. Cox proportional hazards regressions were carried out to estimate the 3-year risk of BPS/IC following a diagnosis of RE. The incidence of BPS/IC following a diagnosis of RE was 4.3% during the follow-up period for all subjects. They found that patients with RE were at a higher risk than with comparison patients for having been subsequently diagnosed with BPS/IC during longitudinal follow-up. They suggest that their results can provide a basis to explore non-esophageal disease in RE patients, but emphasise that further studies are advised to confirm their findings and elucidate the pathomechanism underpinning the associations detected in this study. The study had a number of deficiencies as noted by the authors in this article.

ALTERATIONS IN THE NON-NEURONAL ACETYLCHOLINE SYNTHESIS AND RELEASE MACHINERY IN ESOPHAGEAL EPITHELIUM.

Wolf-Johnston AS, Hanna-Mitchell AT, Buffington CA, Shinde S, Roppolo JR, Mayer E, Birder LA. *Life Sci.* 2012 Apr 30. [Epub ahead of print]. PMID: 22569297

Here we have a cat study related to the topic of the study reported above, this time from Pittsburgh. A non-neuronal cholinergic system has been described in epithelial cells including that of the urinary bladder (urothelium) and the upper gastrointestinal tract (esophagus). Epithelial dysfunction has been implicated in the pathophysiology of persistent pain conditions such as painful bladder syndrome as well as functional heartburn. For example, alterations in the ability to synthesize and release acetylcholine may contribute to changes in epithelial sensory and barrier function associated with a number of functional genitourinary and intestinal disorders. Wolf-Johnston and colleagues examined using immunoblot, acetylcholine (ACh)-synthesis and release components in cat esophageal mucosa and whether elements of these components are altered in a naturally occurring model of chronic idiopathic cystitis termed feline interstitial cystitis (FIC). They identified proteins involved in ACh synthesis and release (high affinity choline transporter, CHT1; ACh synthesizing enzyme choline acetyltransferase ChAT and carnitine acetyltransferase CarAT; vesicular ACh transporter VACHT and the organic cation transporter isoforms 1-3 or OCT-1-3) in cat esophageal mucosa from FIC cats. Changes in the vesicular nucleotide transporter (VNUT) and the junctional protein pan-cadherin were also noted. Taken together, these findings suggest that changes in the non-neuronal cholinergic system may contribute to alterations in cell-cell

contacts and possibly communication with underlying cells that may contribute to changes in sensory function and visceral hyperalgesia in functional esophageal pain.

SENSORY NEURO-IMMUNE INTERACTIONS DIFFER BETWEEN IRRITABLE BOWEL SYNDROME SUBTYPES.

Hughes PA, Harrington AM, Castro J, Liebregts T, Adam B, Grasby DJ, Isaacs NJ, Maldeniya L, Martin CM, Persson J, Andrews JM, Holtmann G, Blackshaw AL, Brierley SM. Gut. 2012 Jul 5. [Epub ahead of print]. PMID: 22767422

Hughes and colleagues from Adelaide, Australia note that the gut is a major site of contact between immune and sensory systems and evidence suggests that patients with irritable bowel syndrome (IBS) have immune dysfunction. Here they show how this dysfunction differs between major IBS subgroups and how immunocytes communicate with sensory nerves. Design Peripheral blood mononuclear cell supernatants from 20 diarrhoea predominant IBS (D-IBS) patients, 15 constipation predominant IBS (C-IBS) patients and 36 healthy subjects were applied to mouse colonic sensory nerves and effects on mechanosensitivity assessed. Cytokine/chemokine concentration in the supernatants was assessed by proteomic analysis and correlated with abdominal symptoms, and expression of cytokine receptors evaluated in colonic dorsal root ganglia neurons. They then determined the effects of specific cytokines on colonic afferents. D-IBS supernatants caused mechanical hypersensitivity of mouse colonic afferent endings, which was reduced by infliximab. C-IBS supernatants did not, but occasionally elevated basal discharge. Supernatants of healthy subjects inhibited afferent mechanosensitivity via an opioidergic mechanism. Several cytokines were elevated in IBS supernatants, and levels correlated with pain frequency and intensity in patients. Visceral afferents expressed receptors for four cytokines: IL-1 β , IL-6, IL-10 and TNF- α . TNF- α most effectively caused mechanical hypersensitivity which was blocked by a transient receptor potential channel TRPA1 antagonist. IL-1 β elevated basal firing, and this was lost after tetrodotoxin blockade of sodium channels. The authors concluded that distinct patterns of immune dysfunction and interaction with sensory pathways occur in different patient groups and through different intracellular pathways. They are of the opinion that their results indicate that IBS patient subgroups would benefit from selective targeting of the immune system.

VULVODYNIA

ASSESSMENT AND MANAGEMENT OPTIONS FOR WOMEN WITH VULVODYNIA.

Cox KJ, Neville CE. J Midwifery Womens Health. 2012 May-Jun;57(3):231-40. doi: 10.1111/j.1542-2011.2012.00162.x. Epub 2012 May 3. PMID: 22594863

Cox and Neville from the University of New Mexico College of Nursing have provided an overview of assessment and management of vulvodynia. Vulvodynia is a chronic pain disorder that affects sexual function in adult women. The etiology of vulvodynia is poorly understood, making the condition difficult to diagnose and treat. Women with vulvodynia often suffer significant psychological distress and have difficulty finding a compassionate and supportive health care provider. This article reviews the etiology, diagnosis, educational strategies, and treatment options for vulvodynia with the aim of increasing primary care providers' knowledge and assessment skills. Physical therapy and other nonsurgical treatment modalities are explored in depth.

COMFORT IN DISCUSSING VULVAR PAIN IN SOCIAL RELATIONSHIPS AMONG WOMEN WITH VULVODYNIA.

Nguyen RH, MacLehose RF, Veasley C, Turner RM, Harlow BL, Horvath KJ. J Reprod Med. 2012 Mar-Apr;57(3-4):109-14. PMID: 22523869

The purpose of this study from Minneapolis was to assess women's likelihood of feeling comfortable in discussing vulvar pain. Using a survey of women with self-reported clinician-diagnosed vulvodynia, they assessed the likelihood of comfort in discussing vulvar pain within four types of relationships: husband/partner, mother/sister, best friend, and other women friends. Separate multivariable models were fit for relationship type to determine whether vulvar pain characteristics (length, severity, family history) were associated with likelihood of feeling comfortable in discussing. A total of 67% of women with a partner were comfortable discussing their vulvar pain with that person, whereas 39% were comfortable with family and 26% were comfortable with women friends. Independent of age, the more years women had vulvodynia the less likely they would be comfortable discussing it. Compared to lower levels of vulvar pain, increasing levels (mild, moderate and severe) were associated with greater comfort in discussing their pain with friends; women were 10% more likely to be comfortable with each increase in pain level, and 12% more likely to be comfortable with other women friends. The authors concluded that their data suggest that vulvar pain characteristics may determine how comfortable a woman is to discuss her vulvar pain, but that it varies by relationship type.

RATES OF SELF-REPORTED URINARY, GASTROINTESTINAL, AND PAIN COMORBIDITIES IN WOMEN WITH VULVAR LICHEN SCLEROSUS.

Berger MB, Damico NJ, Menees SB, Fenner DE, Haefner HK. *J Low Genit Tract Dis.* 2012 May 22. [Epub ahead of print]. PMID: 22622339

This study by Berger and colleagues from Michigan aimed to determine the prevalences of comorbid disorders in women with vulvar lichen sclerosus. A retrospective review of self-administered questionnaires regarding the health history of 308 women with lichen sclerosus seen at a vulvar clinic between 2006 and 2011 was performed. Responses to questions about urinary (overactive bladder [OAB], urinary incontinence [UI], and stress UI), gastrointestinal (inflammatory bowel diseases, constipation, and irritable bowel syndrome), thyroid dysfunction and pain (interstitial cystitis, fibromyalgia, temporomandibular joint disorder, and vulvar pain) disorders were collected. The percentage of subjects self-reporting each comorbidity was compared with the published prevalence in the general population using a single-value binomial test. They found that vulvar lichen sclerosus is associated with numerous bladder, bowel, and pain comorbidities. The prevalences of all of these disorders are higher in our subjects than the general population except OAB, which we find at approximately one third of the general population. Patients with lichen sclerosus should be screened for comorbidities that may affect their health and/or quality of life.

FIBROMYALGIA

THE ASSOCIATION BETWEEN OVERACTIVE BLADDER AND FIBROMYALGIA SYNDROME: A COMMUNITY SURVEY.

Chung JH, Kim SA, Choi BY, Lee HS, Lee SW, Kim YT, Lee TY, Moon HS. *Neurourol Urodyn.* 2012 Jun 5. doi: 10.1002/nau.22277. [Epub ahead of print]. PMID: 22674758

Fibromyalgia syndrome (FMS) is the most common disease causing chronic generalized pain, and FMS patients often complain of urinary symptoms such as frequency or urgency. This study from Seoul, Korea focuses on the association of overactive bladder (OAB) and FMS in adults aged 40 and over. A survey of adults aged 40s and over was conducted in the Guri and Yangpyeong areas of South Korea. The response rate was 74.2% (940/1,266). After excluding 20 subjects with incomplete questionnaires, 920 were included in the final analysis. The association of FMS and OAB was analyzed by univariate and multivariate logistic regression analysis. Individuals with FMS had a significantly increased symptoms of OAB after adjustment for gender, age group, and area of residence (odds ratio (OR) 3.39, 95% confidence interval (CI) 1.82-6.31). The association between FMS and severity of OAB was statistical significant (P for trend <0.0001). The authors concluded that OAB is associated with FMS and that FMS increases with severity of OAB. They suggest that a large scale study should be performed by medical specialists (urologists, rheumatologists) to further evaluate the patients and identify the basis of the association between the two diseases.

INTACT COGNITIVE INHIBITION IN PATIENTS WITH FIBROMYALGIA BUT EVIDENCE OF DECLINED PROCESSING SPEED.

Veldhuijzen DS, Sondaal SF, Oosterman JM. *J Pain.* 2012 May;13(5):507-15. PMID: 22564673

Patients with fibromyalgia frequently report cognitive complaints. In this study, Veldhuijzen and colleagues from Utrecht, Netherlands, examined performance on 2 cognitive inhibition tests, the Stroop Color-Word Test (SCWT) and the Multi-Source Interference Test (MSIT), in 35 female patients with fibromyalgia and 35 age-matched healthy female controls. Experimental pressure pain thresholds (PPT) were determined, and fibromyalgia patients rated their current pain on a visual analog scale and completed the pain and fatigue subscales of the Fibromyalgia Impact Questionnaire. Further, all subjects completed questionnaires assessing symptoms of pain catastrophizing, depression, and anxiety. Significant group differences were found for SCWT and MSIT performance in both the neutral (N) and interference (I) conditions with slower reaction times in patients versus controls. However, no significant group differences were found for the difference (I-N) or proportion (I/N) scores, or on the number of errors made. For patients, pain experienced during PPT correlated significantly to several indices of cognition. Psychosocial variables were not related to cognitive test performance. Fibromyalgia patients performed worse on both tests but to a similar extent for the neutral condition and the interference condition, indicating that there is no specific problem in cognitive inhibition. Evidence of decreased mental processing and/or psychomotor speed was found in patients with fibromyalgia. While fibromyalgia patients performed worse on interference tests, no specific problem in cognitive inhibition was found. Decreased reaction time performance may instead point to an underlying problem of psychomotor or mental processing speed in fibromyalgia. Future studies should examine potential deficits in psychomotor function in fibromyalgia patients in more detail.

AUTOIMMUNE DISEASES

NEW TOOLS FOR CLASSIFICATION AND MONITORING OF AUTOIMMUNE DISEASES.

Maecker HT, Lindstrom TM, Robinson WH, Utz PJ, Hale M, Boyd SD, Shen-Orr SS, Fathman CG. Nat Rev Rheumatol. 2012 May 31;8(6):317-28. doi: 10.1038/nrrheum.2012.66. PMID: 22647780

In this review article from Stanford, USA, Maecker and colleagues note that rheumatologists see patients with a range of autoimmune diseases and that phenotyping these diseases for diagnosis, prognosis and selection of therapies is an ever increasing problem. Advances in multiplexed assay technology at the gene, protein, and cellular level have enabled the identification of 'actionable biomarkers'; that is, biological metrics that can inform clinical practice. Not only will such biomarkers yield insight into the development, remission, and exacerbation of a disease, they will undoubtedly improve diagnostic sensitivity and accuracy of classification, and ultimately guide treatment. This review provides an introduction to these powerful technologies that could promote the identification of actionable biomarkers, including mass cytometry, protein arrays, and immunoglobulin and T-cell receptor high-throughput sequencing. In the authors' opinion, these technologies should become part of routine clinical practice for the management of autoimmune diseases. The use of analytical tools to deconvolve the data obtained from use of these technologies is also presented here. These analyses are revealing a more comprehensive and interconnected view of the immune system than ever before and should have an important role in directing future treatment approaches for autoimmune diseases.

SJOGREN'S SYNDROME

AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME: A DATA-DRIVEN, EXPERT CONSENSUS APPROACH IN THE SJÖGREN'S INTERNATIONAL COLLABORATIVE CLINICAL ALLIANCE COHORT.

Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, Schiødt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich AM, Helin P, Kirkham B, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Greenspan J, Daniels T; Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups. Arthritis Care Res (Hoboken). 2012 Apr;64(4):475-87. PMID: 22563590

Shiboski and colleagues propose new classification criteria for Sjögren's syndrome (SS), which are needed considering the emergence of biologic agents as potential treatments and their associated comorbidity. These criteria target individuals with signs/symptoms suggestive of SS. The criteria are based on expert opinion elicited using the nominal group technique and analyses of data from the Sjögren's International Collaborative Clinical Alliance. Preliminary criteria validation included comparisons with classifications based on the American–European Consensus Group (AECG) criteria, a model-based "gold standard" obtained from latent class analysis (LCA) of data from a range of diagnostic tests, and a comparison with cases and controls collected from sources external to the population used for criteria development. Validation results indicate high levels of sensitivity and specificity for the criteria. Case definition requires at least 2 of the following 3: 1) positive serum anti-SSA and/or anti-SSB or (positive rheumatoid factor and antinuclear antibody titer >1:320), 2) ocular staining score >3, or 3) presence of focal lymphocytic sialadenitis with a focus score >1 focus/4 mm² in labial salivary gland biopsy samples. Observed agreement with the AECG criteria is high when these are applied using all objective tests. However, AECG classification based on allowable substitutions of symptoms for objective tests results in poor agreement with the proposed and LCA-derived classifications. These classification criteria developed from registry data collected using standardized measures are based on objective tests. Validation indicates improved classification performance relative to existing alternatives, making them more suitable for application in situations where misclassification may present health risks.

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