

## SCIENTIFIC LITERATURE UPDATE

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

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

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

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

#### [PAINFUL BLADDER FILLING AND PAINFUL URGENCY ARE DISTINCT CHARACTERISTICS IN MEN AND WOMEN WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROMES - A MAPP RESEARCH NETWORK STUDY.](#)

Lai HH, Krieger JN, Pontari MA, Buchwald D, Hou X, Landis JR; MAPP Research Network. *J Urol.* 2015 Jul 17. pii: S0022-5347(15)04413-4. doi: 10.1016/j.juro.2015.05.105. [Epub ahead of print] PMID: 26192257

This MAPP Research Network Study by Lai and colleagues describes bladder-associated symptoms in patients with urologic chronic pelvic pain syndromes (UCPPS) and correlates these symptoms with urologic, non-urologic, psychosocial, and quality of life measures. Participants were 233 women and 191 men with interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome in a multi-center study. They completed a battery of measures, including items asking if their pain worsened with bladder filling ("painful filling") or if their urge to urinate was due to pain, pressure, or discomfort ("painful urgency"). Participants were categorized into 3 groups:

- 1) **both** painful filling and painful urgency,
- 2) **either** painful filling or painful urgency,
- 3) **neither**.

Seventy-five percent of men and 88% of women were categorized as "both" or "either." These bladder characteristics were associated with more severe urologic symptoms (increased pain, frequency, urgency), higher somatic symptom burden, depression, and worse quality of life. A gradient effect was observed across groups (both > either > neither). Compared to those in the "neither" group, men categorized as "both" or "either" reported more frequent UCPPS symptom flares, catastrophizing, and irritable bowel syndrome, and women categorized as "both" or "either" were more likely to have negative affect and chronic fatigue syndrome. It was concluded that men and women with bladder symptoms characterized as painful filling or painful urgency had more severe urologic symptoms, more generalized symptoms, and worse quality of life than participants who reported neither characteristic, suggesting that these symptom characteristics might represent important subsets of UCPPS patients.

#### [WIDESPREAD PSYCHOSOCIAL DIFFICULTIES IN MEN AND WOMEN WITH UROLOGIC CHRONIC PELVIC PAIN SYNDROMES: CASE-CONTROL FINDINGS FROM THE MULTIDISCIPLINARY APPROACH TO THE STUDY OF CHRONIC PELVIC PAIN RESEARCH NETWORK.](#)

Naliboff BD, Stephens AJ, Afari N, Lai H, Krieger JN, Hong B, Lutgendorf S, Strachan E, Williams D; MAPP Research Network. *Urology.* 2015 Jun;85(6):1319-27. doi: 10.1016/j.urology.2015.02.047. PMID: 26099876

The purpose of this MAPP Research Network study was to determine the extent, severity, and sex differences of psychosocial deficits in men and women with urologic chronic pelvic pain syndromes (UCPPS), which in the past have been considered separate bladder (interstitial cystitis-painful bladder syndrome) and prostate (chronic prostatitis-chronic pelvic pain syndrome) disorders. Evaluations of men and women separately suggest UCPPS is associated with increased anxiety and depression. However, studies directly testing deficits in broader psychosocial domains such as cognitive processes, intimate relationships, and trauma history, or tests of sex differences in the pattern of difficulties associated with UCPPS have not been performed. A total of 233 female

and 191 male UCPPS patients and 235 female and 182 male healthy controls (HCs) were recruited from 6 academic medical centers in the United States and evaluated with a comprehensive battery of symptom, psychosocial, and illness impact measures. Primary comparisons of interest were between UCPPS patients and HCs and between men and women with UCPPS. In addition to greater negative effect, male and female UCPPS patients show higher levels of current and lifetime stress, poorer illness coping, increased self-report of cognitive deficits, and more widespread pain symptoms compared with sex- and education-matched HCs. Similar problems were found in male and female UCPPS patients although female UCPPS patients showed increased self-report of childhood adversity and more widespread symptoms of pain and discomfort. Given the significance of psychosocial variables in prognosis and treatment of chronic pain conditions, the results add substantially to our understanding of the breadth of difficulties associated with UCPPS and point to important areas for clinical assessment.

### **IC/BPS/HSB BASIC SCIENCE, DIAGNOSIS AND TREATMENT**

#### **THE ROLE OF GLOMERULATIONS IN BLADDER PAIN SYNDROME – A REVIEW**

Wennevik GE, Meijlink JM, Hanno P, Nordling J. DOI: <http://dx.doi.org/10.1016/j.juro.2015.06.112> 2015 August 26 [E-pub ahead of print]

Glomerulations as a diagnostic marker for bladder pain syndrome/interstitial cystitis (BPS/IC) was first popularized by Messing & Stamey in 1978. Later this was included in the NIDDK criteria for research and consequently used by many urologists as a default diagnostic criterion. Today, the connection between glomerulations and BPS/IC is much debated, as research has found glomerulations in asymptomatic populations. This paper systematically looks at the available research to see if there is valid data to support the use of glomerulations as a marker for BPS/IC. Wennevik and colleagues found no consistent relationship between glomerulations and the diagnosis of BPS/IC. In the reviewed studies, they found evidence of the grade of glomerulations changing over time. Furthermore, many studies showed no link between the severity of symptoms and the number of glomerulations. There were studies that found glomerulations in healthy asymptomatic populations as well as in symptomatic populations with another primary diagnosis. The authors concluded from the reviewed literature, that there is no convincing evidence that glomerulations should be included in diagnosis or phenotyping of BPS/IC. It does not correlate with symptoms and is found in patients without BPS/IC.

#### **TREATMENT OF BLADDER PAIN SYNDROME AND INTERSTITIAL CYSTITIS: A SYSTEMATIC REVIEW.**

Pazin C, de Souza Mitidieri AM, Silva AP, Gurian MB, Poli-Neto OB, Rosa-E-Silva JC. *Int Urogynecol J.* 2015 Aug 14. [Epub ahead of print] PMID: 26272202

Bladder pain syndrome/interstitial cystitis (BPS/IC) has various treatments; however, no standardized treatment has been established. The aim of this review by Pazin and colleagues from Brazil was to analyze different types of treatment of BPS/IC and their effectiveness. A literature review with a search strategy for articles related to BPS/IC published between 1990 and 2014 was conducted on MEDLINE, PUBMED, and SCOPUS. Only randomized controlled trials in women were included in the meta-analysis, while other experimental studies were used as bases for a systematic review of the topic. Clinical trial quality was defined according to the Jadad scale. Of 356 articles, 13 were included in the analysis. The intervention methods were as follows: instillation of hyaluronic acid, botulinum toxin A, intravesical lidocaine, hyperbaric chamber, massage, physiotherapy, phosphate-buffered saline, piroxicam in combination with doxepin, and others. The authors did not find any treatment with at least two randomized controlled trials for meta-analysis. Among the assessment tools for symptoms of BPS/IC, the most frequently used were the visual analogue scale, voiding record, and the O'Leary-Sant questionnaire. It was concluded that existing studies were not able to define the best approach for the treatment of BPS/IC. The lack of standardized treatment may be related to the diversity of interventions used; therefore, further studies with better methodological quality are needed.

#### **RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF BLADDER PAIN SYNDROME. SPANISH UROLOGICAL ASSOCIATION CONSENSUS DOCUMENT.**

[Article in English, Spanish]

Esteban M, Adot JM, Arlandis S, Peri L, Prieto L, Salinas J, Cozar JM; Grupo de trabajo para las recomendaciones en el diagnóstico y manejo del síndrome de dolor vesical. Realizado bajo los auspicios de la Asociación Española de Urología. 2013. *Actas Urol Esp.* 2015 May 27. pii: S0210-4806(15)00029-7. doi: 10.1016/j.acuro.2015.01.006. [Epub ahead of print] PMID: 26026254

Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) and other bladder pathologies share common manifestations, such as the presence of mictional symptoms and a negative impact on the patient's quality of life. To be properly diagnosed and clinically managed, it is important to distinguish between its clinical modalities and diagnostic criteria for adequate exclusion. The purpose of this study from Spain was to standardize criteria for making decisions in BPS management, for its diagnosis, initial treatment and follow-up. A nominal group methodology was employed, using scientific evidence on BPS taken from a systematic (non-exhaustive) literature review for developing recommendations along with specialist expert opinions. The authors found that the diagnosis of BPS should be made based on the patient's clinical history, with emphasis on pain and mictional symptoms as well as excluding other pathologies with similar symptomatology. BPS treatment should be directed towards restoring normal bladder function, preventing symptom relapse and improving patients' quality of life. It is therefore advisable to start with conservative treatment and to adopt less conservative treatments as the level of clinical severity increases. It is also recommended to abandon ineffective treatments and reconsider other therapeutic options. They concluded that quickly identifying the pathology is important when trying to positively influence morbidity and care quality for these patients.

### **THE EFFECTS OF INTRAVESICAL THERAPY WITH HYALURONIC ACID FOR PAINFUL BLADDER SYNDROME: PRELIMINARY CHINESE EXPERIENCE AND SYSTEMATIC REVIEW.**

*Han XM, Wu XH, Li B, Pan F, Li WC, Liu SL, Zeng FQ, Chen M. Taiwan J Obstet Gynecol. 2015 Jun;54(3):240-7. doi: 10.1016/j.tjog.2014.09.007. PMID: 26166334*

This paper by Han and colleagues from China presents the preliminary results of treating a series of Chinese patients with painful bladder syndrome/interstitial cystitis (PBS/IC) using intravesical hyaluronic acid (HA). A series of 13 patients with PBS/IC received first-line therapy followed by HA once-a-week for 4 weeks and then once monthly for 4 months. Outcomes measured included O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ISPI) scores, voiding frequency, and bladder capacity. ISPI and ICSI scores were significantly decreased after treatment. Voiding frequency and functional bladder capacity were significantly decreased and increased respectively after treatment. The authors concluded that their case series supports the efficacy of intravesical HA in the treatment of PBS/IC.

### **INTRAVESICAL TREATMENT WITH CIS-UROCANIC ACID IMPROVES BLADDER FUNCTION IN RAT MODEL OF ACUTE BLADDER INFLAMMATION.**

*Konkol Y, Bernoulli J, Streng T, Jääskeläinen K, Laihia J, Leino L. Neurourol Urodyn. 2015 Jul 14. doi: 10.1002/nau.22818. [Epub ahead of print] PMID: 26175302*

The aim of this study from Finland was to examine the effect of intravesically instilled cis-urocanic acid (cis-UCA) on bladder function in an experimental rat model of acute bladder inflammation. Hyaluronic acid (HA) was used as a comparator compound. Bladder irritation was induced in female rats by intravesical hydrochloric acid (HCl) infusion. Vehicle, 0.5% HA, or 2% cis-UCA solutions were infused intravesically twice a day for three consequent days. On the fourth day, urodynamical measurements were performed, the animals were sacrificed, and the bladders were removed for histopathological assessment. HCl treatment caused significant impairment of bladder function indicated by decreased micturition intervals and voided urine volumes and induced severe voiding dysfunction observed as occurrence of overflow incontinence. These functional changes were accompanied by increased bladder weight, hemorrhage, and infiltration of inflammatory cells into the urothelium. Intravesical cis-UCA treatment recovered bladder function by significantly prolonging the micturition interval, increasing the voided volume, and reducing the occurrence of overflow incontinence. All these changes were comparable to the effects of HA. Intravesical administration of cis-UCA was able to partially recover bladder function impaired by chemical irritation. Cis-UCA may offer a novel intravesical treatment option in some inflammatory conditions of the bladder.

### **CURRENT AND POTENTIAL UROLOGICAL APPLICATIONS OF BOTULINUM TOXIN A.**

*Jiang YH, Liao CH, Kuo HC. Nat Rev Urol. 2015 Aug 11. doi: 10.1038/nrurol.2015.193. [Epub ahead of print] PMID: 26260879*

In this review paper, Jiang and colleagues from Taiwan report that botulinum toxin subtype A (BoNT-A) is a potent neurotoxin that can selectively modulate neurotransmitter release from nerve endings, resulting in muscular paralysis. BoNT-A might also act on sensory nerves, and have an anti-inflammatory effect. In the first urological use of BoNT-A, injection into the urethral sphincters of patients with detrusor-sphincter dyssynergia resulted in a reduction of urethral resistance and improved voiding efficiency. Subsequently, intravesical BoNT-A injections have received regulatory approval for treatment of neurogenic detrusor overactivity owing to spinal cord lesions or multiple sclerosis, and idiopathic overactive bladder in adults. BoNT-A has also been

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widely used to treat patients with the off-label indications of neurogenic or non-neurogenic voiding dysfunction and male lower urinary tract symptoms owing to BPH and bladder-neck dysfunction. Other indications for which urologists have applied BoNT-A injections include interstitial cystitis/bladder pain syndrome, bladder oversensitivity and chronic pelvic pain syndrome. BoNT-A is currently delivered as an intravesical injection; however, use of liposome encapsulated formulations is also beginning to show some therapeutic potential.

### [NOVEL TREATMENT OF CHRONIC BLADDER PAIN SYNDROME AND OTHER PELVIC PAIN DISORDERS BY ONABOTULINUMTOXINA INJECTION.](#)

*Jhang JF, Kuo HC. Toxins (Basel). 2015 Jun 18;7(6):2232-50. doi: 10.3390/toxins7062232. PMID: 26094697.*

**Free full text, click on title**

Chronic pelvic pain (CPP) is defined as pain in the pelvic organs and related structures of at least 6 months' duration. The pathophysiology of CPP is uncertain, and its treatment presents challenges. Botulinum toxin A (BoNT-A), known for its antinociceptive, anti-inflammatory, and muscle relaxant activity, has been used recently to treat refractory CPP with promising results. In patients with interstitial cystitis/bladder pain syndrome, most studies suggest intravesical BoNT-A injection reduces bladder pain and increases bladder capacity. Repeated BoNT-A injection is also effective and reduces inflammation in the bladder. Intraprostatic BoNT-A injection could significantly improve prostate pain and urinary frequency in the patients with chronic prostatitis/chronic pelvic pain syndrome. Animal studies also suggest BoNT-A injection in the prostate decreases inflammation in the prostate. Patients with CPP due to pelvic muscle pain and spasm also benefit from localized BoNT-A injections. BoNT-A injection in the pelvic floor muscle improves dyspareunia and decreases pelvic floor pressure. Preliminary studies show intravesical BoNT-A injection is useful in inflammatory bladder diseases such as chemical cystitis, radiation cystitis, and ketamine related cystitis. Dysuria is the most common adverse effect after BoNT-A injection. According to Jhang and Kuo, very few patients develop acute urinary retention after treatment.

### [O'LEARY-SANT SYMPTOM INDEX PREDICTS THE TREATMENT OUTCOME FOR ONABOTULINUMTOXINA INJECTIONS FOR REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

*Kuo YC, Kuo HC. Toxins (Basel). 2015 Jul 30;7(8):2860-71. doi: 10.3390/toxins7082860. PMID: 26264022*

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Although intravesical injection of onabotulinumtoxinA (BoNT-A) has appeared to be promising for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS), it is still unclear which type of patient is likely to benefit from this treatment. This study from Taiwan investigated the predictors for a successful treatment outcome. Patients with IC/BPS who failed conventional treatments were enrolled to receive intravesical injection of 100 U of BoNT-A immediately followed by hydrodistention. Variables such as O'Leary-Sant symptom and problem indexes (ICSI and ICPI), pain visual analogue scale (VAS), functional bladder capacity (FBC), voiding diary, and urodynamic parameters were measured at baseline and six months after treatment. A global response assessment (GRA)  $\geq 2$  at six months was defined as successful. 101 patients were enrolled. Significant improvements were observed in mean ICSI, ICPI, OSS (ICSI + ICPI), pain VAS, FBC, frequency, nocturia and GRA at six months after BoNT-A injections. The success rate at six months was 46/101 (45.54%). Multivariate logistic regression revealed that the baseline ICSI was the only predictor for a treatment outcome. ICSI  $\geq 12$  was the most predictive cutoff value for a treatment failure, with a ROC area of 0.70 (sensitivity = 69.1%, specificity = 60.9%).

### [PAIN: BONT-A REDUCES PAIN IN PATIENTS WITH TREATMENT REFRACTORY IC/BPS.](#)

*Sidaway P. Nat Rev Urol. 2015 Jun;12(6):300. doi: 10.1038/nrurol.2015.101. Epub 2015 May 12. PMID:25963967*

The newly published results of a randomized controlled trial reveal that intravesical injections of onabotulinumtoxin-A (BoNT-A) reduce the pain symptoms of patients with interstitial cystitis/bladder pain syndrome (IC/BPS).

### [MRI SUGGESTS INCREASED TONICITY OF THE LEVATOR ANI IN WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)

*Ackerman AL, Lee UJ, Jellison FC, Tan N, Patel M, Raman SS, Rodriguez LV. Int Urogynecol J. 2015 Aug 1. [Epub ahead of print] PMID: 26231233*

In interstitial cystitis/bladder pain syndrome (IC/BPS), pelvic floor dysfunction may contribute significantly to pelvic pain. Ackermann and colleagues from Los Angeles retrospectively compared pelvic measurements

between patients and controls to determine if pelvic floor hypertonicity manifests alterations on magnetic resonance imaging (MRI) in patients with IC/BPS. Fifteen women with IC/BPS and 15 age-matched controls underwent pelvic MRI. Two blinded radiologists measured the pelvic musculature, including the H- and M lines, vaginal length, urethral length and cross-sectional area, levator width and length, and posterior puborectalis angle. MRI measures and clinical factors, such as age, parity, and duration of symptoms, were compared using a paired, two-tailed t test. The authors found no significant differences in age, parity, or symptom duration between groups. Patients with IC/BPS exhibited shorter levator muscles and a wider posterior puborectalis angle compared with controls. The H line was shorter in patients with IC/BPS, while M line did not differ. Total urethral length was similar, but vaginal cuff and bladder neck distances to the H line were longer in patients with IC/BPS. It was concluded that patients with IC/BPS have pelvic floor hypertonicity on MRI, which manifests as shortened levator, increased posterior puborectalis angles, and decreased puborectal distances. They identified evidence of pelvic floor hypertonicity in patients with IC/BPS, which may contribute to or amplify pelvic pain. Future studies are necessary to determine the MRI utility in understanding pelvic floor hypertonicity in patients with IC/BPS.

**STATIN USE IS ASSOCIATED WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS: A POPULATION-BASED CASE-CONTROL STUDY.**

*Huang CY, Chung SD, Kao LT, Lin HC, Wang LH. Urol Int. 2015 Jul 16. [Epub ahead of print] PMID: 26184102*

Statin may induce epithelial dysfunction of the bladder urothelium. Epithelial dysfunction was proposed as one of the major potential etiologies for bladder pain syndrome/interstitial cystitis (BPS/IC). In this study, Huang and colleagues from Taiwan examined the association between statin use and BPS/IC using a population-based study. This case-control study used the Taiwan Longitudinal Health Insurance Database. In total, 815 female subjects with BPS/IC and 4075 randomly selected female controls were included. The authors used a conditional logistic regression to compute the odds ratio (OR) for having previously used statins between cases and controls. A conditional logistic regression analysis showed that the OR of prior statin users for cases was 1.52 (95% confidence interval (CI): 1.19-1.94) compared to controls after adjusting for diabetes, hypertension, coronary heart disease, obesity, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraines, sicca syndrome, allergies, endometriosis, and asthma. Furthermore, adjusted ORs of regular and irregular statin use for cases were 1.58 (95% CI: 1.20-2.08) and 1.53 (95% CI: 1.02-2.31), respectively, compared to controls. They concluded that there was an association between statin use and BPS/IC.

**EVALUATION OF PERCUTANEOUS TIBIAL NERVE STIMULATION FOR TREATMENT OF REFRACTORY PAINFUL BLADDER SYNDROME.**

*Ragab M, Tawfik A, Abo Elenen M, Elnady M, Elgamal O, Elkordy M, Gameel T, Rasheed M. Urology. 2015 Jul 15. pii: S0090-4295(15)00646-9. doi: 10.1016/j.urology.2015.06.041. [Epub ahead of print] PMID: 26188120*

The purpose of this study from Egypt was to evaluate the efficacy of intermittent percutaneous tibial nerve stimulation (PTNS) as a treatment in 20 female patients with refractory painful bladder syndrome/interstitial cystitis; each had a 30-minute session of PTNS per week for 12 successive weeks and the symptoms were assessed before, during and after the treatment sessions by voiding diary, visual analog scale (VAS) for pain, interstitial cystitis symptom and problem indices (ICSI and ICPI) and global response assessment scale (GRA). The scores of the previous questionnaires were evaluated at week 0, 6 and 12. It was concluded that intermittent PTNS is not a satisfactory treatment for refractory PBS/IC. However, it is recommended to perform more studies with other treatment protocols (maybe closer sessions) in order to confirm these results.

**HYDRODISTENSION WITH OR WITHOUT FULGURATION OF HUNNER LESIONS FOR INTERSTITIAL CYSTITIS: LONG-TERM OUTCOMES AND PROGNOSTIC PREDICTORS.**

*Niimi A, Nomiya A, Yamada Y, Suzuki M, Fujimura T, Fukuhara H, Kume H, Igawa Y, Homma Y. Neurourol Urodyn. 2015 Jul 24. doi: 10.1002/nau.22837. [Epub ahead of print] PMID: 26208131*

Hydrodistension of the bladder, with optional fulguration of Hunner lesions, is one of the recommended therapies for interstitial cystitis (IC). The aims of this study by Niimi and colleagues from Japan were to evaluate long-term outcomes of hydrodistension and identify outcome predictors. The study cohort was 191 newly diagnosed IC patients (155 women and 36 men) who underwent hydrodistension with fulguration of Hunner lesions if detected between 2007 and 2013 at the authors' institution. The primary outcome was therapeutic failure, which was defined as repeat hydrodistension, bladder instillation therapy, or narcotic use for pain control. Clinical features, including comorbidities and endoscopic findings, were analyzed along with the outcome. The cohort comprised 126 patients of Hunner type IC and 65 patients of non-Hunner type IC. The

mean time to therapeutic failure was 28.5 months in Hunner type IC and 25.2 months in non-Hunner type IC. The therapeutic failure rate was higher in non-Hunner type IC at 17.3 months; however, the long-term outcomes reversed thereafter. The mean time to therapeutic failure was shorter in patients with lumbar spinal stenosis (LSS) or irritable bowel syndrome (IBS). It was concluded that bladder hydrodistension, with fulguration of the Hunner lesions, improved IC symptoms. The outcome was worse in non-Hunner type IC shortly after hydrodistension but eventually comparable across the two types. Concomitant LSS and IBS were predictors for poor outcome.

### [EFFECT OF LOCAL ESTROGEN THERAPY \(LET\) ON URINARY AND SEXUAL SYMPTOMS IN PREMENOPAUSAL WOMEN WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME \(IC/BPS\).](#)

*Gardella B, Iacobone AD, Porru D, Musacchi V, Dominoni M, Tinelli C, Spinillo A, Nappi RE. Gynecol Endocrinol. 2015 Jul 31:1-5. [Epub ahead of print] PMID: 26229041*

The association between vulvodynia and interstitial cystitis/bladder pain syndrome (IC/BPS) may involve sex hormone-dependent mechanisms regulating vulvo-vaginal health. Gardella and colleagues from Italy aimed to prospectively investigate the effects of 12 weeks of local estrogen therapy (LET) on urinary/bladder and sexual symptoms in premenopausal women with IC/BPS. Thirty-four women diagnosed with IC/BPS were treated vulvo-vaginally three-times/week with estriol 0.5 mg cream and tested by validated questionnaires (ICSI/ICPI, pain urgency frequency [PUF], female sexual function index [FSFI]) and by cotton swab testing, vaginal health index (VHI) and maturation index (MI) before and after treatment. Vulvodynia was present in 94.1% of IC/BPS women. A significant positive effect of LET was evident on urinary and sexual function following 12 weeks, as well as an improvement of the VHI and the MI. The results of this open study indicate that 12 weeks of local estriol cream at vaginal and vestibular level may ameliorate urinary/bladder pain symptoms, as well as may improve domains of sexual function. The authors are of the opinion that the association between vulvar pain and bladder pain could, therefore, be related to a vaginal environment carrying signs of hypoestrogenism, but further studies are needed to clarify this issue.

### [FROM BLADDER TO SYSTEMIC SYNDROME: CONCEPT AND TREATMENT EVOLUTION OF INTERSTITIAL CYSTITIS.](#)

*Dinis S, de Oliveira JT, Pinto R, Cruz F, Buffington CT, Dinis P. Int J Womens Health. 2015 Jul 23;7:735-44. doi: 10.2147/IJWH.S60798. eCollection 2015. PMID: 26229509*

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Interstitial cystitis, presently known as bladder pain syndrome, has been recognized for over a century but is still far from being understood. Its etiology is unknown and the syndrome probably harbors different diseases. Autoimmune dysfunction, urothelial leakage, infection, central and peripheral nervous system dysfunction, genetic disease, childhood trauma/abuse, and subsequent stress response system dysregulation might be implicated. Management is slowly evolving from a solo act by the end-organ specialist to a team approach based on new typing and phenotyping of the disease. However, oral and invasive treatments are still largely aimed at the bladder and are based on currently proposed pathophysiologic mechanisms. Future research will better define the disease, permitting individualization of treatment.

### [UNEXPLAINED ASSOCIATION BETWEEN CYSTITIS GLANDULARIS AND INTERSTITIAL CYSTITIS IN FEMALES: A RETROSPECTIVE STUDY.](#)

*Zhang W, Yao YS, Lin ME, Xie WJ, Pan WW. Int Urogynecol J. 2015 Aug 1. [Epub ahead of print] PMID: 26231232*

An increasing number of female patients have received comorbid diagnoses of cystitis glandularis (CG) and interstitial cystitis (IC) at our institution. In addition, most of these patients suffer from coexisting obstructive lower urinary tract diseases (OLUTDs). In this study, Zhang and colleagues from Sun Yat-sen University, Guangzhou, China present evidence of the possible association between CG and IC and analyze the clinical features of this association. The authors retrospectively reviewed the charts of 395 female patients diagnosed with CG and/or IC. The patients were divided into three groups: group A (CG only), group B (IC only), and group C (CG+IC). Chi-squared tests were applied to compare the prevalence rates of CG in patients with IC and in the general population, the prevalence rates of IC in patients with CG and in the general population, and the prevalence rates of OLUTD in the three patient groups. The prevalence rate of IC in patients with CG was significantly higher than that in the general population, while the prevalence rate of CG in patients with IC was also significantly higher than that in the general population. For groups A, B, and C, 93 (39.2 %), 30 (44.1 %), and 58 (64.4 %) cases respectively presented with OLUTDs, and the prevalence rate of OLUTDs varied significantly among the three groups. It was concluded that this retrospective study found a possible association between CG and IC, and coexisting OLUTDs influenced this association.

**HERPES SIMPLEX VIRUS VECTOR-MEDIATED GENE DELIVERY OF PORELESS TRPV1 CHANNELS REDUCES BLADDER OVERACTIVITY AND NOCICEPTION IN RATS.**

Majima T, Funahashi Y, Takai S, Goins WF, Gotoh M, Tyagi P, Glorioso J, Yoshimura N. *Hum Gene Ther.* 2015 Jul 23. [Epub ahead of print] PMID: 26204493

Increased afferent excitability has been proposed as an important pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) and overactive bladder (OAB). In this study, Majima and colleagues from Pittsburgh, USA and Nagoya, Japan investigated whether herpes simplex virus (HSV) vectors encoding poreless TRPV1, in which the segment in C terminus of TRPV1 receptor is deleted, suppress bladder overactivity and pain behavior using a rat model of chemical cystitis. Replication-defective HSV vectors encoding poreless TRPV1 were injected into the bladder wall of adult female Sprague-Dawley rats. Additionally, vHG vectors were injected as control. Cystometry (CMG) under urethane anesthesia was performed 1 week after viral injection to evaluate bladder overactivity induced by resiniferatoxin (RTx, a TRPV1 agonist). RTx-induced nociceptive behavior such as licking (lower abdominal licking) and freezing (motionless head-turning) was observed 2 weeks after viral injection. GFP expression in L4/L6/S1 dorsal root ganglia and the bladder as well as c-Fos positive cells in the L6 spinal cord dorsal horn were also evaluated 2 weeks after viral injection. In CMG, the poreless TRPV1 vector-treated group showed a significantly smaller reduction in intercontraction intervals and voided volume after RTx infusion than the vHG-treated control group. The number of the RTx-induced freezing events was significantly decreased in the poreless TRPV1 group than in the vHG group whereas there was no significant difference of the number of RTx-induced licking events between groups. The number of c-Fos positive cells in the DCM and SPN regions of the L6 spinal dorsal horn was significantly smaller in the poreless TRPV1 group than in the vHG group. The authors' results indicated that HSV vector-mediated gene delivery of poreless TRPV1 had a therapeutic effect on TRPV1-mediated bladder overactivity and pain behavior. This means that the HSV vector mediated gene therapy targeting TRPV1 receptors could be a novel modality for the treatment of OAB and/or hypersensitive bladder disorders such as IC/BPS.

**PURINERGIC SIGNALLING IN THE URINARY BLADDER.**

Andersson KE. *Auton Neurosci.* 2015 Sep;191:78-81. doi: 10.1016/j.autneu.2015.04.012. Epub 2015 Apr 30. PMID: 25979768

It is well established that in most species, exocytotic vesicular release of ATP from parasympathetic neurons contributes to contraction of the bladder. However, ATP is released not only from parasympathetic nerves, but also from the urothelium. During bladder filling, the urothelium is stretched and ATP is released from the umbrella cells thereby activating mechanotransduction pathways. ATP release can also be induced by various mediators present in the urine and and/or released from nerves or other components of the lamina propria. Urothelial release of ATP is mainly attributable to vesicular transport or exocytosis and, to a smaller extent, to pannexin hemichannel conductive efflux. After release, ATP acts on P2X3 and P2X2/3 receptors on suburothelial sensory nerves to initiate the voiding reflex and to mediate the sensation of bladder filling and urgency. ATP also acts on suburothelial interstitial cells/myofibroblasts generating an inward Ca(2+) transient that via gap junctions could provide a mechanism for long-distance spread of signals from the urothelium to the detrusor muscle. ATP release can be affected by urological diseases, e.g., interstitial cystitis and both the mechanisms of release and the receptors activated by ATP may be targets for future drugs for treatment of lower urinary tract disorders.

**EVALUATION OF OXIDATIVE STRESS STATUS AND ANTIOXIDANT CAPACITY IN PATIENTS WITH PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS: PRELIMINARY RESULTS OF A RANDOMISED STUDY.**

Ener K, Keske M, Aldemir M, Özcan MF, Okulu E, Özayar A, Ergin M, Doluoğlu ÖG, Çakmak S, Erel Ö. *Int Urol Nephrol.* 2015 Aug;47(8):1297-302. doi: 10.1007/s11255-015-1021-1. Epub 2015 Jun 7. PMID: 26049975

This study from Turkey aimed to investigate oxidative stress in etiopathogenesis by analyzing serum total antioxidant capacity (TAC), total oxidant status (TOS), binding capacity of exogenous cobalt to human albumin (IMA), serum advanced oxidation protein products (AOPP), paraoxonase (PON), arylesterase, IgE, and C-reactive protein (CRP) in bladder pain syndrome/interstitial cystitis (BPS/IC). The study included 16 female patients diagnosed with BPS/IC and 25 healthy female subjects forming the control group. A bladder biopsy was performed on all patients in the BPS/IC group by carrying out cystoscopy with hydrodistention under general anesthesia. The results of serum TAC, TOS, IMA, AOPP, PON, arylesterase, IgE, and CRP of the subjects in both groups were compared. The mean age of the 16 female patients in the BPS/IC group was 43.6 ± 14.5 years, and the mean age of the 25 healthy subjects in the control group was 42.0 ± 10.3 years. According to the criteria of International Society for the Study of Interstitial Cystitis (ESSIC), eight patients were

classified as Type 2A, three patients as Type 2B, four patients as Type 2C, and one patient as Type 3C. In the BPS/IC group, while TAC was found significantly lower than in the control group, IMA, IgE, and CRP were found significantly higher. When binary logistic regression analysis was performed, the created model was determined to have 81.3 % sensitivity and 80 % specificity. In the etiology of BPS/IC, mechanism of oxidative damage comes into prominence. In the diagnosis of BPS/IC, IgE, CRP, and TAC are not specific markers when used separately; however, a higher specificity and sensitivity could be reached when used jointly in the suspected patients.

**ATP AS A COTRANSMITTER IN THE AUTONOMIC NERVOUS SYSTEM.**

*Kennedy C. Auton Neurosci. 2015 Sep;191:2-15. doi: 10.1016/j.autneu.2015.04.004. Epub 2015 Apr 25. PMID: 26054908*

The role of adenosine 5'-triphosphate (ATP) as a major intracellular energy source is well-established. In addition, ATP and related nucleotides have widespread extracellular actions via the ionotropic P2X (ligand-gated cation channels) and metabotropic P2Y (G protein-coupled) receptors. Numerous experimental techniques, including myography, electrophysiology and biochemical measurement of neurotransmitter release, have been used to show that ATP has several major roles as a neurotransmitter in peripheral nerves. When released from enteric nerves of the gastrointestinal tract it acts as an inhibitory neurotransmitter, mediating descending muscle relaxation during peristalsis. ATP is also an excitatory cotransmitter in autonomic nerves; 1) It is costored with noradrenaline in synaptic vesicles in postganglionic sympathetic nerves innervating smooth muscle preparations, such as the vas deferens and most arteries. When coreleased with noradrenaline, ATP acts at postjunctional P2X1 receptors to evoke depolarisation, Ca(2+) influx, Ca(2+) sensitisation and contraction. 2) ATP is also coreleased with acetylcholine from postganglionic parasympathetic nerves innervating the urinary bladder and again acts at postjunctional P2X1 receptors, and possibly also a P2X1+4 heteromer, to elicit smooth muscle contraction. In both cases the neurotransmitter actions of ATP are terminated by dephosphorylation by extracellular, membrane-bound enzymes and soluble nucleotidases released from postganglionic nerves. There are indications of an increased contribution of ATP to control of blood pressure in hypertension, but further research is needed to clarify this possibility. More promising is the upregulation of P2X receptors in dysfunctional bladder, including interstitial cystitis, idiopathic detrusor instability and overactive bladder syndrome. Consequently, these roles of ATP are of great therapeutic interest and are increasingly being targeted by pharmaceutical companies.

**A FEASIBILITY STUDY TO DETERMINE WHETHER CLINICAL CONTRAST-ENHANCED MRI CAN DETECT INCREASED BLADDER PERMEABILITY IN PATIENTS WITH INTERSTITIAL CYSTITIS.**

*Towner RA, Wisniewski AB, Wu DH, Van Gordon SB, Smith N, North JC, McElhane R, Aston CE, Shobeiri SA, Kropp BP, Greenwood-Van Meerveld B, Hurst RE. J Urol. 2015 Aug 22. pii: S0022-5347(15)04676-5. doi: 10.1016/j.juro.2015.08.077. [Epub ahead of print] PMID: 26307161*

Towner and colleagues from Oklahoma report that currently diagnosis of IC/BPS is complicated, as patients present with wide ranges of symptoms, physical examination findings, and clinical test responses. One hypothesis is that IC symptoms arise from increased bladder permeability to urine solutes. This study established the feasibility of using contrast-enhanced magnetic resonance imaging (CE-MRI) to quantify bladder permeability in IC patients. Permeability alterations in bladder urothelium were assessed with intravesical administration of a MRI contrast agent (Gd-DTPA) in a small cohort of patients. MRI signal intensities (SI) in IC patient and control bladders were compared regionally and for entire bladders. Quantitative assessment of MRI SI indicated a significant increase in SI within anterior bladder regions compared to posterior regions in IC patients, and significant increases in SI within anterior bladder regions and kurtosis (descriptor of shape of probability distribution) and skewness (measure of asymmetry of probability distribution) associated with contrast enhancement in total bladders for IC patients compared to controls. Regarding symptomatology, IC cases differed significantly from controls for the SF-36, PPUF and ICPI questionnaires with no overlap in range of scores for each group, and were significantly different for ICSI but with a slight overlap in range of scores. The data suggests that CE-MRI provides an objective, quantifiable measurement of bladder permeability that could be used to stratify bladder pain patients and monitor therapy.

**ANESTHETIC BLADDER HYDRODISTENTION IS SUPERIOR TO SUPERIOR HYPOGASTRIC PLEXUS NEUROLYSIS IN TREATMENT OF INTERSTITIAL CYSTITIS-BLADDER PAIN SYNDROME: A PROSPECTIVE RANDOMIZED TRIAL.**

*El-Hefnawy AS, Makharita MY, Abed A, Amr YM, Salah El-Badry M, Shaaban AA. Urology. 2015 May;85(5):1039-44. doi: 10.1016/j.urology.2015.01.018. PMID: 25917730.*



The purpose of this study from Egypt was to evaluate efficacy and safety of superior hypogastric plexus neurolysis (SHN) for treatment of interstitial cystitis (IC)-bladder pain syndrome (BPS) in comparison with bladder hydrodistention (HD). In a prospective study, 24 female patients were randomly allocated to receive either SHN or HD. Patients were evaluated by recording the O'Leary-Sant IC symptom indices, IC problem indices, pain visual analog scale (VAS), number of daytime frequency, and nocturia. Pressure flow study was conducted for all patients. Intraoperative and postoperative changes and adverse events were recorded. The authors found that despite effective pain control in cases with IC-BPS after SHN, it lacks durability. It seems that SHN in its current form is not to be a suitable line of treatment for IC-BPS. Multimodality treatment would be needed for proper control of patients' symptoms.

**[BEYOND A SIMPLE ANESTHETIC EFFECT: LIDOCAINE IN THE DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.](#)**

Henry RA, Morales A, Cahill CM. *Urology*. 2015 May;85(5):1025-33. doi: 10.1016/j.urology.2015.01.021. PMID: 25917728

Henry and colleagues from Canada and USA report that intravesical local anesthetics, in a wide variety of combinations, are increasingly used to treat patients with interstitial cystitis-bladder pain syndrome (IC/BPS). Lidocaine has demonstrated properties that block the neuroinflammatory cycle associated with IC/BPS at many of the interactive points in this cycle. Intravesical lidocaine has been shown to assist in identifying the bladder as the source of pain in patients with pelvic pain. According to the authors, an appreciation of these anti-inflammatory effects and of the pharmacokinetics of intravesical lidocaine in patients with IC/BPS could lead to a safe and effective diagnosis and treatment for an as yet unidentified subset of patients in the IC/BPS spectrum.

**[MACROPHAGE MIGRATION INHIBITORY FACTOR MEDIATES PAR-INDUCED BLADDER PAIN.](#)**

Kouzoukas DE, Meyer-Siegler KL, Ma F, Westlund KN, Hunt DE, Vera PL. *PLoS One*. 2015 May 28;10(5):e0127628. doi: 10.1371/journal.pone.0127628. eCollection 2015. PMID: 26020638

**Free full text, click on title.**

Macrophage migration inhibitory factor (MIF), a pro-inflammatory cytokine, is constitutively expressed in urothelial cells that also express protease-activated receptors (PAR). Urothelial PAR1 receptors were shown to mediate bladder inflammation. Kouzoukas and colleagues from the USA showed that PAR1 and PAR4 activator, thrombin, also mediates urothelial MIF release. They hypothesized that stimulation of urothelial PAR1 or PAR4 receptors elicits release of urothelial MIF that acts on MIF receptors in the urothelium to mediate bladder inflammation and pain. They examined the effect of activation of specific bladder PAR receptors on MIF release, bladder pain, micturition and histological changes. They found that PAR1- or PAR4-AP triggered MIF release from both human urothelial cells in vitro and mouse urothelium in vivo. Twenty-four hours after intravesical PAR1- or PAR4-AP, we observed abdominal hypersensitivity in mice without changes in micturition or bladder histology. PAR4-AP was more effective and also increased expression of bladder MIF and urothelium MIF receptor, CXCR4. Bladder CXCR4 localized to the urothelium. Antagonizing MIF with ISO-1 eliminated PAR4- and reduced PAR1-induced hypersensitivity, while antagonizing CXCR4 with AMD3100 only partially prevented PAR4-induced hypersensitivity. It was therefore concluded that bladder PAR activation elicits urothelial MIF release and urothelial MIF receptor signaling at least partly through CXCR4 to result in abdominal hypersensitivity without overt bladder inflammation. PAR-induced bladder pain may represent an interesting pre-clinical model of Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) where pain occurs without apparent bladder injury or pathology. MIF is potentially a novel therapeutic target for bladder pain in IC/PBS patients.

**[IMAGING: CNS CHANGES IN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.](#)**

Khavari R, Boone T. *Nat Rev Urol*. 2015 Jul;12(7):365-6. doi: 10.1038/nrurol.2015.142. Epub 2015 Jun 9. PMID: 26057055

Brain white matter (axonal) abnormalities associated with interstitial cystitis/bladder pain syndrome in women suggest that neuropathological brain alterations exist in, and might contribute to, chronic pelvic pain syndromes. Advancing our knowledge of central neuropathic mechanisms, which might initiate and/or maintain these syndromes, will help target pain-related neuroplasticity and identify future treatments.

**[IMPAIRED EXPRESSION OF PROSTAGLANDIN E2 \(PGE2\) SYNTHESIS AND DEGRADATION ENZYMES DURING DIFFERENTIATION OF IMMORTALIZED UROTHELIAL CELLS FROM PATIENTS WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME.](#)**

Marentette JO, Hurst RE, McHowat J. *PLoS One*. 2015 Jun 9;10(6):e0129466. doi: 10.1371/journal.pone.0129466. eCollection 2015. PMID: 26057882

**Free full text, click on title.**

The differentiated superficial cells of the urothelium restrict urine flow into the bladder wall. Marentette and colleagues from the USA have demonstrated that urothelial cells isolated from bladders of patients with interstitial cystitis/painful bladder syndrome (IC/PBS) fail to release PGE2 in response to tryptase. This study examines the expression of PGE2 synthesis and degradation enzymes in urothelial cells during differentiation. They measured immunoprotein expression of cyclooxygenase-2 (COX-2), prostaglandin E2 synthase (PGES) and 15-hydroxyprostaglandin dehydrogenase (PGDH) in human urothelial cells and in immortalized urothelial cells isolated from the bladders of IC/PBS patients or normal subjects during stratification and differentiation produced by increased calcium and fetal bovine serum (Ca/FBS) in the culture medium for 1, 3 and 7 days. PGES immunoprotein expression increased during differentiation in normal and IC/PBS urothelial cells. COX-2 expression also increased in cells from normal patients following differentiation. Remarkably, no COX-2 expression was detectable in urothelial cells isolated from 3 out of 4 IC/PBS patients. PGDH immunoprotein expression decreased in normal cells after 1 and 3 days of Ca/FBS addition, but returned to normal after 7 days. PGDH expression was unchanged during differentiation at 1 and 3 days, but was more than 2-fold higher at 7 days compared to day 0 in the IC/PBS cells. Urothelial cells isolated from IC/PBS patients demonstrated no PGE2 release in response to tryptase under any of the experimental conditions studied. Taken together, the authors are of the opinion that their results indicate that PGE2 release is compromised during stratification and differentiation in IC/PBS urothelium and may contribute to impaired barrier function.

#### [WENN DIE BLASE BRENNT: INTERSTITIELLE ZYSTITIS/BLADDER PAIN SYNDROME \(IC/BPS\).](#)

[Article in German]

Scheiner DA, Perucchini D, Fink D, Betschart C. *Praxis (Bern 1994)*. 2015 Aug 20;104(17):909-18. doi: 10.1024/1661-8157/a002102. PMID: 26286495

Article in German from Zurich.

#### **POST-RADIATION CYSTITIS**

#### [SODIUM HYALURONATE AND CHONDROITIN SULFATE REPLENISHMENT THERAPY CAN IMPROVE NOCTURIA IN MEN WITH POST-RADIATION CYSTITIS: RESULTS OF A PROSPECTIVE PILOT STUDY.](#)

Gacci M, Saleh O, Giannessi C, Detti B, Livi L, Monteleone Pasquetti E, Masoni T, Finazzi Agro E, Li Marzi V, Minervini A, Carini M, Gravas S, Oelke M, Serni S. *BMC Urol*. 2015 Jul 7;15:65. doi: 10.1186/s12894-015-0046-1. PMID: 26148853

**Free full text, click on title.**

Radiotherapy is one of the treatment options for prostate cancer (PCa) but up to 25% of men report about severe nocturia (nocturnal voiding). The combination of hyaluronic acid (HA) and chondroitin sulfate (CS) resembles glycosaminoglycan (GAG) replenishment therapy. The aim of this study from Italy was to evaluate the impact of HA and CS on nocturia, in men with nocturia after PCa radiotherapy. Twenty-three consecutive patients with symptomatic cystitis after external radiotherapy for PCa were enrolled. Patients underwent bladder instillation therapy with HA and CS weekly for the first month and, afterwards, on week 6, 8 and 12. Nocturnal voiding frequency was assessed by item 3 (Q3) of the Interstitial Cystitis Symptoms Index (ICSI) and item 2 (Q2) of the Interstitial Cystitis Problem Index (ICPI). Data were analyzed with paired-samples T-test and adjusted for age. Bladder instillation treatment with a combination of HA and CS was effective in reducing nocturnal voiding frequency in men with post-radiation bladder pain for PCa. Randomized, controlled trials with sham treatment are needed to confirm this result.

#### **KETAMINE-INDUCED CYSTITIS**

#### [TRANSLOCATION OF NF-KB AND EXPRESSION OF CYCLOOXYGENASE-2 ARE ENHANCED BY KETAMINE-INDUCED ULCERATIVE CYSTITIS IN RAT BLADDER.](#)

Juan YS, Lee YL, Long CY, Wong JH, Jang MY, Lu JH, Wu WJ, Huang YS, Chang WC, Chuang SM. *Am J Pathol*. 2015 Aug;185(8):2269-85. doi: 10.1016/j.ajpath.2015.04.020. Epub 2015 Jun 12. PMID: 26073037.

Juan and colleagues from Taiwan report that the number of ketamine abusers has increased significantly recently. Ketamine abusers exhibit urinary frequency, urgency, and at times urinary incontinence. Their aim was to investigate the role of transcription factor NF- $\kappa$ B and cyclooxygenase (COX)-2 in ketamine-induced cystitis. Sprague-Dawley rats were distributed into three groups, which received saline or treatment with

ketamine or ketamine combined with a Cox-2 inhibitor (parecoxib). In addition, the toxic effect of ketamine and its metabolites were examined by primary urothelial cell culture. The ketamine-treated group displayed bladder hyperactivity and decreased bladder capacity. Treatment with ketamine + COX-2 inhibitor prevented these bladder dysfunctions. These bladder dysfunctions were accompanied by increases in the expression of NF- $\kappa$ B and COX-2 at the protein and mRNA levels. Ketamine treatment also enhanced bladder interstitial fibrosis, whereas ketamine + Cox-2 inhibitor decreased the intensity of fibrosis. Treatment of primary urothelial cells in vitro with ketamine or urine obtained from ketamine-treated rats stimulated the expression of NF- $\kappa$ B p65 and COX-2. Ketamine also initiated NF- $\kappa$ B translocation from cell cytoplasm to nucleus. Treatment with NF- $\kappa$ B inhibitor suppressed Cox-2 mRNA expression. Promoter-deletion analysis revealed that NF- $\kappa$ B was a necessary transcription factor for COX-2 gene (Ptgs2) activation. These results demonstrate that the regulation of COX-2 via the NF- $\kappa$ B pathway is involved in the inflammatory signaling of ketamine-induced cystitis in rat urinary bladder.

### OVERACTIVE BLADDER & UNDERACTIVE BLADDER

#### RESEARCH FINDINGS ON OVERACTIVE BLADDER.

*Patra PB, Patra S. Curr Urol. 2015 May;8(1):1-21. doi: 10.1159/000365682. Epub 2015 May 20. PMID: 26195957*  
Several physiopathologic conditions lead to the manifestation of overactive bladder (OAB). These conditions include ageing, diabetes mellitus, bladder outlet obstruction, spinal cord injury, stroke and brain injury, Parkinson's disease, multiple sclerosis, interstitial cystitis, stress and depression. This review from Philadelphia discusses research findings in human and animal studies conducted on the above conditions. Several structural and functional changes under these conditions have not only been observed in the lower urinary tract, but also in the brain and spinal cord. Significant changes were observed in the following areas: neurotransmitters, prostaglandins, nerve growth factor, Rho-kinase, interstitial cells of Cajal, and ion and transient receptor potential channels. Interestingly, alterations in these areas showed great variation in each of the conditions of the OAB, suggesting that the pathophysiology of the OAB might be different in each condition of the disease. It is anticipated that this review will be helpful for further research on new and specific drug development against OAB.

#### UNDERACTIVE BLADDER AND DETRUSOR UNDERACTIVITY REPRESENT DIFFERENT FACETS OF VOLUME HYPOSENSITIVITY AND NOT IMPAIRED CONTRACTILITY

*Smith PP, Pregonzer G, Galffy A, Kuchel GA. Bladder 2015;2(2):e17. doi: 10.14440/bladder.2015.60*

**Free full text, click on title.**

Underactive bladder (UAB) and detrusor underactivity (DU) are receiving increasing clinical and research attention. Although lacking a formalized definition, UAB is described as a symptom complex, while DU is a standardized statement of urodynamic function. Both terms nominally suggest impaired detrusor contractility leading to disordered emptying. Smith and colleagues sought to evaluate the relationship between UAB, DU and detrusor contractility. They found that the symptom complex of UAB is not a reliable predictor of the urodynamic observation of DU, and neither condition is associated with a diminished Watts factor. They believe that their results suggest that UAB and DU are typically disorders of volume hyposensitivity rather than of impaired contractility, and may differ in their relationship to bladder perceptions. Thus, these terms should not be used interchangeably.

### CHRONIC (PELVIC) PAIN

#### MULTIMODAL NOCICEPTIVE MECHANISMS UNDERLYING CHRONIC PELVIC PAIN.

*Hellman KM, Patanwala IY, Pozolo KE, Tu FF. Am J Obstet Gynecol. 2015 Aug 20. pii: S0002-9378(15)00908-4. doi: 10.1016/j.ajog.2015.08.038. [Epub ahead of print] PMID: 26299416*

The purpose of this study by Hellman and colleagues from Chicago was to evaluate candidate mechanisms underlying the pelvic floor dysfunction in women with chronic pelvic pain and/or painful bladder syndrome/interstitial cystitis. Notably, prior studies have not consistently controlled for potential confounding by psychological or anatomical factors. As part of a larger study on pelvic floor pain dysfunction and bladder pain sensitivity, the authors compared a measure of mechanical pain sensitivity, pressure pain thresholds, between women with pelvic pain and pain-free controls. They also assessed a novel pain measure using degree and duration of post-exam pain aftersensation, and conducted structural and functional assessments of the pelvic floor to account for any potential confounding. Phenotypic specificity of pelvic floor measures was assessed with receiver-operator characteristic curves adjusted for prevalence. The authors found that both

experimental assessment of pelvic floor pain thresholds and measurement of sustained pain are independently associated with pelvic pain phenotypes. These findings suggest systematic clinical assessment of the time course of provoked pain symptoms, which occurs over seconds for mechanical pain thresholds vs. minutes for aftersensation pain, would be helpful in identifying the fundamental mechanisms of pelvic floor pain. Longitudinal studies of therapies differentially targeting these discrete mechanisms are needed to confirm their clinical significance.

### **GENITAL AND SEXUAL PAIN IN WOMEN.**

*Graziottin A, Gambini D, Bertolasi L. Handb Clin Neurol. 2015;130:395-412. doi: 10.1016/B978-0-444-63247-0.00023-7. PMID: 26003257*

This chapter by Graziottin and colleagues from Italy discusses the all too common problem of sex-related pain in women. Pain is a complex perceptive experience, involving biologic as well as psychologic and relational meanings. They become increasingly important with the chronicity of pain. Neurologists are quite aware of the painful aspect of many neurologic disorders, but lifelong and acquired genital and sexual pain is still neglected in a consistent percentage of women. One reason is the view - still held by many - that psychologic factors play the most important role in sex-related pain complaints. The consequences of diagnostic delay can be dramatic. Persisting tissue inflammation induces pain to change from acute and "nociceptive," which indicates a "friendly signal," alerting one to ongoing tissue damage, to chronic and "neuropathic," a disease per se. Whilst the primary disease is progressing and neuroinflammation becomes a prominent feature, affected women have to bear years of pain and distress, huge quantifiable and non-quantifiable costs, and a progressive deterioration of personal and relational health and happiness. The scenario is even more dramatic when pain complicates an already disabling disease. The main aspects considered in this chapter include neuroinflammation as a key feature of pain; genital and sexual pain as part of neurologic diseases; and genital and sexual pain syndrome (dyspareunia and vaginismus) as primary problems, and their pelvic comorbidities (bladder pain syndrome, endometriosis, irritable bowel syndrome, provoked vestibulodynia/vulvodynia). Finally, they discuss iatrogenic pain, i.e., genital and sexual pain caused by ill-conceived medical, surgical, pharmacologic or radiologic therapeutic interventions.

### **CHALLENGES IN DRUG DISCOVERY FOR OVERCOMING 'DYSFUNCTIONAL PAIN': AN EMERGING CATEGORY OF CHRONIC PAIN.**

*Nagakura Y. Expert Opin Drug Discov. 2015 Jul 9:1-3. [Epub ahead of print] PMID: 26160648*

In this paper from Japan, Nagakura notes that 'Dysfunctional pain', a type of chronic pain, is associated with a broad range of clinical disorders, including fibromyalgia, irritable bowel syndrome and interstitial cystitis. It is emerging as a serious issue due to the negative impact of inexplicable pain on quality of life, lack of effective therapies and health care cost. Although drug discovery efforts in pain research have so far focused primarily on inflammatory and neuropathic pain, this editorial attracts attention to dysfunctional pain research and discusses a possible fundamental framework for tackling this difficult issue. While dysfunctional pain is characterized by chronic widespread or regional pain symptoms and occurrence of pain amplification, underlying pathophysiologies remain to be identified. Thus, a pivotal step in future research would be the exploration of pathophysiological pathways, such as relevant molecular networks, which are responsible for dysfunctional pain. Utilization of developing technologies paves the way for the identification of underlying pathophysiologies and the development of effective drugs which would eventually solve the clinical issues associated with dysfunctional pain.

### **"REAL-LIFE" TREATMENT OF CHRONIC PAIN: TARGETS AND GOALS.**

*Ablin JN, Buskila D. Best Pract Res Clin Rheumatol. 2015 Feb;29(1):111-9. doi: 10.1016/j.berh.2015.04.020. Epub 2015 May 20. PMID: 26267005*

Treating chronic pain is a complex challenge, according to Ablin and Buskila from Israel. While textbooks and medical education classically categorize pain as originating from peripheral (nociceptive), neuropathic, or centralized origins, in real life each and every patient may present a combination of various pain sources, types, and mechanisms. Moreover, individual patients may evolve and develop differing types of pain throughout their clinical follow-up, further emphasizing the necessity to maintain clinical diligence during the evaluation and follow-up of these patients. Rational treatment of patients suffering from chronic pain must attempt at deconstructing complex pain cases, identifying variegated pain generators, and targeting them with appropriate interventions, while incorporating both pharmacological and non-pharmacological strategies, rather than focusing on the total pain level, which represents an integral of all pain types. Failing to recognize the coexistence of different types of pain in an individual patient and escalating medications only on the basis of

total pain intensity are liable to lead to both ineffective control of pain and increased untoward effects. In this review, the authors outline strategies for deconstructing complex pain and therapeutic suggestions.

#### **EFFECTS OF CHRONIC PELVIC PAIN ON HEART RATE VARIABILITY IN WOMEN.**

*Williams DP, Chelimsky G, McCabe NP, Koenig J, Singh P, Janata J, Thayer JF, Buffington CA, Chelimsky T. J Urol. 2015 May 9. pii: S0022-5347(15)03909-9. doi: 10.1016/j.juro.2015.04.101. [Epub ahead of print] PMID: 25963185*

Interstitial cystitis/bladder pain syndrome and myofascial pelvic pain are frequently comorbid chronic pelvic pain disorders. Differences in bladder function between interstitial cystitis/bladder pain syndrome and myofascial pelvic pain suggest that efferent autonomic function may differentiate these syndromes. Heart rate variability, defined as the difference in duration of successive heartbeats, serves as an index of autonomic function by measuring its ability to modify heart rate in response to neurophysiological changes. High frequency heart rate variability was used as a reflection of more rapid vagally mediated (parasympathetic) changes. Low frequency heart rate variability signified slower fluctuations related to the baroreflex and sympathetic outflow. Heart rate variability was derived by autoregressive frequency analysis of the continuous electrocardiogram recording of heart rate with the subject supine for 10 minutes, tilted 70 degrees with the head up for 30 minutes and supine again for 10 minutes. This institutional review board approved study included 105 female subjects, including 32 who were healthy, and 26 with interstitial cystitis/bladder pain syndrome, 12 with myofascial pelvic pain and 35 with interstitial cystitis/bladder pain syndrome plus myofascial pelvic pain. The authors found that patients with interstitial cystitis/bladder pain syndrome had diminished vagal activity and a shift toward sympathetic nervous system dominance. They suggest that overall these data support the hypothesis that changes in autonomic function occur in interstitial cystitis/bladder pain syndrome but not in myofascial pelvic pain. These changes may result from interstitial cystitis/bladder pain syndrome or contribute to its pathophysiology through abnormal self-regulatory function.

### **FIBROMYALGIA**

#### **FIBROMYALGIA AND RELATED CONDITIONS.**

*Clauw DJ. Mayo Clin Proc. 2015 May;90(5):680-92. doi: 10.1016/j.mayocp.2015.03.014. PMID: 25939940.*

Fibromyalgia is the currently preferred term for widespread musculoskeletal pain, typically accompanied by other symptoms such as fatigue, memory problems, and sleep and mood disturbances, for which no alternative cause can be identified. Earlier there was some doubt about whether there was an "organic basis" for these related conditions, but today there is irrefutable evidence from brain imaging and other techniques that this condition has strong biological underpinnings, even though psychological, social, and behavioral factors clearly play prominent roles in some patients. The pathophysiological hallmark is a sensitized or hyperactive central nervous system that leads to an increased volume control or gain on pain and sensory processing. This condition can occur in isolation, but more often it co-occurs with other conditions now being shown to have a similar underlying pathophysiology (eg, irritable bowel syndrome, interstitial cystitis, and tension headache) or as a comorbidity in individuals with diseases characterized by ongoing peripheral damage or inflammation (eg, autoimmune disorders and osteoarthritis). In the latter instance, the term centralized pain connotes the fact that in addition to the pain that might be caused by peripheral factors, there is superimposed pain augmentation occurring in the central nervous system. It is important to recognize this phenomenon (regardless of what term is used to describe it) because individuals with centralized pain do not respond nearly as well to treatments that work well for peripheral pain (surgery and opioids) and preferentially respond to centrally acting analgesics and nonpharmacological therapies.

### **CHRONIC FATIGUE**

#### **THE PREVALENCE OF SEVERE FATIGUE IN RHEUMATIC DISEASES: AN INTERNATIONAL STUDY.**

*Overman CL, Kool MB, Da Silva JA, Geenen R. Clin Rheumatol. 2015 Aug 15. [Epub ahead of print] PMID: 26272057*

Fatigue is a common, disabling, and difficult-to-manage problem in rheumatic diseases. Prevalence estimates of fatigue within rheumatic diseases vary considerably. Data on the prevalence of severe fatigue across multiple rheumatic diseases using a similar instrument is missing. The aim of Overman and colleagues from the Netherlands was to provide an overview of the prevalence of severe fatigue across a broad range of rheumatic diseases and to examine its association with clinical and demographic variables. Online questionnaires were filled out by an international sample of 6120 patients (88 % female, mean age 47) encompassing 30 different

rheumatic diseases. Fatigue was measured with the RAND(SF)-36 Vitality scale. A score of  $\leq 35$  was taken as representing severe fatigue (90 % sensitivity and 81 % specificity for chronic fatigue syndrome). Severe fatigue was present in 41 to 57 % of patients with a single inflammatory rheumatic disease such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Sjögren's syndrome, psoriatic arthritis, and scleroderma. Severe fatigue was least prevalent in patients with osteoarthritis (35 %) and most prevalent in patients with fibromyalgia (82 %). In logistic regression analysis, severe fatigue was associated with having fibromyalgia, having multiple rheumatic diseases without fibromyalgia, younger age, lower education, and language (French: highest prevalence; Dutch: lowest prevalence). In conclusion, one out of every two patients with a rheumatic disease is severely fatigued. As severe fatigue is detrimental to the patient, the near environment, and society at large, unraveling the underlying mechanisms of fatigue and developing optimal treatment should be top priorities in rheumatologic research and practice.

### **SYMPATHOMIMETIC AMINES ARE A SAFE, HIGHLY EFFECTIVE THERAPY FOR SEVERAL FEMALE CHRONIC DISORDERS THAT DO NOT RESPOND WELL TO CONVENTIONAL THERAPY.**

*Check JH. Clin Exp Obstet Gynecol. 2015;42(3):267-78. PMID: 26151991*

The purpose of this study was to evaluate the efficacy of sympathomimetic amine therapy for women with chronic disorders including, but not limited to, pelvic pain. Dextroamphetamine sulfate 15-mg extended release capsules were given to women with a variety of treatment refractory conditions including, but not limited to, pelvic pain. The dosage could be increased to 60 mg depending on tolerance to the medication and degree of improvement of the condition. A very high percentage showed marked amelioration of their symptoms despite previous failure with medical or surgical therapy. The authors notes that the human species, especially women, seem to be more prone to certain specific tissue permeability defects and diminished sympathetic tone, which compounds the problem, since the sympathetic nervous system controls permeability. Thus, besides pelvic pain and interstitial cystitis, dextroamphetamine sulfate, which seems to restore sympathetic tone possibly by increasing dopamine secretion to the nerve fiber, provides gratifying relief to a variety of chronic disorders. These other disorders include: severe headaches, inflammatory bowel disease, gastrointestinal motility disorders, fibromyalgia, and other musculoskeletal pain, chronic fatigue syndrome, and urticaria.

### **LUPUS CYSTITIS**

### **LUPUS CYSTITIS IN KOREAN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RISK FACTORS AND CLINICAL OUTCOMES.**

*Koh JH, Lee J, Jung SM, Ju JH, Park SH, Kim HY, Kwok SK. Lupus. 2015 Jun 1. pii: 0961203315588575. [Epub ahead of print] PMID: 26038343*

This study from South Korea was performed to investigate the clinical characteristics of lupus cystitis and determine the risk factors and clinical outcomes of lupus cystitis in patients with systemic lupus erythematosus (SLE). Ko hand colleagues retrospectively reviewed 1064 patients at Seoul St. Mary's Hospital in Seoul, Korea, from 1998 to 2013. Twenty-four patients had lupus cystitis. Lupus cystitis was defined as unexplained ureteritis and/or cystitis as detected by imaging studies, cystoscopy, or bladder histopathology without urinary microorganisms or stones. Three-quarters of patients with lupus cystitis had concurrent lupus mesenteric vasculitis (LMV). The initial symptoms were gastrointestinal in nature for most patients (79.2%). High-dose methylprednisolone was initially administered to most patients (91.7%) with lupus cystitis. Two patients (8.3%) died of urinary tract infections. Sixty-five age- and sex-matched patients with SLE who were admitted with other manifestations were included as the control group. Patients with lupus cystitis showed a lower C3 level, higher SLE Disease Activity Index score, and higher ESR upon admission; more frequently had a history of LMV prior to admission; and less frequently had a history of neuropsychiatric lupus than did patients with SLE but without lupus cystitis. The occurrence of lupus cystitis was associated with a history of LMV. The median follow-up period was 3.4 years, and the cumulative one-year mortality rate was 20%. Complications developed in 33.3% of patients with lupus cystitis and were related to survival. The authors are of the opinion that their results suggest that the possibility of lupus cystitis should be considered when a patient with SLE and history of LMV presents with gastrointestinal symptoms or lower urinary tract symptoms. Development of complications in patients with lupus cystitis can be fatal. So intensive treatment and follow-up are needed, especially in the presence of complications.

### **VULVODYNIA/VULVAL PAIN SYNDROME**

**LOWER URINARY TRACT AND FUNCTIONAL BOWEL SYMPTOMS IN WOMEN WITH VULVAR DISEASES AND CONTROLS.**

Swenson CW, Menees SB, Haefner HK, Berger MB. *Female Pelvic Med Reconstr Surg.* 2015 Jul-Aug;21(4):211-4. doi: 10.1097/SPV.000000000000184. PMID: 26052645

This study from Michigan aims to compare the prevalences of lower urinary tract symptoms (LUTS), irritable bowel syndrome (IBS) and constipation in women with vulvar diseases to those from the general population. Three groups of women were recruited from the University of Michigan Gynecology Clinics, women with: (1) biopsy proven lichen sclerosus (LS), (2) non-LS vulvar diseases (vulvar controls, VC), and (3) presenting for annual examinations (AE). All patients completed self-administered surveys and validated pelvic floor symptom questionnaires. 317 subjects were enrolled: 101 with LS, 86 VCs, and 130 AEs. Compared to women in the VC and AE groups, LS subjects were older and of higher parity, and also had a higher prevalence of overactive bladder and urinary incontinence. The IBS was more common in the LS and VC groups compared to the AE group but no difference in constipation was seen. Similar results were found when all women with vulvar disease (LS and VC) were compared to the AEs. Age and IBS were the 2 variables predictive of overactive bladder. Urinary incontinence was predicted by age, vulvar disease categorization and IBS. They found a significantly greater prevalence of LUTS and IBS in women with vulvar disease compared to women presenting for annual gynecologic exams, but no difference in constipation. Similar rates of LUTS, IBS, and constipation were seen in women with LS and non-LS vulvar disease.

**SJÖGREN'S SYNDROME**

**PAIN IN PRIMARY SJÖGREN'S SYNDROME.**

Vitali C, Del Papa N. *Best Pract Res Clin Rheumatol.* 2015 Feb;29(1):63-70. doi: 10.1016/j.berh.2015.05.002. Epub 2015 Jun 6. PMID: 26267000

Joint and muscle pain are commonly observed in patients with primary Sjögren's syndrome (pSS). Different types of pain can be distinguished, that is, articular pain, neuropathic pain and widespread pain. Articular pain is due to more or less evident synovitis, usually involving peripheral joints such as hand joints, wrists, knees and ankles. Drugs used to treat rheumatoid arthritis, or lupus synovitis, are also employed for articular involvement in pSS. Pure sensory neuropathies and, more often, small fibre neuropathies are responsible for neuropathic pain in pSS. This is usually localised in the legs and arms with a characteristic glove or sock distribution. Widespread pain, often assuming the features of fibromyalgia, has also been reported in patients with pSS. The pathological mechanisms underlying both neuropathic pain and widespread (fibromyalgia) pain in pSS have not been so far completely clarified.

**RENAL INVOLVEMENT IN PRIMARY SJÖGREN'S SYNDROME.**

Evans R, Zdebik A, Ciurtin C, Walsh SB. *Rheumatology (Oxford).* 2015 Sep;54(9):1541-8. doi: 10.1093/rheumatology/kev223. Epub 2015 Jun 11. PMID: 26070939

Sjögren's Syndrome (SS) is a prevalent and underdiagnosed systemic disease that primarily affects epithelial tissue. It may affect renal function either as epithelial disease causing tubulointerstitial nephritis or as an immune complex-mediated glomerulopathy. These lesions may cause a variety of clinical features, both overt and occult. The epithelial disease is mediated by B and T cells, notably the Th17 subtype. Evans and colleagues from London review the prevalence of renal SS, its presentation, likely pathogenesis and treatment.

**TEMPOROMANDIBULAR PAIN DISORDER**

**SPECIFIC AND NUMBER OF COMORBIDITIES ARE ASSOCIATED WITH INCREASED LEVELS OF TEMPOROMANDIBULAR PAIN INTENSITY AND DURATION.**

Dahan H, Shir Y, Velly A, Allison P. *J Headache Pain.* 2015 Dec;16:528. doi: 10.1186/s10194-015-0528-2. Epub 2015 May 20. PMID: 26002637

**Free full text, click on title.**

Temporomandibular pain disorder (TMD) is a common pain condition in the face. People with TMD report multiple pain comorbidities. The presence of fibromyalgia and migraine in people with TMD is associated with an increase in TMD pain intensity and duration. However, data on the relationship between increasing number of pain comorbidities and TMD pain are rare. The aims of this study from Montreal were: firstly to evaluate the extent to which increasing number of comorbidities is associated with increasing TMD pain intensity and duration; and secondly to evaluate the extent to which the presence of specific comorbidities is associated with increasing TMD pain intensity and duration. The comorbidities of migraine, chronic fatigue syndrome, irritable

bowel syndrome, interstitial cystitis and restless leg syndrome were diagnosed by 5 validated diagnostic questionnaires. The associations were analyzed by linear regression, controlling for confounders. There was a positive association between the number of comorbidities present and TMD pain intensity and between the number of comorbidities present and TMD pain duration. Also, the presence of migraine was positively associated with TMD pain intensity and the presence of chronic fatigue syndrome was positively associated with TMD pain intensity and with TMD pain duration. When TMD patients were separated into groups, these associations did not change for the myofascial pain group, whereas in the non-myofascial pain group, the relationship between number of comorbidities and TMD pain duration was the only one still present. This study shows that the number of comorbidities is positively associated with TMD pain duration and intensity. The presence of specific conditions, such as migraine and chronic fatigue syndrome, is associated with an increase in TMD intensity and duration.

## **IRRITABLE BOWEL SYNDROME**

### **RECENT DEVELOPMENTS IN THE PATHOPHYSIOLOGY OF IRRITABLE BOWEL SYNDROME.**

*El-Salhy M. World J Gastroenterol. 2015 Jul 7;21(25):7621-36. doi: 10.3748/wjg.v21.i25.7621. PMID: 26167065*

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

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder, the pathophysiology of which is not completely known, although it has been shown that genetic/social learning factors, diet, intestinal microbiota, intestinal low-grade inflammation, and abnormal gastrointestinal endocrine cells play a major role. Studies of familial aggregation and on twins have confirmed the heritability of IBS. However, the proposed IBS risk genes are thus far nonvalidated hits rather than true predisposing factors. There is no convincing evidence that IBS patients suffer from food allergy/intolerance, with the effect exerted by diet seemingly caused by intake of poorly absorbed carbohydrates and fiber. Obesity is a possible comorbidity of IBS. Differences in the microbiota between IBS patients and healthy controls have been reported, but the association between IBS symptoms and specific bacterial species is uncertain. Low-grade inflammation appears to play a role in the pathophysiology of a major subset of IBS, namely postinfectious IBS. The density of intestinal endocrine cells is reduced in patients with IBS, possibly as a result of genetic factors, diet, intestinal microbiota, and low-grade inflammation interfering with the regulatory signals controlling the intestinal stem-cell clonogenic and differentiation activities. Furthermore, there is speculation that this decreased number of endocrine cells is responsible for the visceral hypersensitivity, disturbed gastrointestinal motility, and abnormal gut secretion seen in IBS patients.

### **THE ROLE OF MAST CELLS IN FUNCTIONAL GI DISORDERS.**

*Wouters MM, Vicario M, Santos J. Gut. 2015 Jul 20. pii: gutjnl-2015-309151. doi: 10.1136/gutjnl-2015-309151. [Epub ahead of print] PMID: 26194403*

Functional gastrointestinal disorders (FGIDs) are characterized by chronic complaints arising from disorganized brain-gut interactions leading to dysmotility and hypersensitivity. The two most prevalent FGIDs, affecting up to 16-26% of worldwide population, are functional dyspepsia and irritable bowel syndrome. While their etiopathogenic mechanisms remain unclear, recent observations reveal low-grade mucosal inflammation and immune activation, in association with impaired epithelial barrier function and aberrant neuronal sensitivity. These findings come to challenge the traditional view of FGIDs as pure functional disorders, and relate the origin to a tangible organic substrate. The mucosal inflammatory infiltrate is dominated by mast cells, eosinophils and intraepithelial lymphocytes in the intestine of FGIDs. It is well established that mast cell activation can generate epithelial and neuro-muscular dysfunction and promote visceral hypersensitivity and altered motility patterns in FGIDs, postoperative ileus, food allergy and inflammatory bowel disease. This review will discuss the role of mucosal mast cells in the gastrointestinal tract with a specific focus on recent advances in disease mechanisms and clinical management in irritable bowel syndrome and functional dyspepsia.

### **IRRITABLE BOWEL SYNDROME: DIETARY INTERVENTIONS.**

*Ford AC, Vandvik PO. BMJ Clin Evid. 2015 Jul 30;2015. pii: 0410. PMID: 26226510*

The prevalence of irritable bowel syndrome (IBS) varies depending on the criteria used to diagnose it, but it ranges from about 5% to 20%. IBS is associated with abnormal gastrointestinal motor function and enhanced visceral perception, as well as psychosocial and genetic factors. People with IBS often have other bodily and psychiatric symptoms, and have an increased likelihood of having unnecessary surgery compared with people without IBS. Ford and Vandvik from Leeds, UK conducted a systematic overview, aiming to answer the following clinical question: What are the effects of dietary modification (gluten-free diet, a diet low in



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fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [FODMAPs]) in people with irritable bowel syndrome? At this update, searching of electronic databases retrieved 33 studies. After deduplication and removal of conference abstracts, 19 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 14 studies and the further review of five full publications. Of the five full articles evaluated, three RCTs were included. Based upon their own search, the contributor(s) added two additional RCTs that did not meet Clinical Evidence inclusion criteria; these have been added to the Comment section. They performed a GRADE evaluation of the quality for two PICO combinations. In this systematic overview, they categorised the efficacy for two interventions based on information relating to the effectiveness and safety of dietary modification (gluten-free diet or a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [FODMAPs]).

### [DRUG DISCOVERY APPROACHES TO IRRITABLE BOWEL SYNDROME.](#)

*Hornby PJ. Expert Opin Drug Discov. 2015 Aug;10(8):809-24. doi: 10.1517/17460441.2015.1049528. PMID: 26193876*

Irritable bowel syndrome (IBS) is defined by symptoms of abdominal pain and altered bowel habits without detectable organic disease. Antidepressants and serotonin receptor modulators are used to treat IBS, but rare serious adverse events highlight the safety hurdle. Newer drugs with secretory and motility effects via local gut mechanisms have been successfully approved for IBS, often by registering first in a related, non-IBS condition to optimize dosing, formulation and therapeutic window. This review looks at approaches for novel IBS drug discovery. The underlying pathologies can be tackled locally from the 'outside-in' (intestinal lumen, mucosa and neuromuscular) to identify therapeutic targets. The article discusses the mechanisms associated with bile acid malabsorption, microbial dysbiosis, decreased intestinal barrier function, immune dysregulation, motility and visceral hypersensitivity. Challenges for new drug discovery are the unknown mechanisms underlying IBS, making it difficult to predict clinically efficacious molecular targets, limited options for translational research and disease progression biomarkers. Drugs acting locally via multiple targets (e.g., eluxadoline [The U.S. Food and Drug Administration approved Viberzi (eluxadoline) for IBS-D on May 27th 2015], crofelemer) to validated mechanisms are proving successful with tolerable safety margins. Novel mechanisms, identified and optimized based on the emerging role of nutrient signaling, probiotics or microbial products, are promising. Therapeutic treatment earlier in disease progression may improve response and have longer term benefits.

*The IPBF is an associate member of the International Alliance of Patients' Organizations (IAPO) [www.patientsorganizations.org](http://www.patientsorganizations.org), the European Organization for Rare Diseases (EURORDIS) [www.eurordis.org](http://www.eurordis.org), the Continence Promotion Committee (CPC) of the International Continence Society (ICS) [www.ics.org](http://www.ics.org), the International Pelvic Pain Partnership (IPPP) and Pain Alliance Europe (PAE) <http://www.pae-eu.eu>.*

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