



PROFESSIONAL PERSPECTIVES

FALL 2008

PUTTING PAIN MANAGEMENT IN YOUR IC PRACTICE

You can't always leave your IC patient's pain management to pain management physicians. There simply aren't enough pain management physicians and clinics, especially interdisciplinary ones, to serve all the patients in chronic



they need more education to do that effectively. That's what the PAINWeek conference in Las Vegas in September provided. The ICA was there to increase IC awareness and to bring you information you can use in your IC practice.

Leaders in pain management research, practice, and policy as well as complementary care practitioners outlined the latest developments in pain control and the best strategies for incorporating pain care into practice. Experts in some of the less well known and understood chronic pain syndromes, including IC and vulvodynia, also educated frontline practitioners, with sessions facilitated by participating patient and professional organizations, including the Interstitial Cystitis Association, the National Vulvodynia Association, the National Fibromyalgia Research Association, the American Headache Society, and the Trigeminal Neuralgia Association.

Many providers at PAINWeek had heard of IC and knew that patients who have it may also have other chronic pain syndromes—evidence of how far IC education has come. But many pain management providers already treating IC patients wanted to learn about all the treatment options, since patients were sometimes referred to them nearly immediately, sometimes after only one oral medication had been tried.

The conference had a strong emphasis on fibromyalgia and on issues with using opioids in practice, including chronic noncancer pain, safety and efficacy, addiction, and legal concerns.

NEW PAIN DRUGS WILL ACHIEVE BETTER CONTROL, AVOID PITFALLS

Because very few drugs are in the pipeline specifically for IC and treating IC pain is a top priority, many new pain drugs discussed here at PAINWeek will be important additions to the IC armamentarium. These new medications, some of which came to market recently and others on the horizon, should treat breakthrough pain more effectively; achieve consistent, long-term pain control; target pain locally; minimize side effects and withdrawal symptoms, and thwart abuse.

Much of the development manipulates opioid molecules or makes end runs around their undesirable properties to achieve these goals. But nonopioid or partial opioid therapies are coming through the pipeline as well, noted Kathryn Walker, PharmD, who teaches at the University of Maryland School of Pharmacy, Baltimore.

Nonopioid Pain Armamentarium Expanding

Milnacipran, which may be approved before the end of the year, is a norepinephrine serotonin reuptake inhibitor (NSRI), similar to duloxetine (Cymbalta), that has been commercially available in Europe and Asia for many years. It has a higher ratio (one-to-one) of norepinephrine to serotonin activity than SNRIs, which is thought to make it more active against pain. In clinical trials, the drug reduced pain intensity by about 50 percent, and fatigue

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was also reduced. One reported side effect was dysuria, so IC clinicians may need to use this cautiously.

Tapentadol combines norepinephrine reuptake inhibition with mu opioid receptor agonism. In studies, the extended release formulation was effective against chronic pain. The drug is said to be as potent as oxycodone but with fewer side effects. The immediate-release formulation was recently approved in the United States for moderate to severe pain and is expected to become available in the second quarter of 2009.

Cannabinoids are promising for IC because they are useful in neuropathic pain, and bladder-based cannabinoids have shown positive results in animal studies. But a new systemic cannabinoid is unlikely to be approved in the United States unless side effects are eliminated. Canada, however, has approved a cannabinoid oral spray, Sativex (tetrahydrocannabinol and cannabidiol) for neuropathic pain in multiple sclerosis. Tolerance to side effects develops with time but not to the drug effects. Cannabinoid agonists for the CB2 receptor only, which are unlikely to produce euphoria, are still in the earliest stages of research.

Speeding Up Relief

Managing breakthrough pain is one of clinicians' difficult challenges, said Dr. Walker. Oral opioids' fairly low bioavailability and slow onset of action limit their usefulness for breakthrough pain, so development has focused on buccal, sublingual, and intranasal delivery.

The recently approved fentanyl buccal tablet (Fentora) speeds delivery with OraVescent technology, which releases carbon dioxide and drops pH, prompting dissolution and membrane penetration. Compared with Actiq (sometimes referred to as fentanyl "lollipops"), drug levels peak faster and plasma concentrations are higher, meaning doses are not equivalent, so proper conversion is important when switching.

A number of other rapid fentanyl formulations are under development. Sublingual Rapinyl, in phase 3 trials in the United States and approved in Europe, dissolves rapidly and has carriers that adhere to oral mucosa, allowing the drug to enter the bloodstream quickly. BEMA fentanyl, for buccal administration, has a small, dissolvable polymer disk that adheres to the mucosa and offers pain reduction

within 15 minutes. A decision from the FDA on marketing approval is expected soon, said Dr. Walker.

A sublingual formulation of sufentanil (Sufentanil NanoTab) is also being investigated. The tiny tablets are given through an electronic dispenser, which records a dosing history that can be downloaded to a computer. In addition, the formulation's bioavailability is limited if it is crushed or used intravenously.

Intranasal formulations of morphine, ketamine, and the nonsteroidal anti-inflammatory drug ketorolac are also in development, as is a fentanyl for inhalation. Rylomine, an intranasal morphine in phase 3 trials, is similar in onset and profile to IV morphine. The intranasal ketamine PMI-150 has about a four-minute onset. ROX 888, an intranasal ketorolac, given with opioids, has allowed patients to tolerate decreased opioid doses with improved pain relief. TAIFUN, an inhaled fentanyl, which begins to decrease pain in five minutes, has already been approved in 10 countries for use with other drugs.

Hitting Where it Hurts

Many IC clinicians have been prescribing local therapies, such as lidocaine patches and compounded ketoprofen gel. And new developments should offer even more local therapy options.

In fact, two ketoprofen formulations are in later development: a patch, EN3269, which is in phase 3 trials, and a gel, Transfersome, also in phase 3 and already marketed in Europe. Another NSAID patch, Flector (diclofenac), recently came on the market for mild to moderate sprains and contusions.

A new bupivacaine patch, Eladur, may prove even more useful than current lidocaine patches because bupivacaine is active longer and penetrates deeper. Now in phase 2 trials for postherpetic neuralgia, the patch uses TRANS-DUR technology that delivers anesthetic continuously for up to three days. POSIDUR, a long-acting bupivacaine gel, has a delivery system that forms a high-viscosity depot that releases the drug slowly. This is only administered to the surgical site during surgery, but the technology may find other useful applications.

Improving Long-term Delivery

New approaches to long-acting and patient-controlled opioid analgesia have recently or will soon come to market. Opana, a new oxycodone in immediate and extended release forms, was approved recently. As the active metabolite of oxycodone, it has the advantage of having only mu rather than both mu and kappa opioid activity. Recently completing phase 3 trials is a controlled release formulation of Vicodin (hydrocodone/acetaminophen), which will allow 12-hour dosing.

Two fairly new approaches to extended release have been applied to morphine. Avinza, with both immediate and extended release components, uses a SODAS (spherical oral drug absorption system) technology with polymer beads that develop permeable pores, allowing the drug to dissolve out at a regular rate. Kadian achieves long-term delivery with beads coated in several different polymers that are pH dependent, allowing diffusion as the pill moves through the gastrointestinal tract.

The already familiar OROS technology used in Ditropan XL (oxybutynin), which increases the bioavailability of water insoluble drugs and controls delivery through a small orifice in the capsule, is being applied to hydrocodone. Approved for marketing in Germany, OROS Hydromorphone is in phase 3 trials aimed at US approval, with results expected soon.

New technology for transdermal delivery will make patient-controlled analgesia more portable in the future. A preprogrammed, adhesive patch package with fentanyl, Ionsys, releases a dose when the patient pushes a button on the package, and a low electrical current iontophoretically “pushes” it across the skin. This has to be refined before it can become an outpatient system, however. Also in development is the hydromorphone/fentanyl PassPort Patch. To release a dose, the patient gives the patch a “buzz” of thermal energy, which transiently creates micropores in the skin surface that the drug passes through.

TRANSDUR technology improves speed of onset and continuous, long-term delivery in a small sufentanil patch, EN3270, which is used for seven days. It is in phase 2 trials for moderate to severe chronic pain.

Countering Constipation

One of the most troublesome side effects of opioids is constipation, which is difficult for any pain patient but can

be especially troublesome for IC patients. Stool softeners and laxatives don't always ease the problem. New peripherally acting opioid antagonists that don't cross the blood-brain barrier and counteract opioid effects in the gut are expected to be helpful solutions. Methylnaltrexone (Relistor) and alvimopan (Entereg) have already been approved but are not for office use. Another, NKTR-118, is still being investigated.

Thwarting Abuse

Based on National Survey on Drug Use and Health figures, most prescription medication abuse—90 percent—is ultimately within control of the healthcare system, Dr. Walker pointed out. That's why techniques to deter abuse were included in so many of these educational sessions at this meeting. She outlined some of the ways drug makers are trying to ameliorate the problem.

Tampering deterrents in opioid formulations are being tried, such as in Remoxy (oxycodone), which is in phase 3 trials. It is resistant to crushing but also to extraction because of its viscous gel carrier. Aversive deterrents, such as capsaicin or a sequestered emetic, in combination with opioids are also being studied. An oxycodone formulation in phase 3 trials includes a subtherapeutic dose of immediate-release niacin, which will cause unpleasant side effects in excessive amounts. Also being investigated are combinations of opioids with naltrexone that is released only when the pills are tampered with—Embeda, a combination with extended-release morphine, in phase 2 trials, and OxyNal, a combination with oxycodone, soon to start phase 3 trials.

Another new approach in opioid development is to combine agonists and antagonists, sometimes in the same molecule, to avoid tolerance or dependence and even increase effectiveness. A combination of oxycodone with an ultra low dose of naltrexone (Oxytrex), in phase 3, may keep dependence from developing without reversing analgesia and may even potentiate opioid activity, allowing lower doses. Farther in the future are opioids that bind to multiple receptors. The concept that opioids bind to one receptor is fading as research shows that receptors can form dimers and interact. A drug that acts on both receptors at the same time can give a very different effect from a combination of drugs that act on two different receptors, Dr. Walker explained. Bivalent ligands with both delta antagonists and mu agonists may increase the potency of analgesia while reducing tolerance and dependence. One of these may be 20 times as potent as a mu agonist alone.

HOW TO USE OPIOIDS TO MANAGE CHRONIC PAIN

Pain management professionals lecturing at PAINWeek emphasized multidisciplinary management of chronic pain. But drug therapy remains the foundation and, even though there are controversies, opioids are still the mainstays. David Fishbain, MD, from the Department of Psychiatry and Behavioral Sciences at the University of Miami, helped attendees learn how to weigh the benefits and risks and how and when to use short- or long-acting opioids. He pointed to two meta-analyses and a systematic review that showed opioids to be more effective than other drugs and placebo and to significantly improve functional outcomes in chronic pain.

For effectiveness, the medical literature doesn't support one opioid over another. The choice depends heavily on whether a short- or long-acting opioid fits your patient's needs best. The short-acting opioids include morphine, codeine, hydrocodone, oxycodone, hydromorphone, oxymorphone, and fentanyl. Many of these are also available in pharmaceutically long-acting preparations. (These are often drugs of abuse because abusers try to circumvent the controlled release mechanisms.) Methadone and levorphanol are, however, pharmacologically long-acting.

Should you begin with long- or short-acting opioids? Dr. Fishbain's answer was that the literature doesn't support one over the other. "If you initiate with a short acting opioid, remember that they have very short half lives—two to six hours," he said. That means that six-hour dosing can lead to breakthrough pain, so four-hour dosing may be needed for adequate pain relief. Short-acting drugs do have advantages, however—obviously for breakthrough pain—but also for finding the appropriate dose when you start therapy. No evidence supports as-needed versus regular dosing as a better way to initiate therapy.

PRN dosing, however, may reinforce addictive behavior. And substance abusers prefer short-acting opioids, Dr. Fishbain said, citing ICA Medical Advisory Board member Daniel Brookoff, MD, PhD, who found that 60 percent reported they don't like the long-acting pain drugs.

One solution is to start the opioid-naïve patient with regular dosing, beginning at the lowest available dose, and increasing every three to four days. You can use regular plus PRN dosing for breakthrough pain, and in that case, you can increase the PRN dosing every 24 hours, splitting it over regular dosing intervals every three to four days.

Long-acting drugs, of course, provide steady blood levels for long-term relief. They may also lessen the severity of end-of-dose pain, let patients sleep through the night, and have less intense side effects. You can start opioid therapy with a long-acting drug, except for a fentanyl patch (Duragesic), which should be used only with tolerance. Switching from short- to long-acting is appropriate when there's frequent breakthrough pain, large PRN use, a desire to simplify the regimen, or when side effects and compliance are concerns.

To switch from a short- or long-acting drug to the other type, find equivalent doses with morphine equivalence tables—but with caution. "They're only a guide," said Dr. Fishbain. Tables are more dangerous for converting from a short-acting to a long-acting drug than vice versa.

Switching opioids, called opioid rotation, can be helpful. Individuals respond differently to different opioids, so you may find a more effective one and reduce side effects. Rotation may avoid hyperalgesia as well as tolerance because cross-tolerance among opioids isn't complete.

You can use conversion tables for an immediate switch, but gradual conversion is likely safer, said Dr. Fishbain. This can be done by decreasing the opioid dose by a third and adding the new one three times a day to make up the dose according to conversion tables and continuing that strategy every three days until the conversion is complete. Interestingly, opioid-induced hyperalgesia is a concept based on animal studies, and there is no equivalent in humans; some case reports indicate it may occur, but if it does, it is likely with very large doses, said Dr. Fishbain.

Adjuvant therapy, the literature indicates, can allow opioid doses to be reduced and maybe even make them more effective. Adjuvants include nonsteroidal anti-inflammatory drugs, antidepressants, antiepileptics, antispasmodics, antimigraine drugs, or even peripheral agents, such as lidocaine or capsaicin. Do not, however, use benzodiazepines, except clonazepam, for this purpose or carisoprodol (Soma), he cautioned.

Addiction, Diversion

Many PAINWeek sessions, including Dr. Fishbain's, showed attendees how to manage the risks of addiction and diversion. You can protect yourself while effectively managing your patients' chronic pain by following the principles of responsible opioid prescribing: evaluating patients thoroughly, implementing a treatment plan, and documenting scrupulously.

Evaluation includes assessing for behavior that predicts addiction and monitoring for aberrant drug behavior. A number of screening tools can help you do that (see box below). Among the red-flag behaviors are a preference for short-acting opioids, unwillingness to taper the dose, selling, and forgery. Somewhat less predictive are hoarding or obtaining prescription drugs from nonmedical sources. It's important, said Dr. Fishbain, to distinguish between real and "pseudoaddiction," the behavior of a patient whose pain isn't controlled. For example, those patients stop escalating the dose when their pain is controlled, whereas addicts will continue escalating it.

As part of your treatment plan, resolve concerns about the patient's behavior, consider nonopioid modalities, and judge whether you can manage this patient's pain on your own or need to enlist others, such as pain or addiction specialists. Once you decide to prescribe opioids, you can choose the drug, plan how to manage adverse effects, and draw up, sign, and file compliance agreements between you and your patient. (Get downloadable forms from the American Academy of Pain Medicine: www.painmed.org.)

You also need to monitor compliance, using random drug urine tests or staying alert for continual requests for early refills. But tests have false negatives and positives, so results do not always indicate addiction. Unexpected results may also indicate pseudoaddiction, forgetfulness, or fear of social stigma.

Screening Tools for Aberrant Drug Behavior

- ◆ CAGE-AID
Source: Brown RL, Rounds LA. *Wisconsin Med J* 1995;94:135-140.
- ◆ TICS (Two-item Conjoint Screen)
Source: Brown RL et al. *J Am Board Fam Pract* 2001;14:95-106.
- ◆ SISAP (Screening Instrument for Substance Abuse Potential)
Source: Coombs RB et al. *Pain Res Manage* 1996;1:155-162.
- ◆ SOAPP (Screener and Opioid Assessment for Patients with Pain)
Source: Butler SF et al. *Pain* 2004;112:65-75.
- ◆ Opioid Risk Tool (ORT)
Source: Webster LR, Webster RM. *Pain Med* 2005;6:432-442
- ◆ DIRE (Diagnosis, Intractability, Risk Efficacy)
Source: Belgrade MJ et al. *J Pain* 2006;7:671-681

These instruments are available at:
<http://lib.adai.washington.edu/instruments>
or
www.emergingsolutionsinpain.com

Documentation, he emphasized, is critical. You need to document what actions you take when a patient does not comply, not just that noncompliance occurred.

Can a previously nonaddicted patient become addicted because you prescribe opioids for chronic pain? That's highly unlikely, said Dr. Fishbain. Based on an analysis of 23 studies of 2,168 patients prescribed opioids, the rate of addiction is 3.7 percent. However, in studies that select patients out for no history of addiction, the risk of de novo addiction is only 0.29 percent.

MAKING PAIN MANAGEMENT MULTIDISCIPLINARY FOR YOUR PATIENTS

That the approach to pain management needs to be a multidisciplinary one was a given for the faculty here at PAINWeek. Indeed, many courses were designed to help providers evaluate and integrate behavioral therapy, mind-body techniques, acupuncture, and other complementary and alternative approaches into their practices.

To give your patient access to this kind of pain care today, you may have to integrate these techniques into your own practice or make multiple outside referrals. That's because the number of multidisciplinary pain management clinics has been shrinking—not because they haven't been shown to improve patients' function and reduce healthcare costs but because of insurance industry and hospital trends to "cut costs" without using an evidence base and to focus on liability rather than ethics. The result is that the number of these types of clinics in the United States fell from a high of about 1,000 in the 1990s to only about 200 in 2005, said psychologist Michael E. Schatman, PhD, Assistant Professor of Family Medicine at the Pacific Northwest University of Health Sciences College of Osteopathic Medicine in Yakima, Washington, who cited the ICA's own story on the 2005 media coverage of the state of pain care. He urged providers to help resurrect interdisciplinary pain management by getting articles published, volunteering to participate on insurance company and hospital panels, and supporting organizations and political candidates that advocate for this type of care.

Easing the suffering component of pain was the common denominator of nearly all the adjunctive therapies discussed here. That, of course, must be in addition to easing its physical component, not instead of it.

For IC patients, cognitive behavioral therapy (CBT) has been the most-discussed nonmedical adjunctive therapy. As psychologist and behavioral medicine specialist Gerylyn

Datz, PhD, noted, this kind of therapy is not about changing pain scores but about increasing patients' ability to deal with the pain that they have. Indeed, an NIH assessment found CBT to be only moderately successful for chronic pain.

The goal of CBT in pain management, she said, is to alter patients' belief that pain is unmanageable, educate them to become resourceful problem solvers instead of helpless and hopeless, help them learn to monitor pain sensations and their emotional and behavioral responses to it, develop techniques to cope better with pain and emotional distress, and develop strategies to cope after treatment ends.

If you aren't a psychologist, you can still do some assessment and use some techniques to help patients. The patient pain profile (P3) is a brief, 44-item measure that assesses anxiety, depression, and "somatization" (available at www.pearsonassessments.com). You can use this as a teaching tool with your patients or even just explain the gate control theory of pain to help patients understand how psychological factors can affect their experience of pain. And a referral for even brief psychotherapy, she said, can be very helpful. Individual therapy is usually designed to be short term, from 8 to 16 sessions that are very present oriented and problem focused.

She pointed out that your patient isn't always the only one who needs to modify attitudes about pain. The family may need to as well. It's a big problem when patients' families believe patients are addicts, have pain because they aren't working hard enough for their recovery, have pain because they aren't spiritual enough—attitudes that are common. As your IC patients' primary medical provider, you may help affect those beliefs by talking to the family members about the nature of IC pain, said Dr. Datz, who is Director of the Pain Management Program at Forrest General Hospital in Hattiesburg, Missouri.

"Taking the suffering out of a painful condition," was indeed how hypnosis practitioners and instructors Daniel Cleary and Michael Ellner described the goal of medical hypnosis in pain management. An NIH expert panel called evidence of its effectiveness "strong" in chronic pain from cancer. The panel also said the literature suggested effectiveness in other chronic pain conditions such as irritable bowel syndrome and temporomandibular disorders, conditions sometimes associated with IC.

Many think of hypnosis as trance, but it includes other techniques, such as direct and indirect suggestion, that you can easily incorporate into your practice, said Ellner and Cleary. For example, because hypnosis is about changing perception, just the language that you use with patients can be "hypnotic" and alter that perception. For example, asking your patient to describe "that pain there" is a technique of dissociation, making the pain an object and helping the patient dissociate emotions from it. Other techniques, such as imagining the pain as a different size, can help change patients' perception of the discomfort.

While Cleary and Ellner demonstrated the potential of providers' positive suggestions with the language of success, such as "I can help," they also urged providers to get away from negative suggestions they may not realize are "hypnotic" and can undermine progress. Examples of those included, "You have to live with it," which they likened to a life sentence, or "It's all in your head," which shatters rapport, promotes depressive feelings, and increases pain and dysfunction.

Meditation, imagery, and deep relaxation are also hypnotic techniques, Cleary and Ellner explained. In IC, these are being researched and used with some success by Ragi Doggweiler, MD, at the University of Tennessee, Knoxville, and Ken Peters, MD, and the team at William Beaumont Hospital in Royal Oak, Michigan. You can encourage your patients to use guided imagery and relaxation recordings, and you can perform simple guided-imagery exercises with them that take only a couple minutes and help reduce pain (see box below).

Too "out there" for you or some of your patients? Try tickling their funny bone instead, urged Hob Osterlund, APRN, from the Department of Pain and Palliative Care at the Queen's Medical Center in Honolulu, Hawaii.

Mind-Body Tools for Practitioners

Pain Reduction Hypnotic Exercise

www.therapytimes.com/blog

Go to Michael Ellner's blog and to the 8/22/06 entry
"Adding Hypnotic Tools to Your Toolbox"

Association for Applied and Therapeutic Humor

www.aath.org

Health, Humor & Hospitals, Inc.

www.chucklechannel.com

She is also President and Producer at Health, Humor & Hospitals, Inc, which produces the Chuckle Channel for in-hospital broadcasting, and she performs healthcare standup as her alter ego, nurse Ivy Push.

But seriously, humor is becoming evidence-based medicine, just as hypnosis and other mind-body techniques are. Indeed, the effects may be just as good. Osterlund pointed to a randomized controlled trial that found humor increased pain thresholds just as much as relaxation did. Research has demonstrated significant humor-induced increases in endorphins, growth hormone, NK cell activity, and immunoglobulins G, A, and M. A number of other studies have shown increases in pain thresholds with humor treatment.

Osterlund is a principal investigator for the COMIC (comedy in chemotherapy) Study at the Queen's Medical Center, a randomized, controlled trial looking at comedy's impact on stress, the immune system, and cancer symptoms in chemotherapy patients. Preliminary results showed significant positive effects of humor videos on pain, appetite, tiredness, depression, and general well-being. The effects are also being assessed on symptoms and levels of salivary IgA and cortisol.

Advise patients to put humor in their life and even make them laugh yourself, as long you keep the humor gentle, inclusive, and appropriate, said Osterlund. After all, the bladder gives IC clinicians a golden opportunity to make their patients smile.

LATEST IC RESEARCH HIGHLIGHTS

Mouracade P, Lang H, Jacqmin D, Saussine C. [Using the interstitial cystitis new diagnostic criteria in daily practice: About 156 patients.] *Prog Urol*. 2008 Nov;18(10):674-7. Epub 2008 Jul 1. French.

Sakthivel SK, Singh UP, Singh S, Taub DD, Novakovic KR, Lillard JW Jr. CXCL10 blockade protects mice from cyclophosphamide-induced cystitis. *J Immune Based Ther Vaccines*. 2008 Oct 28;6(1):6.

Siegel JF, Sand PK, Sasso K. Vulvodynia & pelvic pain? Think interstitial cystitis. *Nurse Pract*. 2008 Oct;33(10):40-5.

Erickson DR, Schwarze SR, Dixon JK, Clark CJ, Hersh MA. Differentiation Associated Changes in Gene Expression Profiles of Interstitial Cystitis and Control Urothelial Cells. *J Urol*. 2008 Oct 23.

Linksvan Ophoven A. [From end-organ disease to a classifiable bladder pain syndrome : Paradigm shift in the understanding of urological pain syndromes exemplified by the condition currently called interstitial cystitis.] *Urologe A*. 2008 Oct 24. German.

Yokoyama H, Sasaki K, Franks ME, Goins WF, Goss JR, Degroat WC, Glorioso J, Chancellor MB, Yoshimura N. Gene therapy for bladder overactivity and nociception with herpes simplex virus vectors expressing preproenkephalin. *Hum Gene Ther*. 2008 Oct 15.

Saldone MC, Vodovotz Y, Tyagi V, Barclay D, Philips BJ, Yoshimura N, Chancellor MB, Tyagi P. Multiplex Analysis of Urinary Cytokine Levels in Rat Model of Cyclophosphamide-induced Cystitis. *Urology*. 2008 Oct 8.

Mishell DR Jr, Dell J, Sand PK. Evolving trends in the successful management of interstitial cystitis/painful bladder syndrome. *J Reprod Med*. 2008 Sep;53(9):651-6.

Saban R, Saban MR, Maier J, Fowler B, Tengowski M, Davis CA, Wu XR, Culkun DJ, Hauser P, Backer J, Hurst RE. Urothelial expression of Neuropilins and VEGF receptors in control and interstitial cystitis patients. *Am J Physiol Renal Physiol*. 2008 Sep 24.

Seth A, Teichman JM. Differences in the clinical presentation of interstitial cystitis/painful bladder syndrome in patients with or without sexual abuse history. *J Urol*. 2008 Nov;180(5):2029-33.

Alp BF, Akyol I, Adayener C, Senkul T, Gultepe M, Baykal K, Iseri C. The significance of potassium chloride sensitivity test and urinary uronic acid level in the diagnosis of chronic pelvic pain syndrome. *Int Urol Nephrol*. 2008 Sep 16.

Kaczmarek P, Keay SK, Tocci GM, Koch KR, Zhang CO, Barchi JJ Jr, Grkovic D, Guo L, Michejda CJ. Structure-activity relationship studies for the peptide portion of the bladder epithelial cell antiproliferative factor from interstitial cystitis patients. *J Med Chem*. 2008 Oct 9;51(19):5974-83.

Nickel JC, Egerdie B, Downey J, Singh R, Skehan A, Carr L, Irvine-Bird K. A real-life multicentre clinical practice study to evaluate the efficacy and safety of intravesical chondroitin sulphate for the treatment of interstitial cystitis. *BJU Int*. 2008 Sep 3.

Klumpp DJ, Rudick CN. Summation model of pelvic pain in interstitial cystitis. *Nat Clin Pract Urol*. 2008 Sep;5(9):494-500.

Goldstein HB, Safaeian P, Garrod K, Finamore PS, Kellogg-Spadt S, Whitmore KE. Depression, abuse and its relationship to interstitial cystitis. *Int Urogynecol J Pelvic Floor Dysfunct*. 2008 Dec;19(12):1683-6. Epub 2008 Sep 3.

Saini R, Gonzalez RR, Te AE. Chronic pelvic pain syndrome and the overactive bladder: the inflammatory link. *Curr Urol Rep*. 2008 Jul;9(4):314-9.

Klutke CG, Klutke JJ. Interstitial cystitis/painful bladder syndrome for the primary care physician. *Can J Urol*. 2008 Aug;15 Suppl 1:44-52; discussion 52-3. Review.

Nordling J, van Ophoven A. Intravesical glycosaminoglycan replenishment with chondroitin sulphate in chronic forms of cystitis. A multi-national, multi-centre, prospective observational clinical trial. *Arzneimittelforschung*. 2008;58(7):328-35.

Fenton BW, Palmieri PA, Fanning J. Receiver operating characteristic curves of symptom scores in the diagnosis of interstitial cystitis/painful bladder syndrome. *J Minim Invasive Gynecol*. 2008 Sep-Oct;15(5):601-4.

Soler R, Bruschini H, Freire MP, Alves MT, Srougi M, Ortiz V. Urine is necessary to provoke bladder inflammation in protamine sulfate induced urothelial injury. *J Urol*. 2008 Oct;180(4):1527-31. Epub 2008 Aug 16.

Lin YH, Liu G, Kavran M, Altuntas CZ, Gasbarro G, Tuohy VK, Daneshgari F. Lower urinary tract phenotype of experimental autoimmune cystitis in mouse: a potential animal model for interstitial cystitis. *BJU Int*. 2008 Aug 14.

Clemens JQ, Brown SO, Calhoun EA. Mental health diagnoses in patients with interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome: a case/control study. *J Urol*. 2008 Oct;180(4):1378-82.

Warren JW, Langenberg P, Greenberg P, Diggs C, Jacobs S, Wesselmann U. Sites of pain from interstitial cystitis/painful bladder syndrome. *J Urol.* 2008 Oct;180(4):1373-7. Epub 2008 Aug 15.

Braunstein R, Shapiro E, Kaye J, Moldwin R. The role of cystoscopy in the diagnosis of Hunner's ulcer disease. *J Urol.* 2008 Oct;180(4):1383-6. Epub 2008 Aug 15.

Zaslau S, Riggs DR, Perlmutter AE, Jackson BJ, Osborne J, Kandzari SJ. Sexual dysfunction in patients with painful bladder syndrome is age related and progressive. *Can J Urol.* 2008 Aug;15(4):4158-62.

Seth A, Teichman JM. What's new in the diagnosis and management of painful bladder syndrome/interstitial cystitis? *Curr Urol Rep.* 2008 Sep;9(5):349-57.

do Socorro Teixeira Moreira Almeida M, Carvalho LL, Carvalho AG, Almeida JV, Borges E Silva J. Interstitial cystitis and systemic lupus erythematosus in a 20-year-old woman. *Rheumatol Int.* 2008 Dec;29(2):219-21. Epub 2008 Aug 12.

Binder I, Rossbach G, Ophoven A. [The complexity of chronic pelvic pain exemplified by the condition currently called interstitial cystitis.] *Aktuelle Urol.* 2008 Jul;39(4):289-97. German.

Chaban VV. Visceral sensory neurons that innervate both uterus and colon express nociceptive TRPv1 and P2X3 receptors in rats. *Ethn Dis.* 2008 Spring;18(2 Suppl 2):S2-20-4.

Shoskes DA, Nickel JC, Rackley RR, Pontari MA. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. *Prostate Cancer Prostatic Dis.* 2008 Jul 22. Daha LK, Riedl CR, Lazar D, Simak R, Pflugger H.

Effect of intravesical glycosaminoglycan substitution therapy on bladder pain syndrome/interstitial cystitis, bladder capacity and potassium sensitivity. *Scand J Urol Nephrol.* 2008 Jan 8:1-4.

Kuromitsu S, Yokota H, Hiramoto M, Morita S, Mita H, Yamada T. Increased concentration of neutrophil elastase in urine from patients with interstitial cystitis. *Scand J Urol Nephrol.* 2008;42(5):455-61.

The **Interstitial Cystitis Association (ICA)** is committed to finding more effective treatments and a cure for interstitial cystitis. The authoritative source of interstitial cystitis information in the United States, the ICA:

- ◆ Promotes and funds research
- ◆ Educates the medical community and public
- ◆ Advocates for IC patients, healthcare providers, and researchers
- ◆ Offers support for IC patients and their families

The ICA is dedicated to helping all those living with interstitial cystitis, as well as the healthcare providers and researchers who strive to improve the lives of IC patients. Our work is made possible through the generosity and vision of individuals, foundations, and corporations.

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