



ICA Professional Perspectives

Winter 2006

A Newsletter for Healthcare Professionals
Interested in the Research and Treatment of Interstitial Cystitis

The Interstitial Cystitis Association / Patients, Researchers, Caregivers ~ *Putting the Pieces Together*

ICA Partners with the CDC to Launch National IC Awareness and Education Campaign



Five months into the nation's first IC Awareness and Education Campaign, the ICA is working closely with the Centers for Disease Control and Prevention (CDC) and social marketing partner Reingold, Inc., of Washington, DC, to change the way healthcare practitioners and the general public view IC.

Over the course of the multi-year campaign, the ICA and its partners will employ creative strategies including media and public relations, partnership building, Web outreach, and advertising/public service announcements to educate medical professionals and females aged 25 to 54 about interstitial cystitis. This unprecedented opportunity is the result of years of ICA advocacy and leadership, as well as commitment from our friends on Capitol Hill.

"This campaign is going to change the way the medical community looks at IC," said Vicki Ratner, Founder and President of the ICA. "In five years, we hope to see faster diagnoses for patients and many more healthcare practitioners who are comfortable treating IC."

Our first priorities—to create strategic alliances and gather intelligence to ensure campaign success—already are underway. Currently, the team is conducting interviews nationwide with healthcare providers and IC patients. Our goal is to learn when and where both groups get information about IC, how they use it, and what their experiences are. This important data will help us tailor a campaign to our audiences, ensuring that they receive the right information, and then act on it.

The ICA will rely on many of its supporters and partners—including patients, members, physicians, and other non-profit organizations—to ensure this initiative is successful and its opportunity fully realized.

Partners already on board include:

- ◆ American Chronic Pain Association (ACPA)
- ◆ American Urological Association (AUA)
- ◆ Association of Health Insurance Plans (AHIP)
- ◆ The Medtronic Foundation
- ◆ National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- ◆ The National Vulvodynia Association
- ◆ Ortho Urology
- ◆ The Society for Women's Health Research
- ◆ US Department of Health and Human Services - Office of Women's Health

A public campaign launch is scheduled for November 2006. We will work with our committed cadre of allies and partners to ensure it kicks off with the right media coverage and exposure.

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NIDDK Conference Brings New Perspectives on Pelvic Pain in Men



Thinking about IC and chronic prostatitis seems to be undergoing a major shift. That

was apparent at the Chronic Pelvic Pain/Chronic Prostatitis Scientific Workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) that took place in Baltimore last October. Although a major focus was on chronic prostatitis/chronic pelvic pain (CP/CPPS) in men, the conference also focused on IC.

That's because researchers' attention is moving away from looking at the prostate and bladder alone as treatment targets and more toward treating pain itself in both conditions.

IC and CP/CPPS researchers and clinicians discussed how similar or different the two conditions might be. At the moment, the disparity in symptoms and levels of antiproliferative factor (APF) highlight the differences, but the question isn't settled and won't be until we know more about the genetics of each condition. What was clear, however, was that both sets of patients may benefit from looking at these syndromes as neuropathic pain conditions.

Focus Shifts to Nervous System

The first session of the conference, in fact, was focused on neuropathic pain. John Loeser, MD, a neurologist from the University of Washington, Seattle, strongly urged the participants to shift their research focus away from the apparent end organs and onto the nervous system, especially the mechanisms of pain transmission and centralization.

Pelvic pain and vulvodynia expert Ursula Wesselmann, MD, PhD, from Johns Hopkins University in Baltimore, Maryland, has researched potential mechanisms for the shift of acute to chronic pain. Pelvic pain conditions seldom occur alone, she pointed out. IC patients, for example, often have vulvodynia. Her research has demonstrated how an insult to one pelvic organ can later increase sensitivity to pain in other pelvic organs and even the body wall.

Gerald Gebhart, PhD, a pharmacologist at the University of Iowa in Iowa City, is changing the way we think about how pelvic organs are innervated and how pain is transmitted from them. Visceral pain has been thought to be transmitted to the central nervous system only by sympathetic nerves, but evidence is growing that the vagus nerve plays a role in chemi-nociception. Now, visceral nerves are also known to become sensitized, contrary to the assumption that sensitization takes place only centrally. These new concepts may explain why it is difficult to tell which organ the pain might be coming from, how visceral pain is referred to the body wall, and how normally quiescent sensory nerves in the viscera may be activated and contribute to hypersensitivity.

Ob/gyn and anesthesiologist John McDonald, MD, from the Harbor UCLA Medical Center in Torrance, California, spoke from a practical standpoint about the relationship between pelvic pain and nerve pain. He has seen many patients with pudendal neuralgia, whose pelvic pain had gone undiagnosed or misdiagnosed for years. To relieve pudendal neuralgia pain, he uses both perineural and sacral anesthetic injections. He has also had success with nerve blocks for vulvar vestibulitis. He speculated that the local anesthetic may somehow downregulate central pain, offering long-term relief, especially after repeat injections.

New Drug Therapies on the Horizon

The neuropathic pain session also included reports of research that could lead to new drugs for pelvic pain. Margaret Vizzard, PhD, from the University of Vermont College of Medicine, is studying a "superhormone" called pituitary adenylate cyclase activating polypeptide (PACAP), a prominent modulator of bladder sensation and function. She found administering a PACAP antagonist intrathecally or intravesically reversed cyclophosphamide-induced bladder overactivity. She is also researching a nerve growth factor inhibitor, ReN1820, which reduced bladder nonvoiding contractions and voiding frequency and increased behaviors unassociated with pain in experimental animals with cyclophosphamide-induced cystitis.

Research on the role of inflammation in pelvic pain also pointed to new potential drug targets. Anti-macrophage migration inhibitory factor (MIF) was an exciting prospect. Pedro Vera, PhD, a research physiologist at the University of South Florida in Tampa, has been researching MIF, a key regulator of inflammation and immunity. This proinflammatory cytokine is also expressed in peripheral and central nerves that innervate pelvic viscera. Intravesical anti-MIF reversed or prevented MIF-induced inflammatory changes in the bladder and prostate. Research presented by David Klumpp, PhD, from Northwestern University's Feinberg School of Medicine in Chicago, has demonstrated that the inflammatory cytokine tumor necrosis factor alpha (TNF-alpha) stimulates bladder mast cell migration into the lamina propria, which may lead to TNF-induced urothelial apoptosis and lesions. The research suggests that anti-TNF therapy may be a useful treatment for IC.

Alan Cowan, PhD, a pharmacist from Temple University in Philadelphia, Pennsylvania, spoke about more immediate drug options for pain control and drugs in development. The latter includes drugs that affect receptors for neuropeptides, cannabinoids, NMDA, and TRPV1. Dr. Cowan pointed out that the pace of new drug development has been slow, with pharmaceutical company focus shifting from developing new drugs to developing newer forms of existing drugs or drug combinations. Some of the new combinations are more effective than the individual drugs, such as combinations of neuropathic pain drugs and opioids. New ways of delivering old drugs, such as transdermal delivery of opioids, have also been a boon to pelvic pain patients. Dr. Cowan sees potential in the irritable bowel

drug tegaserod (Zelnorm), which may also provide analgesia for visceral pain in addition to its effects on bowel function.

Opiate Argument Erupts

In the discussion of how to treat pain, a mini "opiate war" erupted among the experts. Last May, Christopher Payne, MD, from Stanford (California) made a plea at the American Urological Association Annual Meeting for urologists to learn to use opioids to treat chronic pelvic pain. In an apparent reaction to that speech, some clinicians at the workshop cited dangers of their use and reacted against using them at all for people with pelvic pain. Chronic prostatitis expert Curtis Nickel, MD, from Queens University in Kingston, Ontario, argued that patients taking opiates long term suffer from side effects, such as amenorrhea and galactorrhea and don't get good long-term pain control because they develop hyperalgesia. Pain expert and ICA Medical Advisory Board member Daniel Carr, MD, however, warned against oversimplifying the issue into an "all-or-none, forever-or-never dichotomy." His own review of controlled studies of opioids has confirmed opioids' effectiveness for chronic pain. As always, the side effects have to be weighed against the benefits, and few other types of drugs are effective for the worst levels of pain. Side effects can be treated directly or minimized by administering appropriate opioids, restricting opioids to treatment of flares, or using effective drug combinations. Dr. Carr pointed to recent studies indicating a synergistic effect between neuropathic pain drugs, such as venlafaxine (Effexor), and opioids, giving better pain control with fewer side effects at lower doses than monotherapy.

Genes, Sex Can Determine Pain Sensitivity

What makes a patient more sensitive to pain than others? Two researchers had great insight on that question. Richard J. Bodnar, PhD, from Queens College, City University of New York in Flushing, is investigating how sex differences affect pain perception. He noted that, compared with men, women have lower thresholds for pain, feel pain in more body areas, feel more persistent pain over their lifetime, and have more pain syndromes. Although men and women don't show much difference in how they respond to mu opioids (morphine and relatives), women respond more to kappa opioids, such as pentazocine (Talwin) and nalbuphine (Nubain). His own research on rats has shown how sex hormones affect responses to opioids. Intact males get more pain control from opioids than castrated males do, and ovariectomized females also get more control with opioids than intact animals. Females also respond differently throughout their menstrual cycles, getting the most pain control during proestrus and the least in estrus, when estrogen levels are highest. Hormones in early life also make a difference. Females androgenized shortly after birth respond to opioids like males, and castrated males respond like females. "Sex differences have to be acknowledged and have to be paid attention to in the treatment of pain," said Dr. Bodnar.

Jeffrey Mogil, PhD, showed that both genetics and sex play huge roles in the response to pain and opioids. Genetic differences likely explain the vast differences—as much as 40-fold—in patients' response to opioids. He is identifying genes responsible for controlling responses to pain and to opioids in mice, but he believes the research may apply to humans. In fact, he found a gene mutation responsible for higher response to kappa opioids in mice that also happens to be responsible for differences in pain perception and response in humans—and in females not males. The gene happens to be one that codes for the melanocortin-1 receptor (Mc1r). In humans, variants of this gene also result in red hair. Dr. Mogil found that, indeed, Mc1r redheaded women respond better to kappa opioids and can withstand ischemic pain better than any non-redhead or male redheads. That's at odds with some earlier research showing that redheaded women may be more sensitive to pain, but he noted that the earlier research didn't check for Mc1r variants. In addition, he has found that genes can be very specific for different types of pain. For example, a gene may affect how an animal senses thermal pain but not inflammatory pain. In the future, this kind of research may give clinicians tests to see which analgesic and dose will be most effective for individual patients and may also lead to development of new pain drugs. But for now, said Dr. Mogil, that tremendous genetic variability should at least de-stigmatize pain-sensitive patients.

New Approaches to Measuring Pain

Pain is a complex phenomenon, so how should we measure it? Because experts are recognizing that pelvic pain may be a neurologic disorder, neurologic tests can help with research and in the clinic, said Clare Yang, MD, a urologist at the University of Washington, Seattle. The tests she uses may be useful as objective tests of pain therapy's effectiveness, and some tests may even demonstrate when pain has become centralized.

Dennis Turk, PhD, from the University of Washington, urged pelvic pain experts to rethink how pain should be measured in clinical trials. He asked them to consider who decides what is important—the researchers or the patient. Just because an outcome, such as reduction in pain on a scale of 1 to 10, is statistically significant to the researchers doesn't mean that it's meaningful to patients, so researchers should try to find the measures that are, he said. Change should also be weighed from the patient's perspective, for example, by finding out whether patients consider the extra cost of a new drug worth it for the amount of relief they get. Dr. Turk also recommended that researchers in this field get together to agree on what kinds of measurements should be used and to find out whether different treatments will be useful for different subsets of patients.

Psychological, Physical Therapies Being Integrated

It was apparent at this workshop that pain management is becoming broader, focusing not just on medical therapy but also on mechanical, psychological, and social factors as well. Chronic pain isn't always treatable with painkillers, and dif-

ferent explanations as to why suggested different approaches. There was a significant focus on the types of psychological treatment that can help patients cope with and even reduce pain, although moderately. Also, use of physical therapy in treatment of both men and women was much more apparent at this conference than in the past.

Psychologist and neurophysiologist Catherine Bushnell, PhD, from McGill University in Montreal has looked – literally – at how attention and emotion affect pain with functional magnetic resonance imaging (fMRI). Distraction actually reduced pain intensity in the pain-sensing areas of the brain in fMRI images. Negative emotion had more widespread effects in the brain. She said that she believes pain is seldom just created psychologically, but psychological factors can have a strong influence on pain perception and pain-related neural activity. Psychological research shows that depression, anxiety, and "catastrophizing" can contribute to pain, said clinical psychologist Jennifer Hathornthwaite, PhD, from Johns Hopkins University. Psychological research is also showing that certain psychological therapies, such as cognitive behavioral therapy, that help patients cope can help reduce pain, said Judith Turner, PhD, a psychologist from the University of Washington. The pain reduction seems to be real, although moderate. Julia Heiman, PhD, who is director of the Kinsey Institute at Indiana University in Bloomington, said that psychologists have moved away from considering pain with sex to be psychological to recognizing that it is, in fact, physical. Research is just beginning to teach us more about how chronic pelvic pain and, specifically, how pain with sex affect both relationships and daily living in men and women, she said.

David Wise, PhD's presentation about the Stanford protocol for paradoxical relaxation and trigger point release demonstrated the growing acceptance of physical therapy for pelvic pain syndromes and the idea that muscle tension and its detrimental effects on nerves, muscles, and organs of the pelvis may be a major cause of pelvic pain. Dr. Wise is coauthor of *A Headache in the Pelvis*, which describes Stanford's combination of pelvic floor physical therapy, breathing techniques to quiet anxiety, and relaxation training that focuses attention on the effortless acceptance of tension (thus paradoxical relaxation). Recently, Dr. Wise and his colleagues reported that this therapy achieved a 72 percent improvement in men with chronic pelvic pain who weren't helped by other treatments.

The Latest IC Treatments in Development

There are several new IC therapies in development. From oral medications, bladder instillations and injections, to neuromodulation devices, companies are developing new products and clinical trials are underway.

Here are the latest developments in the IC treatment pipeline:

Oral Medications

Amitriptyline (Elavil)

Low doses of amitriptyline (Elavil—a tricyclic antidepressant) have been found to be a helpful treatment for IC pain and urinary frequency/urgency. This medication, one of the first tricyclic antidepressants ever developed (in the 1930s), has been used "off label" to treat IC for many years with just a handful of small studies that have indicated its value. It has unique properties that are unlike those of the newer antidepressants that are currently on the market, such as the selective serotonin reuptake inhibitors (SSRIs) and the selective norepinephrine reuptake inhibitors (SNRIs), as well as several other novel variations.

It was only recently that, for the first time ever, a double-blind, placebo-controlled study was conducted using amitriptyline to treat IC. This study from Germany used the medication to treat IC in 50 patients, and the study was reported on in the August 2004 issue of the *Journal of Urology* (van Ophoven et al).

Now, a new study is testing amitriptyline to confirm its potential to alleviate bladder pain for which there is no known cause and no uniformly effective therapy. Thousands, if not millions, of patients may benefit. The study is funded by the National Institutes of Health (NIH).

For more information:

www.niddk.nih.gov/patient/iccrn/iccrn.htm

MN-001

MediciNova, Inc. is conducting a national clinical trial to test a new medication for its potential use as a treatment for IC. The experimental medication, MN-001, has been shown in previous medical studies to be useful in treating the inflammatory response in asthma. Since IC is also thought to involve an inflammatory component, MediciNova is conducting a phase II (human study with 100-300 participants), randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of two dosing regimens of MN-001 in patients with interstitial cystitis.

For more information: www.bladderpainstudy.com OR www.medicinova.com/mn001_ic.html

IP 751

Indevus is developing IP 751, a novel anti-inflammatory and analgesic compound for specialty disease states, including interstitial cystitis, with additional applications in the treatment of pain and inflammation. IP 751 is a non-psychoactive synthetic cannabinoid that appears to suppress inflammatory cytokines. The compound has significant activity in multiple pre-clinical models of pain and inflammation and, most recently, IC. Unlike most available NSAIDs, in pre-clinical studies IP 751 did not appear to produce gastrointestinal ulceration.

For more information: www.indevus.com

Suplatast tosilate

The oral drug, suplatast tosilate (Astellas), is already on the Japanese market and is indicated for asthma and allergies. Phase II trials for IC are planned for the United States.

This medication acts somewhat earlier in the allergic process than histamine or leukotriene blockers by affecting IgE. Suplatast tosilate actually helps suppress the production of IgE. The drug also helps to block production of cytokines. In addition, suplatast tosilate suppresses allergy-related eosinophils.

From more information:

www.astellas.com/global/about/news/yamanouchi/030123.html

ERB-041

Wyeth is beginning testing of ERB-041, which is an orally active estrogen receptor beta agonist with potent anti-inflammatory activity. In addition to being studied as a potential IC therapy, it is also being studied for use in the treatment of endometriosis and rheumatoid arthritis. The ERB-041 IC study a multicenter, randomized, double-blind, placebo-controlled, parallel-design, exploratory study of orally administered ERB-041 in subjects with active IC. The primary objectives of this study will be to investigate ERB-041's activity on levels of urinary APF, explore the gene expression response in peripheral blood mononuclear cells (PBMC), and evaluate the safety of ERB-041 in women with active IC.

For more information:

www.clinicaltrials.gov/ct/gui/show/NCT00275379

Bladder Instillations

U101

Vancouver-based Urigen Inc. announced in October 2005 that the FDA has accepted the company's investigational new drug (IND) application to initiate a Phase IIb clinical trial with its lead product, U101. U101 is a proprietary intravesical formulation of FDA-approved components that has been demonstrated to provide near-immediate relief of symptoms associated with IC.

Urigen's Phase IIb clinical trial is a prospective, randomized, double-blind, placebo-controlled Phase II study of U101 in adult subjects with chronic pelvic pain and urgency of bladder origin. The objective of the study is to evaluate the safety and efficacy of U101 in a multicenter trial.

For more information: www.urigen.com

Bladder Injections

Botulinum Toxin Type A

Botulinum toxin type A (BTX-A or Botox) (Allergan) is being used to treat many conditions of the bladder, including IC. BTX-A is thought to work by blocking the sensory nerves in the bladder that transmit pain, spasticity and inflammation. At this time BTX-A requires direct needle injections into the bladder.

While BTX-A is not FDA-approved for the treatment of IC, it is being used at various institutions throughout the United States as a potential IC treatment when other standard therapies have failed. The University of Washington is currently recruiting participants for a randomized, double-blind, placebo-controlled efficacy study of BTX-A.

For more information:

www.clinicaltrials.gov/ct/show/NCT00194610?order=1

Electrostimulation/Neuromodulation

MiniatURO I Implantable System

A new form of neuromodulation, the MiniatURO I Implantable System (BioControl Medical), is being tested throughout Europe and other parts of the world for use in several bladder conditions including overactive bladder, incontinence, and IC. It is currently undergoing trials for female patients suffering from pelvic pain and/or urinary frequency associated with IC. The MiniatURO I is a minimally invasive implantable device for patients who have failed to respond to conservative treatment.

Urgent PC Neuromodulation System

In October, the FDA approved pre-market clearance of Uroplasty's Urgent PC Neuromodulation System [formerly known as the Stoller Afferent Nerve Stimulator (SANS) and as Post-Tibial Nerve Stimulation (PTNS)]. Urgent PC is a minimally invasive nerve stimulator designed for office-based treatment of overactive bladder symptoms of urge incontinence, urinary urgency and urinary frequency with or without pain. Uroplasty is planning to market the device in the United States, Europe, and Canada by the end of 2005.

Through the use of a very thin needle placed in the ankle/tibia region, Urgent PC delivers low frequency electrical stimulation (neuromodulation). This process is thought to recondition the misfiring nerves that affect bladder function. The tibial nerve carries the signal to the portion of the spine that controls bladder function.

For more information: www.uroplasty.com

Bion

Bion (Advanced Bionics Corporation) is an implantable matchstick-size device that calms overactive bladder by stimulating the pudendal nerve. This nerve carries sensations from the sacral nerves to external genitals and the lower rectum.

Currently, clinical trials are underway to study the use of the Bion device for overactive bladder and incontinence. Though not yet FDA-approved for use in IC, some researchers and clinicians are hopeful that Bion will also be effective in the treatment of IC.

For more information: www.advancedbionics.com

The Latest Published IC Research

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Please plan to attend

The NIDDK's

Frontiers in Painful Bladder Syndrome and Interstitial Cystitis Symposium 2006

Tentatively scheduled for late October/early November 2006 in the Washington, DC area.

Further details forthcoming.

Upcoming Events

SUNA 2006 ANNUAL SYMPOSIUM

Marriott Marquis, New York, NY
March 16-18, 2006
www.suna.org or call toll free 1-888-TAP-SUNA.

NATIONAL FIBROMYALGIA ASSOCIATION 2006 NATIONAL PATIENT SUMMIT

Hyatt Regency Hotel Orange County, CA
March 17-19, 2006
<http://fmawareorg0.web120.discountasp.net/events/2006/fame/fame.asp>

AMERICAN PAIN SOCIETY

San Antonio, TX
May 3-6, 2006
www.ampainsoc.org/meeting/annual_06/

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS ANNUAL MEETING

Washington, DC
May 6-10, 2006
www.acog.org

AMERICAN UROLOGICAL ASSOCIATION ANNUAL MEETING

Atlanta, GA
May 20-25, 2006
www.aua2006.org/am06



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