Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last):		
Home Address (including Apartment or Suite #):		
City:	State: CT	Zip Code:
Telephone Number:	E-mail Address:	

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

INTERSTITIAL CYSTITIS

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

SEE ATTACHED

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

ULTRACET IS A PRN MEDICATION THAT OFTEN CAUSES SEVERE NAUSEA AND VOMITING & THE EFFECTIVENESS IS UNRELIABLE.

Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Section J: Submission of Petition

In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.

- Attach additional pages as necessary. PROOF OF TREATMENT INCONSISTENCY & POOR QUALITY OF LIFE IS INCLUDED AS A SUPPLEMENTAL TESTIMONY TO THE BENEFICIAL PROPERTIES FOR THIS DISEASE. IC IS NOT AN OVERALL WELL-UNDERSTOOD CONDITION AND AS SUCH RESEARCH ESPECIALLY HOW SYMPTOMS ARE AFFECTED BY MARIJUANA PAIN MANAGEMENT IS LIMITED. MY PERSONAL EXPERIENCE AND RESEARCH INTO WHAT IS AVAILABLE ALONG WITH DISCUSSIONS IN THE IC COMMUNITY HAS LED ME TO BELIEVE THAT APPROVAL FOR THE CTMMP WILL SIGNIFICANTLY IMPROVE QUALITY OF LIFE FOR CT IC PATIENTS.

I hereby certify that the above information is correct and complete.

My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.

Sign: [redacted]	Date Signed: 18 JANUARY 2019

JOURNAL OF WOMEN'S HEALTH & GENDER-BASED MEDICINE
Volume 8, Number 6, 1999
Mary Ann Liebert, Inc.

SECTION I

Review

Interstitial Cystitis: Update on Etiologies and Therapeutic Options

DEBORAH R. ERICKSON, M.D.

ABSTRACT

Interstitial cystitis (IC) is a syndrome of pelvic and/or perineal pain, urinary urgency, and frequency. It is now agreed that IC is a multifactorial syndrome, not a single condition. A variety of etiologies for IC have been proposed, but none has been definitively proven. Since the etiologies for IC remain unknown, the current treatments are empiric. This article will review the major theories of etiology for IC and discuss the current treatment options with relevance to the proposed etiologies. No single treatment is effective for all IC patients. Therefore, the approach is to try different treatments, alone or in combination, until symptom relief is satisfactory. In some cases, none of the empiric IC treatments are successful. These patients require adjunctive pain management, and a small minority of IC patients resort to surgery if all other options fail.

INTRODUCTION

INTERSTITIAL CYSTITIS (IC) IS A poorly understood syndrome that remains a major women's health problem.[1] About 90% of IC patients are female. The symptoms vary for different patients but usually include some combination of pelvic pain, perineal pain, pain increased by holding urine (which leads to urinary frequency), nocturia, urinary urgency, and constant sensation of urge to void. IC patients also show variability in other clinical features, such as cystoscopic findings, bladder biopsy findings, and levels of urinary disease markers (such as histamine or cytokines). Because of these variations, it is generally agreed that IC is a multifactorial syndrome rather than a single disease (for reviews on IC, see refs. 1–3).

Because IC is not a single disease, it is very unlikely that we will ever find a single treatment that cures all IC patients. In fact, at this time, no cures for any types of IC are known. Some patients enter long periods of symptom remission, and others keep their symptoms reasonably well controlled with the various treatments described later. For some patients, however, symptoms persist in spite of multiple treatments.

As no treatment is universally effective, the usual clinical approach is to try a series of empiric treatments until good symptom relief occurs. At this time, there is very little information to help clinicians choose which treatment might

Pennsylvania State University, College of Medicine, Section of Urology, Hershey, Pennsylvania.
Presented at the Sixth Annual Congress on Women's Health, June 21–24, 1998, Washington, DC.

be most effective for a specific IC patient. Therefore, the usual practice is to start with the safest and least invasive treatments and progress to others (with more potential morbidity) if the initial treatments are not effective.

This article discusses the current therapeutic options for IC. As some of the treatments are directed toward specific theories of etiology for IC, we start by describing the major etiological theories, then discuss therapeutic options and their relevance to the proposed etiologies for IC.

THEORIES OF ETIOLOGY FOR IC

Several different etiologies have been proposed for IC, but none has been definitively proven. Because IC is a multifactorial syndrome rather than a single disease, it is likely that several of these etiologies are true for different subsets of patients. The etiologies also may be interrelated (e.g., bladder inflammation may cause the epithelial cells to slough, which would increase bladder permeability). Descriptions of the major etiological theories for IC follow.

Bladder epithelial permeability

Normal urine has many unphysiological characteristics, including pH, osmolarity, concentration of potassium and ammonium ions, and so on. Therefore, it is essential for the bladder epithelium to act as a barrier. One of the most popular theories for IC is that the bladder epithelium is abnormally permeable, so urine components penetrate and irritate the bladder.

Although this theory is commonly stated, it has not been proven and remains an area of active research. The theory is supported by several lines of indirect evidence. First, some IC patients have increased pain after eating certain foods, such as citrus fruits and tomatoes, which are high in potassium and acid. Second, some IC patients had pain when 0.4 M potassium chloride was instilled into the bladder, whereas most healthy controls did not.[4,5] Third, after taking fluorescein orally, IC patients had higher blood fluorescein levels than healthy controls. This was attributed to increased fluorescein reabsorption across the bladder wall in IC.[6] Fourth, urea concentration was decreased when a urea solution was left for 45 minutes in IC bladders, suggesting urea absorption by the bladder.[7] However, none of these studies measured bladder permeability directly. In the only direct study published to date, radio-labeled diethylenetriamine pentaacetic acid (DTPA) was instilled into the bladder, and blood samples were assayed.[8] IC patients showed higher blood levels of DTPA than healthy controls, but the difference was not statistically significant ($p = 0.075$). This small study (10 IC patients, 9 controls) may have lacked statistical power to detect a true difference. Thus, the issue of increased bladder permeability in IC remains unresolved.

If epithelial permeability truly is increased in IC, the reasons are still unknown. In some cases, IC bladder biopsies reveal a simple explanation: the epithelium is visibly disrupted or lost.[9,10] However, in other IC patients, the epithelium appears intact. If these bladders are permeable, the most common explanation is that the bladder epithelial glycocalyx is deficient. Ordinarily, large negatively charged molecules, such as glycoproteins and glycosaminoglycans (GAG), line the epithelium and are thought to contribute to the permeability barrier.[11] Several studies have shown that IC patients had decreased levels of glycoproteins and GAG in both bladder and the urine.[12–17] It is not known whether these changes represent causes or effects of IC, and no studies have correlated these changes with increased bladder permeability. In spite of these uncertainties, GAG (such as heparin, hyaluronic acid, and pentosan polysulfate [PPS]) are widely used to treat IC. The rationale is that GAG are thought to replace the deficient epithelial glycocalyx. Details on the specific GAG regimens are given in the Treatment section of this review.

Mast cell activation

Mast cells are inflammatory cells that secrete a variety of mediators relevant to IC symptoms, for example, histamine, prostaglandins, leukotrienes, cytokines, and chemotactic factors.[18] Some of these mediators are synthesized *de novo* when mast cells are activated. Others are stored in intracellular granules, which are released when the mast cells are activated. The classic stimulus for degranulation is antigen binding to IgE on the mast cell surface (type I hypersensitivity). However, a variety of other stimuli can also degranulate mast cells, including acetylcholine, iodinated contrast and other drugs, hormones, cold, and trauma.[18]

A popular theory for IC is that bladder mast cells are activated and release their inflammatory and nociceptive mediators, especially histamine.

This theory is supported by studies of urine and of bladder biopsies. Several studies have shown that IC patients had increased urine levels of mast cell mediators, including histamine,[19,20] histamine metabolites,[20,21] and tryptase.[22] Some IC bladder biopsy specimens contain mast cells, but mast cells are not specific to IC and can also be found in other bladder disorders.[23] In studies using electron microscopy of IC bladder biopsy specimens, mast cells were seen to be releasing their granules, often adjacent to sensory nerve fibers.[24–27] This prompted the hypothesis that IC represents a type of neurogenic inflammation. Neurogenic inflammation starts when sensory nerves are stimulated. They release neuropeptides (such as substance P) that promote inflammation by several mechanisms, including activation of mast cells.[24] Mast cell mediators produce pain, which further stimulates the sensory nerve fibers, creating a vicious cycle. If this theory is true, future strategies may be developed to break the cycle. Currently, mast cell stabilizers and antihistamines are used to treat IC. These are discussed in the Treatment section of this review.

Inflammation

Most biopsies of IC bladders show some degree of inflammation,[3,9,10,23,24,28,29] ranging from mild chronic (lymphocytic) inflammation to intense infiltration that may include T cells, T cell aggregates, B cells, germinal centers, plasma cells, neutrophils, eosinophils, and mast cells.[9,10,28,29] Several inflammatory mediators are increased in IC patients' urine, including interleukin-6 (IL-6), IL-2, kallikrein, and neutrophil chemotactic factor.[29–33]

The stimuli that start and perpetuate inflammation in IC are unknown. Possibilities include the following: (1) neurogenic inflammation as described, (2) if the bladder epithelium is permeable, noxious urine components may penetrate and irritate the bladder, (3) allergy or hypersensitivity to urine components,[34] (4) occult infection,[3,35–43] and (5) autoimmune processes (for reviews, see refs. 44–46). Because inflammation is evident in many cases of IC, various types of anti-inflammatory or immunosuppressive treatments have been used to treat IC. These are discussed in detail in the Treatment section of this review.

Toxic urine components

Occasionally, refractory IC is treated by diverting the urine to a bowel conduit or reservoir. Anecdotal reports have described patients who went on to develop IC in the bowel segment.[47,48] This suggests that a urine-borne factor may cause IC. Several studies have compared IC and control urine for toxicity. When rabbit bladders were exposed to human IC or control urine, the IC group developed signs of IC, and the control group did not.[49] In other studies, cultured bladder epithelial cells were exposed to IC and control urine. IC urine did not increase cell death in an immortalized cell line,[48] but it did inhibit proliferation of human epithelial cells in primary culture.[50,51] The antiproliferative factor was found to be a low molecular weight protein.[50] After the protein is completely characterized, strategies to neutralize it may be developed to treat IC.

Occult infection

Routine urine cultures in IC are negative. However, many investigators have suspected that IC is an occult infection. Several studies have looked for bacteria, fastidious organisms, fungi, and viruses using special techniques, but no organisms were found to be consistently associated with IC.[35–40] More recent studies used polymerase chain reaction (PCR) to look for bacterial DNA in IC bladder biopsy specimens. The initial study showed that 29% of IC patients had bacterial DNA,[41] but two other studies from different investigators did not confirm this finding.[42,43]

Although ongoing infection has not been shown to perpetuate IC, it is possible that infection might initiate IC. For example, infection may cause long-term damage to the epithelium,[34,52,53] initiate an autoimmune process,[34,35] or initiate a cascade of neurogenic inflammation.[24] The use of antibiotics to treat IC is discussed in the Treatment section of this review.

Neuropathic changes

IC patients can have severe pain with a normally innocuous stimulus, such as bladder filling. This suggests that altered innervation may contribute to the symptoms.

Evaluating bladder biopsy specimens, several studies have consistently shown increased nerve fiber density in IC bladders.[26,54–57] When evaluating the specific type of nerve fibers (e.g., sensory, sympathetic, parasympathetic), different investigators have reported contradictory results.[26,56,57] These differences are probably due to differences in the IC patients, effects of bladder distention or other IC treatments, and the mutual

interactions among different nerve types (e.g., sympathetic nerve stimulation modulates the activity of sensory nerves). After these interactions are clarified, new treatments may be developed to modify them.

As described in the section on mast cell activation, bladder innervation may be altered by a process of neurogenic inflammation.[24] It has also been proposed that IC is a type of reflex sympathetic dystrophy to the bladder,[58] with abnormal spinal sympathetic activity.[59] One center reported good relief with lumbar epidural blockade, which is thought to break the pain cycle of reflex sympathetic dystrophy.[60] This treatment is currently being investigated at other centers.

A major concern with chronic pain is that changes may occur in the central nervous system (CNS) that amplify or perpetuate pain signals, even if the initial noxious stimulus is no longer present (for reviews, see refs. 61–64). This neural plasticity is probably the reason why some IC patients never find relief with any treatment, including cystectomy.[65]

THERAPEUTIC OPTIONS

A large variety of treatment options are used for IC. Many are directed toward specific etiological theories. However, almost no studies have been done to help clinicians identify which patients would respond best to which treatments. In most cases, treatment choices are made empirically, by clinician and patient preference. In some cases, several treatments must be tried (or combined) before adequate symptom relief occurs. The more commonly used IC treatments are described.

Conservative treatments

Various conservative treatments have been promoted to improve IC symptoms. These include diet changes, changes in clothing or hygienic practices, stress reduction, heat or ice, exercise, physical therapy, various forms of coping mechanisms, and bladder holding protocols. Some of these are reviewed in reference 66, and extensive information is available from the Interstitial Cystitis Association. For most of these treatments, there is little or no documentation that they affect the pathophysiology or course of IC. However, anything that can improve patients' discomfort with minimal morbidity is certainly of value.

The most commonly used treatment is probably dietary changes. Many IC patients are very clear that certain foods increase their symptoms. The classic offenders are coffee, chocolate, ethanol, carbonated drinks, citrus fruits, and tomatoes. The mechanism of symptom increase is unknown but may be related to the acid or potassium content of these foods. Some patients find that an over-the-counter supplement, Prelief (calcium glycerophosphate; AkPharma, Pleasantville, NJ), allows them to tolerate these foods. The responses to specific foods are highly variable among patients, so there is no standardized diet that works for everyone. I usually recommend eliminating all foods listed in Table 1 for 1–2 weeks, then reintroducing the foods one at a

TABLE 1. FOODS TO AVOID[a]

All alcoholic beverages
Apples, apple juice
Aspartame (NutraSweet, Deerfield, IL)
Avocados
Bananas
Cantaloupes
Carbonated drinks
Cheese (except American, cottage, ricotta, cream)
Chicken livers
Chilies/spicy foods
Chocolate
Citrus fruits
Coffee (except no-acid type)
Corned beef
Cranberries
Grapefruit, grapefruit juice
Grapes, grape juice
Guava
Lemons, lemon juice
Lentils
Lima beans
Limes, lime juice
Mayonnaise
Nuts (almonds, peanuts, and pine nuts are tolerable)
Onions
Oranges, orange juice
Peaches
Pickled herring
Pineapple
Plums
Prunes
Raisins
Rye bread
Saccharine
Sour cream
Soy sauce
Strawberries
Tea (except sun tea)
Tomatoes (except low-acid types)
Vinegar
Vitamins buffered with aspartate
Yogurt

[a]Adapted from Gillespie.[67]

time to see which foods increase the symptoms for that patient.

Another conservative treatment is a bladder holding protocol. This is best suited for patients with frequency and urgency but not severe pain. The specific techniques vary but generally include diary keeping, timed voiding, and a gradual increase in voiding intervals.[68,69]

Bladder distention

Bladder distention is one of the oldest treatments for IC. It must be done under general or regional anesthesia, and the bladder is distended at 80 cm water pressure for 2–8 minutes.[2,3,29,70] This procedure also can be diagnostic by showing submucosal hemorrhages (glomerulations) or bladder ulcers after distention.[2,3,70]

For most patients, the symptoms worsen for a few days after distention, but after that, some patients experience impressive symptom relief, with complete resolution of pain and greatly improved voiding frequency. The duration of this excellent relief varies but is usually 6–12 months. If symptoms recur, repeat distention usually provides another period of prolonged improvement.

The mechanism of symptom relief is unknown. Bladder distention decreases sympathetic nerve density in the bladder,[57] which may be the mechanism for IC relief. Another possibility is that distention may cause all the bladder mast cells to degranulate at once, and the symptoms remain quiescent until new mast cells migrate to the bladder. It has also been proposed that distention causes the (presumably defective) epithelium to slough, and the new epithelium that grows back has normal function.

Although the mechanisms of symptom relief are unknown, it is clear that distention does give excellent relief for a subset of patients. Patients who have severe inflammation on bladder biopsy are more likely to achieve good symptom relief than patients with mild inflammation.[29] High urine levels of kallikrein also are predictive of good symptom relief after distention.[30] As patients with severe bladder inflammation are generally older,[9,29] I tend to recommend distention more strongly for patients over age 50 because I am more confident that they will experience good (although temporary) symptom relief.

Glycosaminoglycans (GAG)

A popular theory for IC etiology is that the epithelial glycocalyx is deficient. Exogenous GAG are used to treat IC, with the rationale that they may supplement or replace the deficient epithelial glycoconjugates. The GAG with published trials to date include PPS (Elmiron; Alza Pharmaceuticals, Palo Alto, CA), heparin, and hyaluronic acid. Some IC patients use over-the-counter preparations of chondroitin sulfates, but no studies on these agents are published.

PPS is given orally, usually 100 mg t.i.d., on an empty stomach. It has very few side effects, and occasional nausea, diarrhea, or alopecia is reversible if the drug is stopped. As PPS resembles heparin, it has a weak anticoagulant activity and should be used with caution in patients with coagulopathies. In healthy patients, problems with bleeding or bruising with PPS are very rare. The main drawback to PPS is expense (currently about US$100–150/month). Another drawback is that 3–6 months of PPS therapy is usually needed before symptoms improve, so patients must be encouraged to stay on it.

PPS was tested in three open-label trials,[71–73] which all showed good response in some patients. One trial made an interesting distinction. IC patients with bladder ulcers showed significantly less improvement than the nonulcer patients.[73] This suggests that ulcer and nonulcer patients have different pathophysiologies for their IC symptoms.

PPS was tested in four placebo-controlled trials.[75–77] Three trials, conducted in the United States, showed that PPS was more effective than placebo.[74–76] This was the basis for approval by the U.S. Food and Drug Administration (FDA) of PPS to treat IC. The fourth trial, conducted in Europe, showed no significant differences between the PPS and placebo groups.[77] This discrepancy may be the result of different methods of data analysis. The European study looked at mean values (such as mean number of voids per day) for the entire PPS or placebo groups. In contrast, the U.S. studies defined a certain level of improvement as a "responder," then compared the percents of responders in the PPS and placebo groups. Another possible explanation is that the European IC population may have a higher proportion of patients with bladder ulcers, and these patients are less likely to improve on PPS.[73]

Another GAG, heparin, has been evaluated in open-label studies to treat IC. Subcutaneous heparin was effective in a European study of 8 patients.[78] However, because long-term systemic heparin can cause osteoporosis, intravesical heparin is more commonly used. Parsons et al.[79] pub-

lished a trial of intravesical heparin, 10,000 U three times a week, but their current practice is to use 20,000 U daily.[80] In the published report, 27 of 48 patients (56%) had at least a 50% improvement in IC symptoms. In another open-label study, monthly instillations of 10,000 U heparin prolonged remission after dimethylsulfoxide (DMSO) treatment.[81]

A purified preparation of high molecular weight hyaluronic acid (Cystistat; Bioniche, Montreal, Quebec, Canada) was used in an open label study.[82] Forty milligrams of Cystistat was given intravesically weekly for 4 weeks, then monthly. After 6 months, 25% of patients had a complete remission, and 25% of patients had partial response. Cystistat is not available in the United States but has been obtained by mail order from Canada for IC patients here.

Thus, all three GAG (PPS, heparin, and hyaluronic acid) have been used to treat IC, and some patients have had a good response, although the mechanisms of symptom relief are not known. As described in the section on Etiology, it has never been proven that bladder permeability is increased in IC or that any increase in bladder permeability is caused by a deficiency in epithelial GAG. Therefore, the notion that these agents acts as GAG replacements may not be correct. Other possible mechanism include (1) these large polyanionic molecules may bind urinary cations (such as K^+ and NH_4^+) that would otherwise irritate the bladder, (2) heparin has several anti-inflammatory effects, including stabilization of mast cells, and (3) hyaluronic acid modulates inflammation and cell proliferation and acts as a free radical scavenger.

For the clinician treating IC, several questions remain unanswered. Which of these three GAG is the best initial choice for treating IC? If one GAG fails (e.g., heparin), should the patient try another (e.g., PPS), or does failure with one GAG predict that the other GAG also will not relieve the symptoms? Is there any benefit to combining GAG therapy (e.g., oral PPS and intravesical heparin)? Clearly, more research in this area is needed.

Dimethylsulfoxide (DMSO)

Until the recent approval of PPS, DMSO was the only agent to treat IC that had been approved by the FDA. It has been described in several open-label trials (for review, see ref. 83) and one placebo-controlled study,[84] in which symptoms were markedly improved in 53% of patients using DMSO and 18% of patients using placebo.

The usual practice is to instill 50 ml of 50% DMSO into the bladder weekly for 6 weeks. After initial symptom response, some patients require maintenance treatments at 2–8-week intervals. DMSO is sometimes combined with other ingredients, such as heparin and steroids, but no published studies have directly compared these combinations with DMSO monotherapy.

Treatments directed against mast cells

Mast cells are thought to contribute to IC pathophysiology by releasing several mediators, primarily histamine. Therefore, both the H_1 antagonist hydroxyzine and the H_2 antagonist cimetidine have been used to treat IC, although neither has been evaluated in placebo-controlled trials. In an open-label study of hydroxyzine, 50 mg p.o. at bedtime, the mean improvement in symptom score was 3.5 on a 10-point scale.[85] It can take up to 3 months for hydroxyzine to provide good symptom relief, so patients must be encouraged to stay on it. Hydroxyzine is sedating but otherwise has few side effects. Nighttime sedation is often a benefit for IC patients, as they suffer from nocturia and sleep deprivation. In two small studies of cimetidine, 300 mg p.o. b.i.d., approximately two thirds of patients had an excellent response.[86,87] Side effects were minimal, but cimetidine does have several drug interactions because of its effect on microsomal enzymes. Other related H_2 antagonists (ranitidine, famotidine, nizatidine) have not been tested for efficacy in IC.

Cromolyn sodium stabilizes mast cells and is used intravesically in treating some IC patients. In the only published study to date,[88] 9 IC patients received 100 ml of 4% cromolyn sodium daily for 12 days. Of the 9 patients, 2 were cured, and 4 were improved.

As described in the section on GAG, heparin stabilizes mast cells, and this may be its main mechanism for symptom relief in IC.

Amitriptyline

Amitriptyline is one of the most commonly used IC treatments. Its exact mechanisms for IC relief are unknown. Amitriptyline has several actions that, in theory, should help relieve the

symptoms of IC. It has antihistaminic activity and may stabilize mast cells through its anticholinergic effects (however, this is probably not its main action for IC, as pure anticholinergics, such as oxybutynin or hyoscyamine, are usually not effective for IC). Nighttime sedation improves sleep and may help with nocturia. Amitriptyline also inhibits nociception in the CNS, so it is used for many types of chronic pain other than IC pain.

Amitriptyline has been effective for IC in several open-label trials (for review, see ref. 89). The usual dose is 25–75 mg p.o. at bedtime. Side effects include sedation, anticholinergic effects, and weight gain. Other tricyclic antidepressants, such as imipramine, doxepin, and desipramine, have not been formally studied in IC.

Calcium channel blockers

Calcium channel blockers have several actions that may theoretically benefit IC patients. They increase bladder blood flow, inhibit detrusor contractions, depress cell-mediated immune response, and decrease nociception. Nifedipine was used to treat IC in a small open-label study.[32] Unlike most IC treatment trials, this study measured an objective marker (urine IL-2 inhibitor) as well as symptom scores. For all 9 patients, the urine IL-2 inhibitor levels decreased to zero or near zero on nifedipine treatment. However, some patients continued to be symptomatic, suggesting that these patients' symptoms were not related to an IL-2-mediated immune response. It is unknown whether any other calcium channel blockers besides nifedipine would affect IC symptoms.

Arginine

Recent studies found that IC patients had decreased nitric oxide synthase activity in their urine.[90] Therefore, the investigators administered oral L-arginine to increase nitric oxide synthesis in IC patients. Symptoms improved in 10 of 10 patients,[91] and urine levels of nitric oxide synthase activity increased in 8 of 8 patients.[92] Side effects were minimal. Recently, the same investigators reported a placebo-controlled trial of L-arginine to treat IC.[93] Overall, symptom responses in the arginine and placebo groups did not differ significantly. In subset analysis, the response to arginine was greatest for those patients with a bladder capacity under anesthesia of at least 800 ml or for patients with a history of recurrent urinary tract or vaginal infections.[93]

Bacillus Calmette-Guérin (BCG)

Intravesical BCG is commonly used by urologists to treat bladder cancer. It was serendipitously found to relieve IC symptoms in one patient, which prompted an open-label study,[94] followed by a placebo-controlled study.[95] In the latter study, BCG had a 60% response rate compared with 27% for placebo. The treatment regimen was 6 weekly instillations of BCG. A follow-up study showed that the results were durable.[96] The mechanism of symptom relief is unknown. One theory is that BCG changes bladder inflammation from a predominantly T-helper cell type 2 (Th2) response to a Th1 response, which is more indolent.[96] Another theory is that BCG may increase nitric oxide synthase activity in the bladder.[96] The major concern with BCG is that this live organism occasionally causes sepsis when used to treat bladder cancer. To date, BCG sepsis has not occurred in the IC population.

Immunosuppression

Because IC may be an autoimmune disease in some patients, several small open-label trials of different immunosuppressive drugs have been reported. These include oral cyclosporine,[97] oral hydroxychloroquine,[98] and intravesical doxorubicin.[99] None of these agents have follow-up studies or placebo-controlled trials reported.

Oral steroids are rarely used for IC because the potential complications are so severe. Some practitioners, however, use intravesical steroids, either alone or in combination with other agents, including heparin, sodium bicarbonate, local anesthetics, and DMSO. Typical drugs and doses are hydrocortisone 100 mg or triamcinolone 10 mg. Formal studies of these agents have not been published.

Currently, immunosuppression is not a standard treatment for IC. The main reason for not using immunosuppression is that only a subset of patients is likely to benefit. If immunosuppression were a routine IC treatment, many patients would face the risks of immunosuppression yet receive no benefit. A major advance would be to find an objective marker (e.g., serum autoantibodies) to predict which IC patients would re-

spond to immunosuppression. At this time, no such studies are available.

Antibiotics

Routine urine cultures in IC are negative. Accordingly, most IC patients do not improve on antibiotics, and antibiotics are not standard therapy for IC. On the other hand, IC may represent a subclinical infection in some cases, and anecdotal reports describe some IC patients who improved on long-term antibiotic therapy.[35,100]

Currently, there is no good evidence to help clinicians decide which IC patients should try antibiotics or which antibiotics to use. Until this information is provided by well-controlled prospective studies, the routine use of antibiotics to treat IC is not recommended.

Treatments for pain

Pain is often a major component of IC symptoms. Specific treatments for pain are useful adjuncts to IC treatment regimens. In some cases, consultation with a pain management specialist can be very helpful. Transcutaneous electrical nerve stimulation (TENS) was reported to relieve symptoms in some patients.[101] Patients with bladder ulcers were more likely to have a good response than nonulcer patients (54% response rate vs. 26% response rate). As noted previously, this difference in treatment response suggests that ulcer and nonulcer patients have different pathophysiologies for their IC symptoms.

Capsaicin (the pungent ingredient in hot peppers) can decrease pain by desensitizing sensory nerve fibers. It has been used in many human neuropathic disorders, such as postherpetic neuralgia and diabetic neuropathy. A few small, open-label studies have reported symptom improvement after instilling capsaicin into the bladders of patients with IC-like symptoms.[102,103] However, in the only placebo-controlled trial published to date, the difference in pain scores between the capsaicin and placebo groups was not statistically significant.[104] It may be that higher or more frequent dosing is needed. An analog of capsaicin, resiniferatoxin, is also under investigation and may be an effective IC treatment in the future.

Specialists in pain management use such drugs as gabapentin, clonazepam, and mexiletine to treat various types of neuropathic pain. These drugs have not been formally studied for IC pain, but it is reasonable to try them.

If other measures fail, chronic narcotics may be very helpful for returning patients to a more normal lifestyle. The pain of IC is real, and the risk of addiction is low. The long-acting formulations, such as MS Contin (Purdue Fredericks, Norwalk, CT) or oxycontin, provide a chronic steady-state drug level, avoiding the cycle of highs and subsequent pain that can occur with shorter-acting drugs.

Surgical treatments

The most important point to keep in mind is that surgery is indicated for only a small minority of IC patients (<5%). The vast majority of patients can keep their symptoms under control with less invasive methods. However, when all other treatments fail, surgery can relieve symptoms and restore quality of life in appropriately selected patients.

A variety of bladder denervation procedures have been suggested for IC (for reviews, see refs. 105, 106). These include peripheral denervation (cystolysis), sympathetic denervation, and selective sacral rhizotomy. Most of these procedures give good short-term relief, but in most cases, the symptoms recur within a few years. Currently, these procedures are used rarely (if at all) to treat IC.

If the patient has bladder ulcers, transurethral fulguration of the ulcers may give significant (although usually temporary) relief.[105,106] A neodynium:YAG laser has been used to treat IC bladder ulcers,[107] and 78% of patients treated had immediate pain relief, which lasted for several months. The main concern about this treatment is that laser energy can penetrate the bladder and cause bowel injury. Also, as the majority of IC patients in the United States have the nonulcer type of IC, laser treatment would not apply to them.

Bladder augmentation (enlarging the bladder by attaching an isolated segment of bowel to it) has been used for IC patients who have a small bladder capacity. Most surgeons who treat IC will resect all of the bladder except the trigone (or, in extreme cases, the bladder neck) because the outcome is better if no diseased bladder is left behind.[105,106,108,109] A theoretical disadvantage of augmentation cystoplasty is that if a urine-borne factor causes IC, the disease may recur. The two main practical disadvantages are the risk of urinary retention and the extremely variable success rates. Different publications report success rates varying from 25% to 100%.[106]

Patient selection is probably the main reason for the variable success rates of augmentation cystoplasty. It is clear that patients who have a low bladder capacity under anesthesia (<400 ml) have a better outcome than patients with high-capacity bladders,[65,106] suggesting that the mechanisms of symptoms are different for these two patient groups. A good outcome also is more likely if the patient has no neuropathic pain identifiable.[65] Another interesting observation is that patients who had bladder ulcers responded well to bladder resection leaving the trigone, but in nonulcer patients, it was necessary to resect the trigone for complete symptom relief.[108] These results again support the concept that ulcer and nonulcer patients have distinct types of IC with different pathophysiologies.

Another surgical option is to bypass the native bladder and urethra altogether and create either a conduit or a continent pouch.[65] These procedures tend to be used more frequently in the United States, whereas augmentation with bladder resection is used more frequently in Europe. A continent pouch provides a better body image by avoiding an external appliance but has the risks of stomal complications, the need for inter-

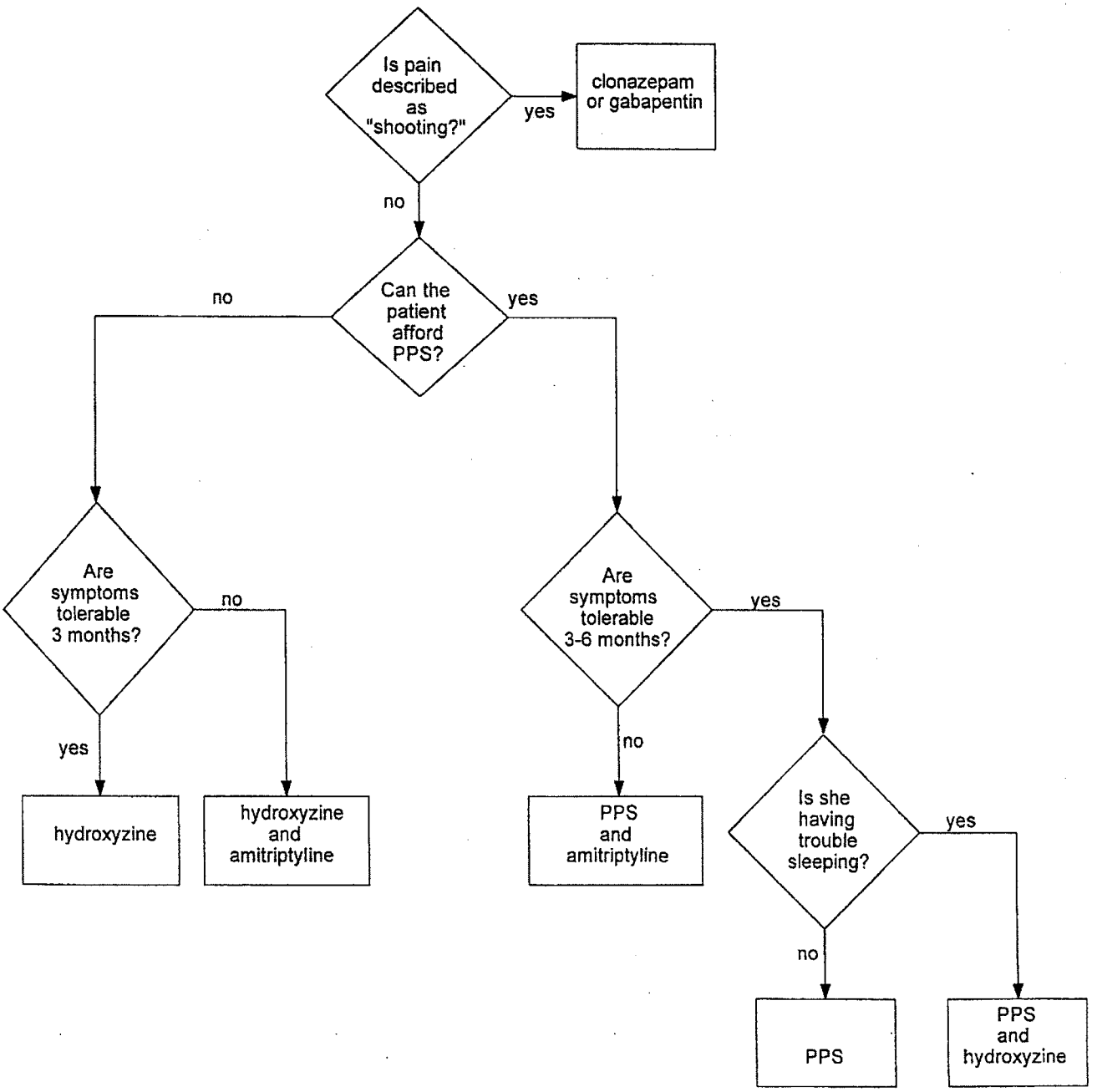


FIG. 1. Sample algorithm for oral IC treatments. PPS, pentosan polysulfate.

mittent catheterization, and the theoretical risk of recurrent IC if a urine-borne factor is involved in the pathogenesis. Opinions vary as to whether the bladder should be removed or left *in situ*. Because these procedures are done so rarely, large series or prospective comparisons are not available. The disadvantages of leaving the bladder in place are that (1) in some patients, pain persists, and a cystectomy is performed later, and (2) infection of the native bladder may occur. The disadvantages of bladder removal are (1) increased surgical morbidity and blood loss, (2) the risk of anterior enterocele formation in women,[110] and (3) a theoretical risk of phantom pain like that experienced by amputees. It is well documented that pelvic pain can persist even after all organs are removed.[111] In these cases, the pain probably originates from altered spinal pathways.[62–64]

Treatments for associated conditions

Some patients with IC also have other conditions that can cause pelvic or perineal discomfort. Examples of these conditions include vulvodynia, levator muscle pain, irritable bowel syndrome, and endometriosis. These conditions usually require separate treatment, although in some cases, one treatment may help with both conditions (e.g., amitriptyline is useful for both vulvodynia and IC).

When IC coexists with other conditions, assessing treatment response is difficult. If pain persists, one must decide if it is caused by continu-

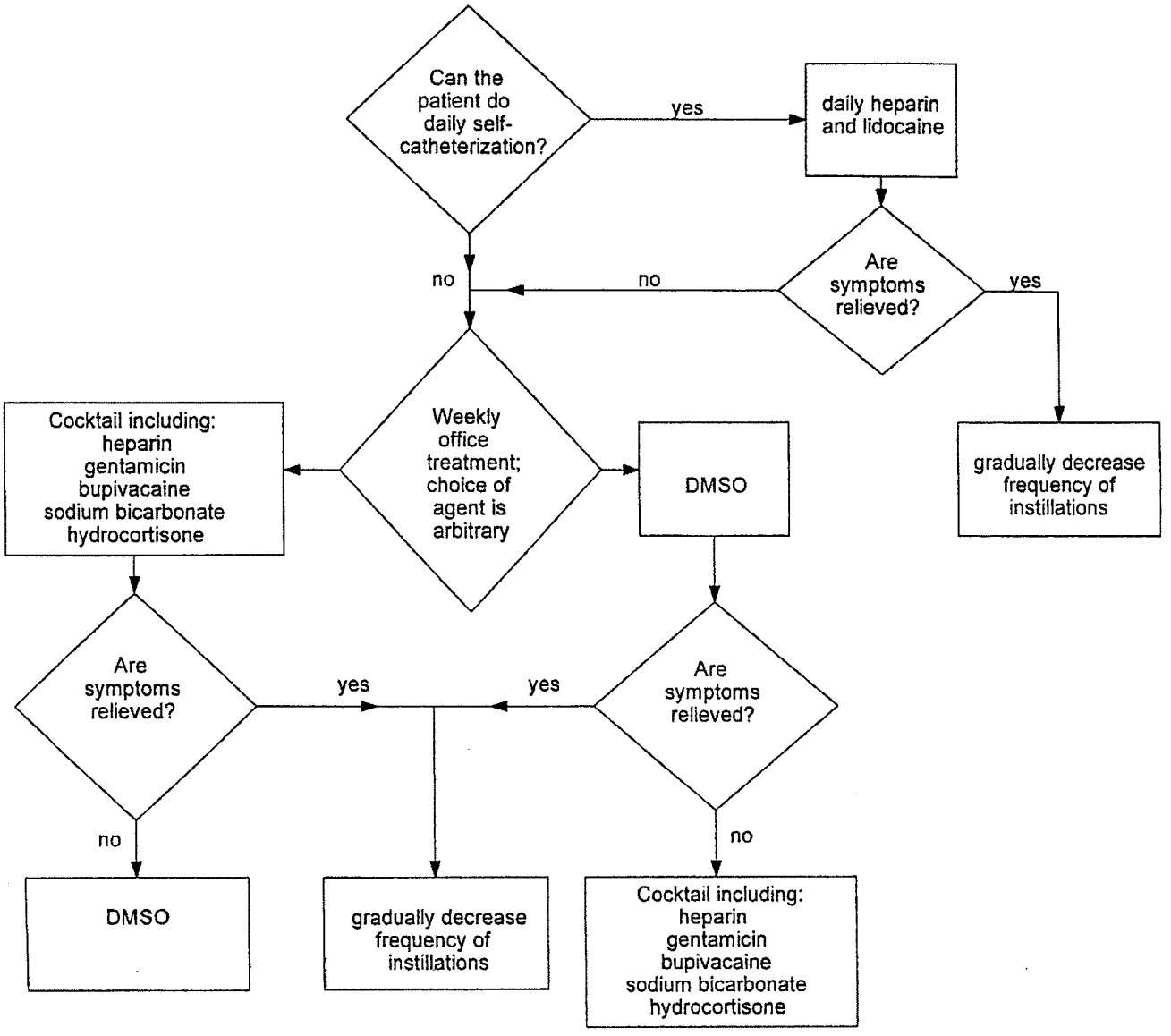


FIG. 2. Sample algorithm for intravesical IC treatments. DMSO, dimethyl sulfoxide.

ing IC (and pursue additional IC treatments) or if the IC has resolved and the other condition requires more treatment. As visceral pain can be difficult to localize, this can be a dilemma for the clinician. Ideally, future research will identify objective markers of IC that can be used to assess disease activity and follow treatment response without relying solely on symptoms.

Choosing initial therapy for IC

With so many treatments available, how does one decide where to start? At this time, there is little evidence to suggest that one treatment is more effective than another. A good general plan is to start with the more innocuous treatments, then go to others if the first treatments fail. Figures 1 and 2 show the plan that I generally follow with a new IC patient. Please remember that these are my personal preferences. They are not supported by specific studies and should not be considered the only correct way to treat IC. I start by asking the patient if she prefers oral or intravesical treatment, then proceed as outlined in Figures 1 and 2.

SUMMARY

IC is a multifactorial syndrome with several proposed etiologies, some of which may be interrelated. The major etiologic theories include (1) increased bladder epithelial permeability, (2) activation of bladder mast cells, (3) allergic or autoimmune processes, (4) toxic substance(s) in the urine, (5) occult infection, (6) neuropathic changes, and (7) neurogenic inflammation.

Various IC treatments are used. Some are directed specifically to one of the proposed etiologies, whereas others are purely empirical. At this time, there is very little knowledge to help clinicians choose which treatments may be most beneficial for specific patients. A few exceptions are: (1) patients will severe bladder inflammation, who also tend to be older, are more likely to respond to bladder distention, (2) patients with elevated urine kallikrein levels are more likely to respond to bladder distention, (3) patients with bladder ulcers are more likely to respond to TENS, and (4) patients without ulcers are more likely to respond to PPS.

In most cases of IC, treatment choices are made by first trying the safest and least invasive options, then progressing to other treatments (which have more potential morbidity) if the initial treatments do not relieve symptoms effectively. Combining treatments is often needed. In theory, combined treatments that address different proposed pathophysiologies (e.g., hydroxyzine and PPS) would be especially beneficial. However, no formal studies have addressed this issue.

If specific IC treatments fail, adjunctive measures should be used, addressed to treat pain in general. These include TENS, drugs to treat neuropathic pain, and narcotics. Consultation with a pain management specialist may be beneficial. If a patient has other conditions besides IC that also cause pelvic or perineal pain, these need to be addressed separately. In carefully selected patients, surgical treatments for IC are indicated. If bladder ulcers are present, they can be treated by fulguration or laser. If all other measures fail, bladder augmentation or urinary diversion may be performed. However, in some patients, symptoms persist even after the bladder is removed. Fortunately, the vast majority of IC patients are successfully treated without surgery.

REFERENCES

1. Ratner V, Slade D. Interstitial cystitis: A women's health perspective. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997:257.
2. Erickson DR, Davies MF. Interstitial cystitis. Int Urogynecol J 1998;9:174.
3. Hanno PM. Interstitial cystitis and related disease. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, eds. Campbell's urology, 7th ed. Philadelphia: WB Saunders Company, 1998:631.
4. Parsons CL, Stein PC, Bidair M, Lebow D. Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. Neurourol Urodynamics 1994;13:515.
5. Parsons CL, Greenberger M, Gabal L, Bidair M, Barme G. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol 1998;159:1862.
6. Buffington CAT, Woodworth BE. Excretion of fluorescein in the urine of women with interstitial cystitis. J Urol 1997;158:786.
7. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol 1991;145:732.
8. Chelsky MJ, Rosen SI, Knight LC, Maurer AH, Hanno PM, Ruggieri MR. Bladder permeability in interstitial cystitis is similar to that of healthy volunteers: Direct measurement by transvesical ab-

sorption of ^{99m}technetium-diethylenetriaminepentaacetic acid. J Urol 1994;151:346.
9. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol 1990;143:1118.
10. Lynes WL, Flynn SD, Shortliffe LD, Stamey RA. The histology of interstitial cystitis. Am J Surg Pathol 1990;14:969.
11. Parsons CL. The therapeutic role of sulfated polysaccharides in the urinary bladder. Urol Clin North Am 1994;21:93.
12. Hurst RE, Roy JB, Min KW, et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology 1996;48:817.
13. Moskowitz MO, Byrne DS, Callahan HJ, Parsons CL, Valderrama E, Moldwin RM. Decreased expression of a glycoprotein component of bladder surface mucin (GP1) in interstitial cystitis. J Urol 1994;151: 343.
14. Erickson DR, Mast S, Ordille S, Bhavanandan VP. Urinary epitectin (MUC-1 glycoprotein) in the menstrual cycle and in interstitial cystitis. J Urol 1996; 156:938.
15. Parsons CL, Hurst RE. Decreased urinary uronic acid levels in individuals with interstitial cystitis. J Urol 1990;143:690.
16. Hurst RE, Parsons CL, Roy JB, Young JL. Urinary glycosaminoglycan excretion as a laboratory marker for interstitial cystitis. J Urol 1993;149:31.
17. Erickson DR, Ordille S, Martin A, Bhavanadan VP. Urinary chondroitin sulfates, heparan sulfate and total sulfated glycosaminoglycans in interstitial cystitis. J Urol 1997;157:61.
18. Sant GR, Theoharides TC. The role of the mast cell in interstitial cystitis. Urol Clin North Am 1994;21:41.
19. Yun SK, Laub DJ, Weese DL, Lad PM, Leach GE, Zimmern PE. Stimulated release of urine histamine in interstitial cystitis. J Urol 1992;148:1145.
20. El-Mansoury M, Boucher W, Sant GR, Theoharides TC. Increased urine histamine and methylhistamine in interstitial cystitis. J Urol 1994;152:350.
21. Holm-Bentzen M, Sondergaard I, Hald T. Urinary excretion of a metabolite of histamine (1,4-methylimidazole-acetic-acid) in painful bladder disease. Br J Urol 1987;59:230.
22. Boucher W, El-Mansoury M, Pang X, Sant GR, Theoharides TC. Elevated mast cell tryptase in the urine of patients with interstitial cystitis. Br J Urol 1995; 76:94.
23. Hanno PM, Levin RM, Monson FC, et al. Diagnosis of interstitial cystitis. J Urol 1990;143:278.
24. Elbadawi A. Interstitial cystitis: A critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. Urology 1997;49(Suppl 5A):14.
25. Theoharides TC, Sant GR, El-Mansoury M, Le Tourneau R, Ucci AA, Meares EM. Activation of bladder mast cells in interstitial cystitis: A light and electron microscopic study. J Urol 1995;153:629.
26. Pang X, Marchand J, Sant GR, Kream RM, Theoharides TC. Increased number of substance P positive nerve fibres in interstitial cystitis. Br J Urol 1995;75:744.
27. LeTourneau R, Pang X, Sant GR, Theoharides TC. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. Br J Urol 1996;77:41.
28. Harrington DS, Fall M, Johansson SL. Interstitial cystitis: Bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. J Urol 1990;144:868.
29. Erickson DR, Belchis DA, Dabbs DJ. Inflammatory cell types and clinical features of interstitial cystitis. J Urol 1997;158:790.
30. Zuraw BL, Sugimoto S, Parsons CL, Hugli T, Lotz M, Koziol J. Activation of urinary kallikrein in patients with interstitial cystitis. J Urol 1994;152:874.
31. Lotz M, Villiger P, Hugli T, Koziol J, Zuraw B. Interleukin-6 and interstitial cystitis. J Urol 1994; 152:869.
32. Fleischmann JD, Huntley HN, Shingleton WB, Wentworth DB. Clinical and immunological response to nifedipine for treatment of interstitial cystitis. J Urol 1991;146:1235.
33. Elgebaly SA, Allam ME, Walzak MP, Oselinsky D, Gillies C, Yamase H. Urinary neutrophil chemotactic factors in interstitial cystitis patients and a rabbit model of bladder inflammation. J Urol 1992;147: 1382.
34. Clemmensen OJ, Lose G, Holm-Bentzen M, Colstrup H. Skin reactions to urine in patients with interstitial cystis. Urology 1988;32:17.
35. Domingue GJ, Ghoniem GM. Occult infection in interstitial cystitis. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997:77.
36. Warren JW. Interstitial cystitis as an infectious disease. Urol Clin North Am 1994;21:31.
37. Wilkins EGL, Payne SR, Pead PJ, Moss ST, Maskell RM. Interstitial cystitis and the urethral syndrome: A possible answer. Br J Urol 1989;64:39.
38. Keay S, Schwalbe RS, Triffilis AL, Lovchik JC, Jacobs W, Warren JW. A prospective study of microorganisms in urine and bladder biopsies from interstitial cystitis patients and controls. Urology 1995;45:223.
39. Fall M, Johansson SL, Vahlne A. A clinicopathological and virological study of interstitial cystitis. J Urol 1985;133:771.
40. Hanash KA, Pool TL. Interstitial and hemorrhagic cystitis: Viral, bacterial and fungal studies. J Urol 1970;104:705.
41. Domingue GJ, Ghoniem GM, Bost KL, Fermin C, Human LG. Dormant microbes in interstitial cystitis. J Urol 1995;153:1321.
42. Haarala M, Jalava J, Laato M, Kilholma P, Nurmi M, Alanen A. Absence of bacterial DNA in the bladder of patients with interstitial cystitis. J Urol 1996; 156:1843.
43. Keay S, Zhang C-O, Baldwin BR, Jacobs SC, Warren

JW. Polymerase chain reaction amplification of bacterial 16S rRNA genes in interstitial cystitis and control patient bladder biopsies. J Urol 1998;159:280.
44. Ratliff TL, Klutke CG, Hofmeister M, He F, Russell JH, Becich MJ. Role of the immune response in interstitial cystitis. Clin Immunol Immunopathol 1995; 74:209.
45. Ochs RL, Tan EM. Autoimmunity in interstitial cystitis. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997:47.
46. Oravisto KJ. Interstitial cystitis as an autoimmune disease. Eur Urol 1980;6:10.
47. McGuire EJ, Lytton B, Cornog JL. Interstitial cystitis following colocystoplasty. Urology 1973;2:28.
48. Beier-Holgersen R, Hermann GG, Mortensen SO, Steven K. The *in vitro* cytotoxicity of urine from patients with interstitial cystitis. J Urol 1994;151:206.
49. Ruggieri MR, Hanno PM, Whitmore KE, Balagani RK. Effect of repeated instillation of interstitial cystitis urine on the rabbit urinary bladder. Urology 1993;42:646.
50. Keay S, Zhang CO, Trifillis AL, et al. Decreased ^{3}H-thymidine incorporation by human bladder epithelial cells following exposure to urine from interstitial cystitis patients. J Urol 1996;156:2073.
51. Keay S, Zhang CO, Hise MK, et al. A diagnostic *in vitro* urine assay for interstitial cystitis. Urology 1998;52:974.
52. Elgavish A, Pattanaik A, Couchman J, et al. Long-term treatment with lipoteichoic acid from *Streptococcus faecalis* affects differentiation and expression and cellular distribution of beta 1 integrins in human urothelial cells. J Cell Physiol 1996;169:52.
53. Elgavish A, Pattanaik A, Lloyd K, Reed R. Evidence for altered proliferative ability of progenitors of urothelial cells in interstitial cystitis. J Urol 1997; 158:248.
54. Lundenberg T, Liedberg H, Nordling L, Theodorsson E, Owzarski A, Ekman P. Interstitial cystitis: Correlation with nerve fibers, mast cells and histamine. Br J Urol 1993;71:427.
55. Christmas TJ, Rode J, Chapple CR, Milroy EJG, Turner-Warwick RT. Nerve fibre proliferation in interstitial cystitis. Virchows Arch A Pathol Anat Histopathol 1990;416:447.
56. Hohenfeller M, Nunes L, Schmidt RA, Lampel A, Thuroff JW, Tanagho EA. Interstitial cystitis: Increased sympathetic innervation and related neuropeptide synthesis. J Urol 1992;147:587.
57. Ruggieri MR, Chelsky MJ, Rosen SI, Shickley TJ, Hanno PM. Current findings and future research avenues in the study of interstitial cystitis. Urol Clin North Am 1994;21:163.
58. Irwin P, Galloway NT. Impaired bladder perfusion in interstitial cystitis: A study of blood supply using laser Doppler flowmetry. J Urol 1993;149:890.
59. Irwin PP, James S, Watts L, Fleming LL, Gallway NT. Abnormal pedal thermoregulation in interstitial cystitis. Neurourol Urodynamics 1993;12:139.
60. Irwin PP, Hammonds WD, Galloway NT. Lumbar epidural blockade for management of pain in interstitial cystitis. Br J Urol 1993;71:413.
61. Brookoff D. The causes and treatment of pain in interstitial cystitis. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997:177.
62. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. Pain 1993;52:259.
63. Myers RR. The pathogenesis of neuropathic pain. Reg Anesth 1995;20:173.
64. Zermann DH, Ishigooka M, Doggweiler R, Schmidt RA. Postoperative chronic pain and bladder dysfunction: Windup and neuronal plasticity—Do we need a more neurological approach in pelvic surgery? J Urol 1998;160:102.
65. Lotenfoe RR, Christie J, Parsons A, Burkett P, Helal M, Lockhart JL. Absence of neuropathic pelvic pain and favorable psychological profile in the surgical selection of patients with disabling interstitial cystitis. J Urol 1995;154:2039.
66. Whitmore KE. Self-care regimens for patients with interstitial cystitis. Urol Clin North Am 1994;21:121.
67. Gillespie L. You don't have to live with cystitis! New York: Avon Books, 1986:244.
68. Chaiken DC, Blaivas JG, Blaivas ST. Behavioral therapy for the treatment of refractory interstitial cystitis. J Urol 1993;149:1445.
69. Parsons CL, Koprowski PF. Interstitial cystitis: Successful management by increasing urinary voiding intervals. Urology 1991;37:207.
70. Hanno PM. Diagnosis of interstitial cystitis. Urol Clin North Am 1994;21:63.
71. Parsons CL, Schmidt JD, Pollen JJ. Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. J Urol 1983;130:51.
72. Hanno PM. Analysis long-term Elmiron therapy for interstitial cystitis. Urology 1997;49 (Suppl 5A):93.
73. Fritjofsson A, Fall M, Juhlin R, Persson BE, Ruutu M. Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: A multicenter trial. J Urol 1987;138:508.
74. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987;138:513.
75. Mulholland SG, Hanno PM, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. Urology 1990;35:552.
76. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol 1993;150:845.
77. Holm-Bentzen M, Jacobsen F, Nerstrom B, et al. A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol 1987;138:503.

78. Lose G, Jespersen J, Frandsen B, Hojensgard JC, Astrup T. Subcutaneous heparin in the treatment of interstitial cystitis. Scand J Urol Nephrol 1985;19:27.
79. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994;73:504.
80. Parsons CL. Epithelial coating techniques in the treatment of interstitial cystitis. Urology 1997;49 (Suppl 5A):100.
81. Perez-Marrero R, Emerson LE, Maharajh DO, Juma S. Prolongation of response to DMSO by heparin maintenance. Urology 1993;41(Suppl):64.
82. Morales A, Emerson L, Nickel JC, Lundie M. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol 1996;156:45.
83. Sant GR, LaRock DR. Standard intravesical therapies for interstitial cystitis. Urol Clin North Am 1994;21:73.
84. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 1988;140:36.
85. Theoharidies TC. Hydroxyzine in the treatment of interstitial cystitis. Urol Clin North Am 1994;21:113.
86. Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. Urology 1994;44:614.
87. Lewi H. Cimetidine in treatment of interstitial cystitis [Letter]. Urology 1995;34:1088.
88. Edwards L, Bucknall TE, Makin C. Interstitial cystitis: Possible cause and clinical study of sodium cromoglycate. Br J Urol 1986;58:95.
89. Hanno PM. Amitriptyline in the treatment of interstitial cystitis. Urol Clin North Am 1994;21:89.
90. Smith SD, Wheeler MA, Foster HE, Weiss RM. Urinary nitric oxide synthase activity and cyclic GMP levels are decreased with interstitial cystitis and increased with urinary tract infections. J Urol 1996; 155:1432.
91. Smith SD, Wheeler MA, Foster HE, Weiss RM. Improvement in interstitial cystitis symptom scores during treatment with oral L-arginine. J Urol 1997; 158:703.
92. Wheeler MA, Smith SD, Saito N, Foster HE, Weiss RM. Effect of long-term oral L-arginine on the nitric oxide synthase pathway in the urine from patients with interstitial cystitis. J Urol 1997;158:2045.
93. Korting GE, Smith SD, Wheeler MA, Weiss RM, Foster HE. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol 1999;161:558.
94. Zeidman EJ, Helfrick B, Pollard C, Thompson IM. Bacillus Calmette-Guérin immunotherapy for refractory interstitial cystitis. Urology 1994;43:121.
95. Peters K, Diokno A, Steinart B, et al. The efficacy of intravesicle Tice strain bacillus Calmette-Guérin in the treatment of interstitial cystitis: A double-blind, prospective, placebo controlled trial. J Urol 1997; 157:2090.
96. Peters K, Diokno AC, Steinert BW, Gonzalez JA. The efficacy of intravesical bacillus Calmette-Guérin in the treatment of interstitial cystitis: Long-term follow-up. J Urol 1998;159:1483.
97. Forsell T, Ruutu M, Isoniemi H, Ahonen J, Alfthan O. Cyclosporine in severe interstitial cystitis. J Urol 1996;155:1591.
98. Oravisto KJ, Alfthan OS. Treatment of interstitial cystitis with immunosuppression and chloroquine derivatives. Eur Urol 1976;2:82.
99. Khanna OP, Loose JH. Interstitial cystitis treated with intravesical doxorubicin. Urology 1990;36:139.
100. Durier JL. The application of anti-anaerobic antibiotics to the treatment of female bladder dysfunctions. Neurourol Urodynamics 1992;11:418.
101. Fall M, Lindstrom S. Transcutaneous electrical nerve stimulation in classic and nonulcer interstitial cystitis. Urol Clin North Am 1994;21:131.
102. Cruz F, Guimaraes M, Silva C, Rio ME, Coimbra A, Reis M. Desensitization of bladder sensory fibers by intravesical capsaicin has long lasting clinical and urodynamic effects in patients with hyperactive or hypersensitive bladder dysfunction. J Urol 1997; 157:585.
103. Barbanti G, Maggi CA, Beneforti P, Baroldi P, Turini D. Relief of pain following intravesical capsaicin in patients with hypersensitive disorders of the lower urinary tract. Br J Urol 1993;71:686
104. Lazzeri M, Beneforti P, Benaim G, Maggi CA, Lecci A, Turini D. Intravesical capsaicin for treatment of severe bladder pain: A randomized placebo-controlled study. J Urol 1996;156:947.
105. Irwin PP, Galloway NTM. Surgical management of interstitial cystitis. Urol Clin North Am 1994;21:145.
106. Hohenfeller M, Linn J, Hampel C, Thuroff JW. Surgical treatment of interstitial cystitis. In: Sant GR, ed. Interstitial cystitis. Philadelphia: Lippincott-Raven, 1997:223.
107. Malloy TR, Shanberg AM. Laser therapy for interstitial cystitis. Urol Clin North Am 1994;21:141.
108. Peeker R, Aldenborg F, Fall M. The treatment of interstitial cystitis with supratrigonal cystectomy and ileocystoplasty: Difference in outcome between classic and nonulcer disease. J Urol 1998;159:1479.
109. Linn JR, Hohenfeller M, Roth S, et al. Treatment of interstitial cystitis: Comparison of subtrigonal and supratrigonal cystectomy combined with orthotopic bladder substitution. J Urol 1998;159:774.
110. Anderson J, Carrion R, Ordorica R, Hoffman M, Arango H, Lockhart JL. Anterior enterocele following cystectomy for intractable interstitial cystitis. J Urol 1998;159:1868.
111. Baskin LS, Tanagho EA. Pelvic pain without pelvic organs. J Urol 1992;147:683.

Address reprint requests to:
Deborah R. Erickson, M.D.
Penn State Geisinger
Section of Urology M.C. H055
P.O. Box 850
Hershey, PA 17033-0850

SECTION C

frontiers in Neuroscience

Front Neurosci. 2012; 6: 114.
Published online 2012 Aug 10. doi: [10.3389/fnins.2012.00114]

PMCID: PMC3415690
PMID: 22907988

Co-Morbidities of Interstitial Cystitis

Gisela Chelimsky,[1] Elizabeth Heller,[2] C. A. Tony Buffington,[3] Raymond Rackley,[4] Di Zhang,[5] and Thomas Chelimsky[6,*]

[1]Department of Pediatric Gastroenterology, Medical College of Wisconsin, Milwaukee, WI, USA
[2]Johns Hopkins University, Baltimore, MD, USA
[3]Veterinary Clinical Sciences, The Ohio State University, Columbus, OH, USA
[4]Department of Urology, The Cleveland Clinic Foundation, Cleveland, OH, USA
[5]Department of Neurology, Case Western Reserve University, Cleveland, OH, USA
[6]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

Edited by: Margaret A. Vizzard, University of Vermont College of Medicine, USA
Reviewed by: Dale E. Bjorling, University of Wisconsin-Madison Medical School, USA; Anna P. Malykhina, University of Pennsylvania, USA

*Correspondence: Thomas Chelimsky, Department of Neurology, Medical College of Wisconsin, 8701 West Watertown Plank Road, Milwaukee, WI 53226-3548, USA. e-mail: tchelimsky@mcw.edu

This article was submitted to Frontiers in Autonomic Neuroscience, a specialty of Frontiers in Neuroscience.

Received 2012 Feb 13; Accepted 2012 Jul 10.

Abstract

Introduction: This study aimed to estimate the proportion of patients with interstitial cystitis/painful bladder syndrome (IC/BPS) with systemic dysfunction associated co-morbidities such as irritable bowel syndrome (IBS) and fibromyalgia (FM). **Materials and Methods:** Two groups of subjects with IC/BPS were included: (1) physician diagnosed patients with IC/BPS and (2) subjects meeting NIDDK IC/PBS criteria based on a questionnaire (ODYSA). These groups were compared to healthy controls matched for age and socio-economic status. NIDDK criteria required: pain with bladder filling that improves with emptying, urinary urgency due to discomfort or pain, polyuria >11 times/24 h, and nocturia >2 times/night. The ODYSA instrument evaluates symptoms pertaining to a range of disorders including chronic fatigue, orthostatic intolerance, syncope, IBS, dyspepsia, cyclic vomiting syndrome, headaches and migraines, sleep, Raynaud's syndrome, and chronic aches and pains. **Results:** IC/BPS was diagnosed in 26 subjects (mean age 47 ± 16 years, 92% females), 58 had symptoms of IC/BPS by NIDDK criteria (mean age 40 ± 17 years, 79% females) and 48 were healthy controls (mean age 31 ± 14 years, mean age 77%). Co-morbid complaints in the IC/BPS groups included gastrointestinal symptoms suggestive of IBS and dyspepsia, sleep abnormalities with delayed onset of sleep, feeling poorly refreshed in the morning, waking up before needed, snoring, severe chronic fatigue and chronic generalized pain, migraines, and syncope. **Discussion:** Patients with IC/BPS had co-morbid central and autonomic nervous system disorders. Our findings mirror those of others in regard to IBS, symptoms suggestive of FM, chronic pain, and migraine. High rates of syncope and functional dyspepsia found in the IC/BPS groups merit further study to determine if IC/BPS is part of a diffuse disorder of central, autonomic, and sensory processing affecting multiple organs outside the bladder.

Keywords: IC/BPS, co-morbidities, migraine headache, orthostatic intolerance, functional gastrointestinal disorders

Introduction

Interstitial cystitis/painful bladder syndrome (IC/BPS) is a syndrome characterized by urinary urgency, frequency, nocturia, and pain in the pelvis that worsens as the bladder fills and improves with emptying (Clemens et al., 2005; Bogart et al., 2007). IC/BPS may affect from 0.5 to 12% of women in the US (Jones and Nyberg, 1997; Clemens et al., 2005) and the quality of life for patients with interstitial cystitis is significantly degraded (Buffington, 2004). IC/BPS associates with other disorders such as irritable bowel syndrome (IBS), Sjogren's syndrome, fibromyalgia (FM) syndrome, chronic fatigue syndrome, anxiety disorders, migraines, and other pain syndromes not related to the bladder. Moreover, these other conditions frequently precede the onset of bladder symptoms (Rodriguez et al., 2009; Warren et al., 2009; Hanno et al., 2010; Nickel et al., 2010). Interestingly, functional gastrointestinal disorders (FGID) like IBS, which often accompanies IC/BPS, have similar co-morbid symptoms as IC/BPS (Chelimsky et al., 2012). Furthermore, IBS harbors co-morbid dysautonomias similar to chronic fatigue (Wyller et al., 2010; Okamoto et al., 2011), FM (Reyes del Paso et al., 2011), and migraine headaches (Rashed et al., 1999). Although still unclear, a common theme to this group of co-morbid disorders could be related to the autonomic nervous system which connects the nervous system to the end-organ. Given the frequent co-existence of these disorders, the aim of this study was to evaluate if a similar number of additional co-morbid diagnoses that are present in FGID may also be associated with IC/BPS and contribute to the poor quality of life.

Materials and Methods

This cross-sectional IRB-approved review used the Ohio Dysautonomia (ODYSA) questionnaire, a thorough clinical instrument designed to approximate the diagnosis of several syndromes that may have associated autonomic dysregulation including: orthostatic intolerance, reflex syncope, cyclic vomiting syndrome (CVS), interstitial cystitis, Raynaud's syndrome, complex regional pain syndrome (CRPS), IBS, functional dyspepsia, functional abdominal pain, migraine headache, FM, and chronic fatigue syndrome. Where validated, published question-based diagnostic were utilized directly or slightly modified (Melzack, 1987; Fukuda et al., 1994; Merskey and Bogduk, 1994; Chelimsky et al., 1995; Drossman et al., 2000; Sheldon et al., 2002, 2006; Olesen, 2004; Li et al., 2008; Low and Benarroch, 2008).

All patients who came to the Autonomic Laboratory at University Hospital Case Medical Center for testing for any type of complaint are asked to complete the ODYSA questionnaire as part of their clinical care, as well as patients seen in urology, neurology, rheumatology, and gastroenterology interdisciplinary autonomic clinics. There were no exclusion criteria.

Control subjects constituted a participant's same gender friend or the spouse's same gender sibling, with intent to closely match socio-economic and geographic factors. The ODYSA questionnaire includes the O'Leary–Sant question-set (O'Leary and Sant, 1997) as well as a separate face-valid question-set designed to assess the probability that IC/BPS is present based on most recent NIDDK (2006) criteria. The probability of having the disease is forced to 0 or 1 (no intermediate values), and was programmed into a database (Filemaker) to automatically generate a score for each subject as the data are entered, obviating any opportunity for subjective interpretation. Data entry was performed by students who had no knowledge of patient diagnosis and was double-checked. NIDDK criteria for IC/BPS were as follows: (1) the subject's pain must worsen with a full bladder and improve with an empty bladder; (2) urinary urgency must result from discomfort or pain (not fear of incontinence); (3) and voiding frequency must exceed 11 times on average in a 24 h period, including at least twice per night. Each criterion scored 1 if fulfilled and 0 otherwise with a total possible range of 0–5, and 4 or greater considered likely IC/BPS.

Three subject groups were used in this study. The first group included those subjects with a clinical diagnosis (ICDx) of IC/BPS made by a specialty physician, a urologist, uro-gynecologist, or gynecologist. The second group comprised subjects with symptoms of IC/BPS based on the NIDDK criteria as per ODYSA question-set (ICSx), and the third group included control subjects enrolled (spouse or friend) who did not meet criteria for IC/BPS. The exclusion criteria were only established for the control subjects, in that they could not meet criteria for IC/BPS. We examined each group for co-morbid disorders using the following criteria based on question-set answers. The symptoms were suggestive of IBS (periumbilical/lower abdomen abdominal discomfort for >6 months with changes in bowel movement frequency or consistency or relieved by a bowel movement) or for dyspepsia (discomfort in chest or upper abdomen with one of the following: bloating, early satiety, or nausea). For symptoms suggestive of CVS, the subjects needed to report more than five episodes in their lifetime of severe stereotypical episodes of nausea or vomiting with return to baseline health in-between. Dizziness was defined by reporting one or more of the following symptoms "when you stand still or exercise a little…" one time per day to two times per week: feel faint, dizzy, lightheaded, or noticed change in vision or thinking is "off." For the history of syncope, the question was phrased as "Do you ever faint (completely lose consciousness)?" We considered positive if >three times/lifetime.

Several questions were asked about sleep issues: "Does it take more than half an hour to fall asleep?" (considered delayed onset of sleep if >30 min), "Do you snore or stop breathing when you sleep?," "Do you wake up before you need to?" "Do you force yourself to stay awake during the day?" (daytime sleepiness), "Do you feel refreshed after you sleep?" For the fatigue, it was phrased as "Do you have unexplained severe fatigue lasting...," being considered positive if >6 months. To have significant headaches, the subjects had to report headaches >50/lifetime and complain of a throbbing quality and moderate to severe intensity (migrainous features). To assess for possible Raynaud's syndrome, we asked if the fingers turned white and turned red in cold temperatures and became painful.

Statistical methods were performed utilizing Microsoft Excel 2010. The Chi-square test was utilized to determine if the individual co-morbid disorders were different between the two IC/BPS groups and between each of the IC/BPS groups and the control group. Statistical significance was considered for $p < 0.05$.

Results

IC/BPS was diagnosed by a physician in 26 subjects (ICDx group: mean age 47 ± 16 years, 92% females), while 58 subjects had symptoms of IC/BPS according to NIDDK IC/BPS criteria (ICSx group mean age 40 ± 17 years, 79% females), and 48 were healthy controls (mean age 31 ± 14 years, 77% females). The most common co-morbid complaints in both IC/BPS groups included gastrointestinal symptoms, sleep abnormalities, severe fatigue and chronic pain, headache, and syncope (Figures 1–4). Orthostatic symptoms were reported in 74% of ICSx subjects and in 32% of ICDx. Syncope was also more prevalent in the ICSx group (45%) than in ICDx (24%). This difference in orthostatic symptoms and syncope probably reflects a referral bias, since subjects are frequently referred to the autonomic laboratory for orthostatic complaints. The other symptoms were present in the two IC/BPS groups without significant difference. In relation to sleep, both groups reported taking >30 min to fall asleep (ICDx = 52%; ICSx = 69%), daytime sleepiness (ICDx = 56%, ICSx = 60%), not feeling refreshed in the morning (ICDx = 84%; ICSx = 67%), awakening before needed in the morning (ICDx = 80%; ICSx = 83%), and snoring or stopping breathing at night (ICDx = 40%; ICSx = 43%). In relation to gastrointestinal symptoms, cyclic vomiting like symptoms were uncommon in all IC/BPS groups, but symptoms suggestive of IBS (ICDx = 44%; ICSx = 27%; controls = 12%) and dyspepsia (ICDx = 40%; ICSx = 43%; controls = 6%) were significantly more common in IC/BPS subjects. IC/BPS subjects had also significantly more complaints of chronic pains lasting longer than 6 months (ICDx = 57%; ICSx = 91%; controls = 31%) and fatigue lasting longer than 6 months (ICDx = 53%; ICSx = 53%; controls = 2%). Interestingly, we could not find a difference between the two groups and the controls in prevalence of migraine headaches though power was too low to know if a difference was truly absent.

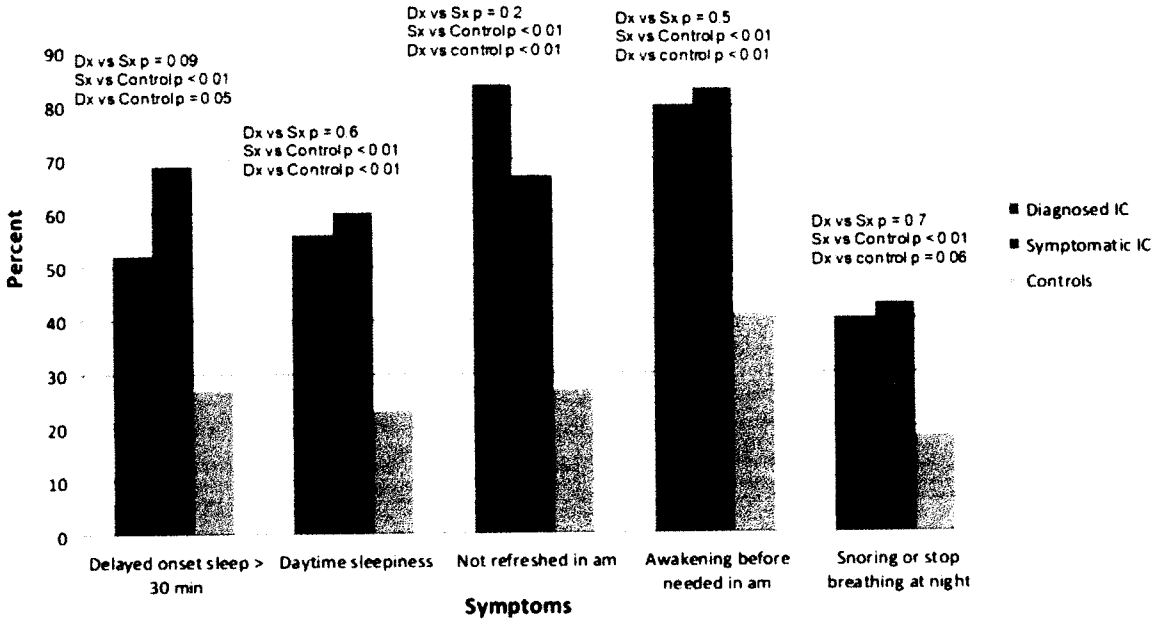


Figure 1

Comparison of effects of IC/BPS on sleep function between healthy controls and patients diagnosed by physician or questionnaire. Dx: corresponds to IC/BPS diagnosed by a physician (diagnosed IC); Sx corresponds to subjects who have symptoms of IC/BPS based on NIDDK criteria (symptomatic IC).

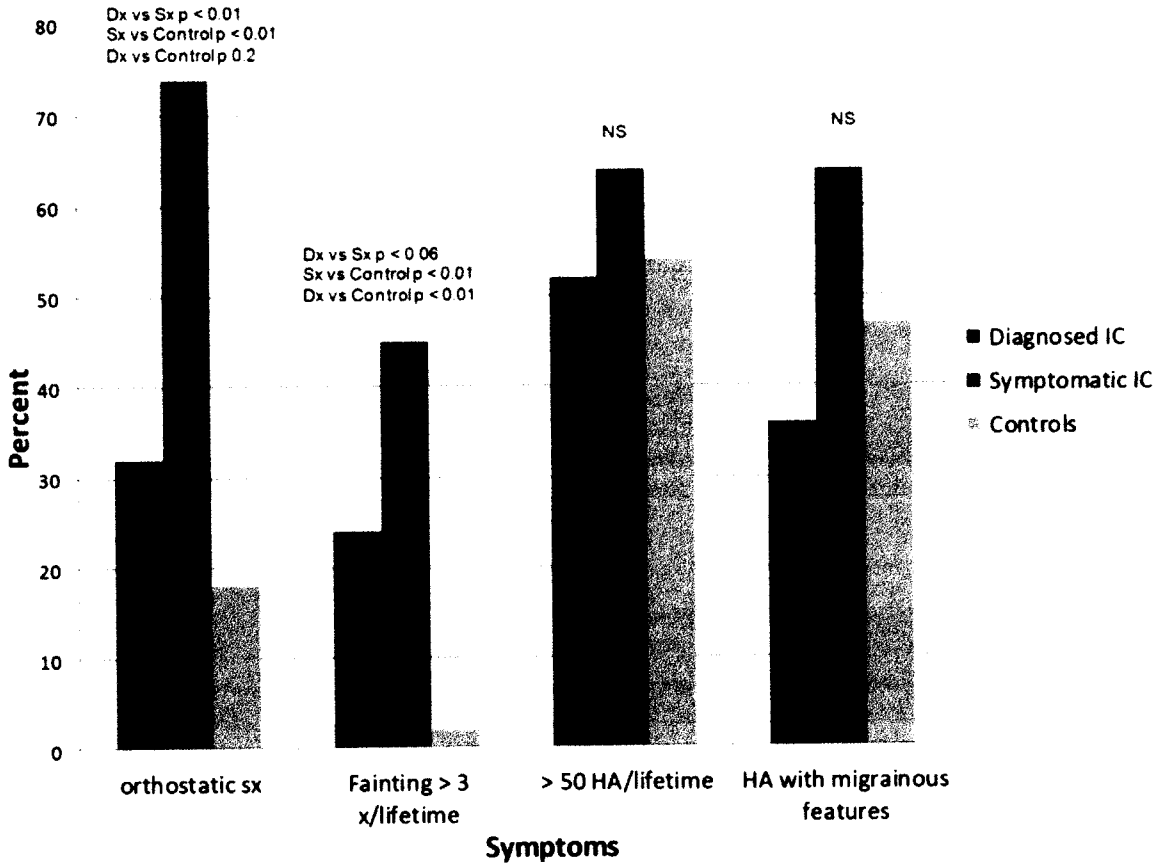


Figure 4

Summary of orthostatic symptoms and headaches. Dx: corresponds to IC/BPS diagnosed by a physician (diagnosed IC); Sx corresponds to subjects who have symptoms of IC/BPS based on NIDDK criteria (symptomatic IC).

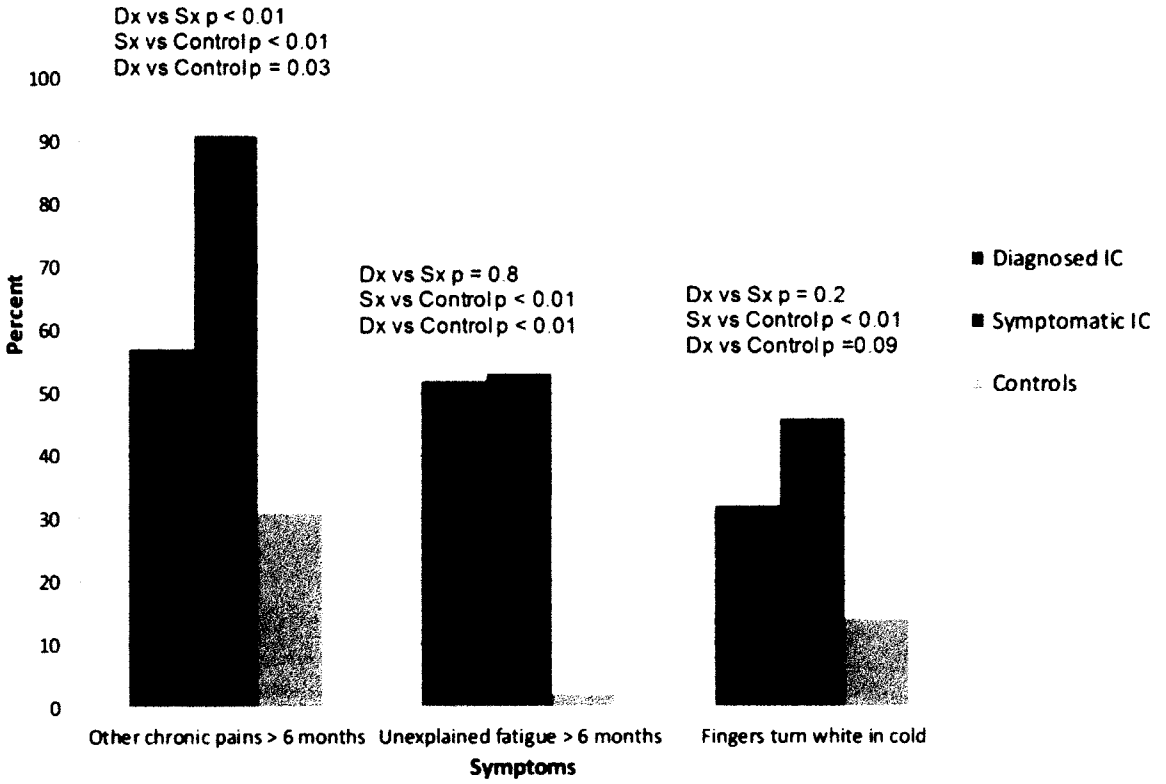


Figure 2

This figure summarizes the complaints of fatigue, chronic pains, and Raynaud's like symptoms. Dx: corresponds to IC/BPS diagnosed by a physician (diagnosed IC); Sx corresponds to subjects who have symptoms of IC/BPS based on NIDDK criteria (symptomatic IC). "Fingers turning white in cold" is purposed for looking at signs of possible Raynaud's syndrome.

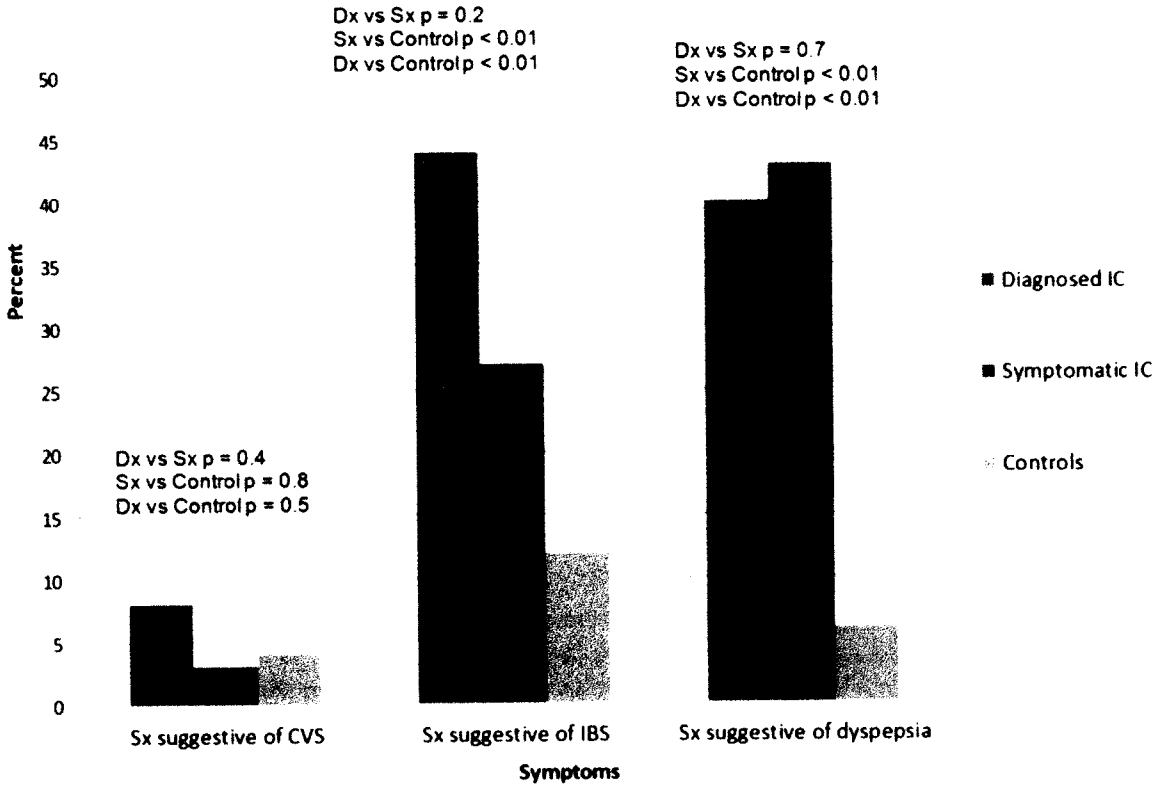


Figure 3

Summary of the gastrointestinal complaints. Dx: corresponds to IC/BPS diagnosed by a physician (diagnosed IC); Sx corresponds to subjects who have symptoms of IC/BPS based on NIDDK criteria (symptomatic IC). CVS, cyclic vomiting syndrome; IBS, irritable bowel syndrome.

Discussion

The present study adds to the list of co-morbid symptom complexes in subjects with IC/BPS, including dyspepsia-like symptoms, chronic body-wide pains, and orthostatic complaints. Our findings support the previously described associations of migraine headaches, FM, IBS, CRPS, significant sleep abnormalities, and chronic fatigue (Nickel et al., 2009, 2010; Tsai et al., 2009; Warren et al., 2009). These co-morbid symptom complexes probably contribute to poor quality of life in ways that physicians may overlook, particularly in a uni-disciplinary context. Importantly, they also influence our conceptualization of this syndrome as originating from some type of systemic process, or from a central nervous system derangement, rather than from the end-organ.

Much of the literature assessing quality of life finds a strong positive correlation between quality of life and marital status, sexual function, and employment (Nickel et al., 2007). These co-morbidities likely contribute to poor quality of life, though patients themselves may not mention them unless specifically queried. For this reason, many centers, including ours, now utilize an interdisciplinary clinic with urology-gynecology, neurology, psychology, anesthesia/pain management, and rehabilitation services. Approaches that address sleep, mood, and chronic pain, for example through the use of a tricyclic agent, and that stress physical reconditioning through exercise may have specific salutary effects on the entire syndrome, not just the end-organ that constitutes the particular focus of the patient's complaint.

The high frequency of co-morbid disorders well beyond geographic contiguity with the bladder region (e.g., headache, sleep disorders, fatigue, etc.) affects our pathophysiologic construct of IC/BPS, suggesting either some type of systemic disorder, a process under central nervous system control, or both. The absence of any frank neuro-inflammation (Nickel, 2002) reduces the likelihood of a disorder of cellular immunity or cytokine activation. An abnormal central nervous system drive, with secondary psycho-neuro-endocrine-immune dysfunction (Irwin and Cole, 2011) seems likely, as occurs in FM, where heart rate variability analysis demonstrates a skew toward low

sympathetic frequencies with reduction or even absence of high parasympathetic frequencies (Staud, 2008). In migraine, an autonomic neuropathy occurs frequently (Rashed et al., 1999) with a similar skew favoring sympathetic over parasympathetic activity.

Although no good data yet exist in patients with IC/BPS, studies in the co-morbid disorder FM have identified several areas of the brain that are activated with application of pain that are not activated in healthy individuals. This "pain matrix" is currently conceptualized as reflecting an afferent processing disorder (Smith et al., 2011). Since the primary brain abnormality must involve both afferent pain processing and efferent autonomic processing simultaneously, good candidates include brainstem structures such as the locus ceruleus or the raphe nuclei. The raphe are particularly attractive as a hypothetical region of origination since they are deeply involved in sleep regulation (Monti, 2010) as well as in the probable generation of migraine headache and associated phenomena (Pringsheim et al., 2003), one of which occurs in many if not the majority of patients with most functional disorders. The raphe are also in close proximity to control areas involved in continence, which include the pons, the periaqueductal gray, the thalamus, insula, anterior cingulate, and prefrontal cortex (Kavia et al., 2005).

The patient group diagnosed with IC/BPS (ICDx) was remarkably similar to the group identified by questionnaire (ICSx) and both differed from control subjects. According to the IC Database study, NIDDK criteria used for ICSx are more restrictive than specialist opinion (ICDx; Hanno et al., 1999), and this could explain the higher rate of "other pains," if they represent a slightly more severe subgroup. The higher rate of orthostatic disorders in the ICSx group represents a referral diagnosis bias to the autonomic lab and clinic from where this population was drawn. The rate of migraine in the healthy control group of 50% was higher than a recent Norwegian study which found a migraine prevalence of 35% (Vetvik et al., 2010), perhaps due to a young predominantly female population that matched the experimental groups in gender, age, and socio-economic status. However, other common functional disorders like IBS, dyspepsia, aches, and pain, were not increased in the control population.

This study has several limitations. Whereas the ICDx group was diagnosed objectively by a physician specializing in interstitial cystitis, the ICSx group used a patient survey with its attendant errors, subject recall-bias, questionnaire fatigue, and misunderstandings of questions. The highly similar occurrence of co-morbid disorders in both groups is reassuring, as is the fact that many ICDx subjects did not meet NIDDK criteria on the questionnaire, since an identical finding occurred with patients in the IC/BPS Database study (Hanno et al., 1999). Finally, moderate patient numbers could lead to a type II error, finding no difference between groups when a difference actually exists. A moderate sample size is not likely to suggest a difference when the truth is that the groups are identical.

In conclusion, this study demonstrates widespread co-morbidities in patients with interstitial cystitis, both physician and questionnaire diagnosed, with very similar findings in the two groups. Known co-morbid disorders were confirmed, including migraine headache, IBS, and widespread pain. New co-morbidities emerged, including dyspepsia-like symptoms and orthostatic intolerance. The multiple involvement of organ systems far from the bladder supports the theory that IC/BPS is not a primary bladder disorder (Warren et al., 2011), but rather the bladder is one more organ system involved in a systemic, possibly neurologic disorder.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

This research was supported by a grant from the Fishbein Foundation (Interstitial Cystitis Association of America) and in part by NIH NIDDK R01DK083538. We wish to thank Sarah Ialacci for her excellent technical support.

References

1. Bogart L. M., Berry S. H., Clemens J. Q. (2007). Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J. Urol. 177, 450–45610.1016/j.juro.2006.09.032 [PubMed] [CrossRef]
2. Buffington C. A. (2004). Comorbidity of interstitial cystitis with other unexplained clinical conditions. J. Urol. 172, 1242–124810.1097/01.ju.0000137953.49304.6c [PubMed] [CrossRef]

3. Chelimsky G. S., Safder S., Chelimsky T. (2012). Functional gastrointestinal disorders in children are associated with many non-psychiatric comorbidities: the tip of an iceberg? J. Pediatr. Gastroenterol. Nutr. 54, 690–69110.1097/MPG.0b013e3182496b1f [PubMed] [CrossRef]
4. Chelimsky T. C., Low P. A., Naessens J. M., Wilson P.R., Amadio P. C., O'Brien P. C. (1995). Value of autonomic testing in reflex sympathetic dystrophy. Mayo Clin. Proc. 70, 1029–104010.4065/70.11.1029 [PubMed] [CrossRef]
5. Clemens J. Q., Meenan R. T., Rosetti M. C., Gao S. Y., Calhoun E. A. (2005). Prevalence and incidence of interstitial cystitis in a managed care population. J. Urol. 173, 98–102; discussion 102.10.1097/01.ju.0000146114.53828.82 [PubMed] [CrossRef]
6. Drossman D., Corazziari E., Talley N., Thompson W., Whitehead W., editors. (eds). (2000). Rome II the Functional Gastrointestinal Disorders Diagnosis, Pathophysiology and Treatment: A Multinational Consensus. McLean, VA: Degnon Associates
7. Fukuda K., Straus S. E., Hickie I., Sharpe M. C., Dobbins J. G., Komaroff A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann. Intern. Med. 121, 953–959 [PubMed]
8. Hanno P., Nordling J., Fall M. (2010). Bladder pain syndrome. Med. Clin. North Am. 95, 55–7310.1016/j.mcna.2010.08.014 [PubMed] [CrossRef]
9. Hanno P. M., Landis J. R., Matthews-Cook Y., Kusek J., Nyberg L., Jr. (1999). The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J. Urol. 161, 553–557 [PubMed]
10. Irwin M. R., Cole S. W. (2011). Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11, 625–63210.1038/nri3042 [PMC free article] [PubMed] [CrossRef]
11. Jones C. A., Nyberg L. (1997). Epidemiology of interstitial cystitis. Urology 49, 2–910.1016/S0090-4295(96)00430-X [PubMed] [CrossRef]
12. Kavia R. B., Dasgupta R., Fowler C. J. (2005). Functional imaging and the central control of the bladder. J. Comp. Neurol. 493, 27–3210.1002/cne.20753 [PubMed] [CrossRef]
13. Li B. U., Lefevre F., Chelimsky G. G., Boles R. G., Nelson S. P., Lewis D. W., Linder S. L., Issenman R. M., Rudolph C. D. (2008). North American society for pediatric gastroenterology, hepatology, and nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. J. Pediatr. Gastroenterol. Nutr. 47, 379–39310.1097/MPG.0b013e318173ed39 [PubMed] [CrossRef]
14. Low P. A., Benarroch E. E., editors. (eds). (2008). Clinical Autonomic Disorders. Philadelphia: Lippincott, Williams and Wilkins, 713–732
15. Melzack R. (1987). The short-form McGill pain questionnaire. Pain 30, 191–19710.1016/0304-3959(87)91453-9 [PubMed] [CrossRef]
16. Merskey H., Bogduk N. (1994). Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. Seattle: IASP Press [PubMed]
17. Monti J. M. (2010). The role of dorsal raphe nucleus serotonergic and non-serotonergic neurons, and of their receptors, in regulating waking and rapid eye movement (REM) sleep. Sleep Med. Rev. 14, 319–32710.1016/j.smrv.2009.11.004 [PubMed] [CrossRef]
18. Nickel J. C. (2002). Interstitial cystitis: characterization and management of an enigmatic urologic syndrome. Rev. Urol. 4, 112–121 [PMC free article] [PubMed]
19. Nickel J. C., Payne C. K., Forrest J., Parsons C. L., Wan G. J., Xiao X. (2009). The relationship among symptoms, sleep disturbances and quality of life in patients with interstitial cystitis. J. Urol. 181, 2555–256110.1016/S0022-5347(09)60349-9 [PubMed] [CrossRef]
20. Nickel J. C., Tripp D., Teal V., Propert K. J., Burks D., Foster H. E., Hanno P., Mayer R., Payne C. K., Peters K. M., Kusek J. W., Nyberg L. M. (2007). Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. J. Urol. 177, 1832–183610.1016/j.juro.2006.10.174 [PubMed] [CrossRef]
21. Nickel J. C., Tripp D. A., Pontari M., Moldwin R., Mayer R., Carr L. K., Doggweiler R., Yang C. C., Mishra N., Nordling J. (2010). Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. J. Urol. 184, 1358–136310.1016/j.juro.2010.06.005 [PubMed] [CrossRef]
22. NIDDK (2006). 2006 NIDDK International Symposium: Frontiers in Painful Bladder Syndrome and Interstitial Cystitis. Available at: http://archives.niddk.nih.gov/fund/other/niddkfrontiers/frontiers%20in%20PBS%20Summary%20Report.pdf

23. Okamoto L. E., Raj S. R., Peltier A., Gamboa A., Shibao C., Diedrich A., Black B. K., Robertson D., Biaggioni I. (2011). Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. Clin. Sci. 122, 183–192 [PMC free article] [PubMed]
24. O'Leary M. P., Sant G. R. (1997). "The interstitial cystitis symptom and problem indices: rationale, development, and application," in Interstitial Cystitis, ed. Sant G. R., editor. (Philadelphia: Lippincott-Raven;), 271–276
25. Olesen J. (2004). The international classification of headache disorders: 2nd edition. Cephalalgia 24(Suppl 1), 9–16010.1111/j.1468-2982.2003.00824.x [PubMed] [CrossRef]
26. Pringsheim T., Diksic M., Dobson C., Nguyen K., Hamel E. (2003). Selective decrease in serotonin synthesis rate in rat brainstem raphe nuclei following chronic administration of low doses of amitriptyline: an effect compatible with an anti-migraine effect. Cephalalgia 23, 367–37510.1046/j.1468-2982.2003.00526.x [PubMed] [CrossRef]
27. Rashed H., Abell T. L., Familoni B. O., Cardoso S. (1999). Autonomic function in cyclic vomiting syndrome and classic migraine. Dig. Dis. Sci. 44, S74–S78 [PubMed]
28. Reyes del Paso G. A., Garrido S., Pulgar A., Duschek S. (2011). Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. J. Psychosom. Res. 70, 125–13410.1016/j.jpsychores.2010.09.012 [PubMed] [CrossRef]
29. Rodriguez M. A., Afari N., Buchwald D. S. (2009). Evidence for overlap between urological and nonurological unexplained clinical conditions. J. Urol. 182, 2123–213110.1016/j.juro.2009.07.036 [PMC free article] [PubMed] [CrossRef]
30. Sheldon R., Rose S., Connolly S., Ritchie D., Koshman M. L., Frenneaux M. (2006). Diagnostic criteria for vasovagal syncope based on a quantitative history. Eur. Heart J. 27, 344–35010.1093/eurheartj/ehi584 [PubMed] [CrossRef]
31. Sheldon R., Rose S., Ritchie D., Connolly S. J., Koshman M. L., Lee M. A., Frenneaux M., Fisher M., Murphy W. (2002). Historical criteria that distinguish syncope from seizures. J. Am. Coll. Cardiol. 40, 142–14810.1016/S0735-1097(02)01940-X [PubMed] [CrossRef]
32. Smith H. S., Harris R., Clauw D. (2011). Fibromyalgia: an afferent processing disorder leading to a complex pain generalized syndrome. Pain Physician 14, E217–E245 [PubMed]
33. Staud R. (2008). Heart rate variability as a biomarker of fibromyalgia syndrome. Fut. Rheumatol. 3, 475–48310.2217/17460816.3.5.475 [PMC free article] [PubMed] [CrossRef]
34. Tsai C. F., Ouyang W. C., Tsai S. J., Hong C. J., Lin T. L. (2009). Risk factors for poor sleep quality among patients with interstitial cystitis in Taiwan. Neurourol. Urodyn. 29, 568–572 [PubMed]
35. Vetvik K. G., MacGregor E. A., Lundqvist C., Russell M. B. (2010). Self-reported menstrual migraine in the general population. J. Headache Pain 11, 87–9210.1007/s10194-010-0197-0 [PMC free article] [PubMed] [CrossRef]
36. Warren J. W., Howard F. M., Cross R. K., Good J. L., Weissman M. M., Wesselmann U., Langenberg P., Greenberg P., Clauw D. J. (2009). Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology 73, 52–5710.1016/j.urology.2008.06.031 [PubMed] [CrossRef]
37. Warren J. W., Van De Merwe J. P., Nickel J. C. (2011). Interstitial cystitis/bladder pain syndrome and nonbladder syndromes: facts and hypotheses. Urology 78, 727–73210.1016/j.urology.2011.06.014 [PubMed] [CrossRef]
38. Wyller V. B., Barbieri R., Saul J. P. (2010). Blood pressure variability and closed-loop baroreflex assessment in adolescent chronic fatigue syndrome during supine rest and orthostatic stress. Eur. J. Appl. Physiol. 111, 497–50710.1007/s00421-010-1670-9 [PMC free article] [PubMed] [CrossRef]

Irritable Bowel Syndrome and Interstitial Cystitis

Interstitial cystitis and **irritable bowel syndrome (IBS)** are chronic pelvic pain disorders and, not surprisingly, often coexist. Research studies have demonstrated that 40 to 60% of IBS patients exhibit symptoms of IC while up to 52% of IC patients also have symptoms consistent with IBS.1 For patients who struggle with both conditions, the connection is often baffling until you consider the role of the nerves.

The organs of the pelvis communicate in a process known as *"neural cross-talk"* to maintain normal bladder, bowel and reproduction function. Yet, in a surprising twist, these normal communication pathways can also convey irritation. Researcher Michael Pezzone MD was one of the first to demonstrate *bowel-bladder cross-sensitization*. In animal

studies, he showed that when the bowel was acutely irritated in a single event, the bladder showed signs of irritation and when the bladder was irritated, the bowel shows signs of irritation.

Yet, it was his research into longterm, chronic irritation that offered more revealing information. Long-term irritation of the bowel triggered some of the familiar symptoms of IC including increased frequency and decreased urinary volume, as well as evidence of inflammation and increased numbers and activation of mast cells in the bladder wall. Dr. Pezzone wrote *"In other words, after colonic (bowel) irritation, the very nerves that carry signals for uncomfortable bladder sensation had become hypersensitive..."* 1

How does this happen? It turns out that the bladder and bowels outgoing, afferent nerves meet and combine near the spine thus providing both access and opportunity for "cross-talk." This was proven when Dr. Pezzone injected tracers into the bowel and bladder. He found BOTH sets of tracers in the same nerve cells in the dorsal root ganglia. Dr. Pezzone and his peers now suggest that chronic pelvic pain develops after an acute injury or chronic irritation to perhaps just one of the pelvic organs (i.e the bladder, the bowel or the reproductive tract), pelvic floor muscles, nerves and/or perhaps even the skin of the perineum. Other proximal organs or muscles can then become involved through this "crosstalk" sensitization pathway if the irritation/ inflammation persists.
Pelvic pain specialists agree that treatment should be focused on calming and soothing every condition in the pelvis (IC, IBS, endometriosis, vulvodynia) that is producing pain and/or discomfort.

IBS is not a disease

Irritable bowel syndrome is estimated to affect 3 to 20 percent of the population, with most studies ranging from 10 to 15 percent.2 However, less than one-third of people with the condition see a health care provider for diagnosis. 3 IBS affects about twice as many women as men and is most often found in people younger than 45 years.

Four Subtypes of IBS

According to the National Institutes of Health, *"Irritable bowel syndrome is a functional gastrointestinal (GI) disorder, meaning it is a problem caused by changes in how the GI tract works. People with a functional GI disorder have frequent symptoms, but the GI tract does not become damaged. IBS is not a disease; it is a group of symptoms that occur together."*4

Box 1: Four Subtypes of IBS

IBS with constipation (IBS-C)
- hard or lumpy stools at least 25 percent of the time
- loose or watery stools less than 25 percent of the time

IBS with diarrhea (IBS-D)
- loose or watery stools at least 25 percent of the time
- hard or lumpy stools less than 25 percent of the time

Mixed IBS (IBS-M)
- hard or lumpy stools at least 25 percent of the time
- loose or watery stools at least 25 percent of the time

Unsubtyped IBS (IBS-U)
- hard or lumpy stools less than 25 percent of the time
- loose or watery stools less than 25 percent of the time

Heather Van Vorous, author of First Year: IBS, offered *"IBS is considered a brain gut disorder and there are two aspects of that. The enteric nervous system is dysfunctional in people who have IBS. But, so is the way that the brain interprets messages from the enteric nervous system...We call it a hypersensitivity of the gut. That's why stress and food are the two greatest triggers. They both affect the gut and the gut overacts to both of those things, creating the symptoms of IBS. It's important that you realize that stress and diet doesn't cause IBS but they*definitely trigger the symptoms just like IC."5

Some patients with irritable bowel syndrome struggle with painful cramping and diarrhea after eating certain foods or heavy meals while others struggle with chronic constipation and hard, lumpy stools. Patients may feel urgency to have a bowel movement or feel that their bowel movement is incomplete. Small, hard stools and/or straining to have a bowel movement can occur. Discomfort usually improves after having a bowel movement.

For IBS to be diagnosed, the symptoms must have started at least six months prior and must have occurred at least three days per month for the previous three months. Further testing is not usually needed though the health care provider may do a blood test to screen for other problems. Additional diagnostic tests may be needed based on the results of the screening blood test and for people who also have signs such as fever, rectal bleeding, weight loss, anemia or a family history of colon cancer, IBS or celiac disease. Based upon those findings, patients will be given a classification (see box 1).

What causes IBS?

The causes of IBS are still unclear though Dr. Pezzone has made a good case for pelvic organ cross-talk and neurosensitization. Some IBS patients can point to an initial bowel trauma, such as a severe case food poisoning, bacterial gastroenteritis, surgery or perhaps even childbirth. A brain-gut signaling problem or perhaps some GI motility issues may contribute in some cases. Slow motility can lead to constipation and fast motility can lead to diarrhea. Genetics could also play a role. Quite a few patients report food sensitivity issues, such as with foods high in caffeine, MSG, coffees, fats, etc.

Heather believes that the gastrocolic reflex, the normal message that the stomach sends to the colon after you've eaten that triggers a bowel movement, has become hypersensitive. She said *"In people with IBS this reflex goes haywire. Their colon is contracting too much, too hard, too fast, or it's in spasms or not contracting enough. They may have too few contractions, not strong enough, or be irregularly timed. This can then cause abdominal pain, diarrhea, constipation, bloating, and trapped gas. And that's all stemming from the hypersensitive gastrocolic reflex."*

IBS Diet Modification Tips

IBS patients learn, fairly quickly that certain foods can trigger symptoms. Heather offered *"There are two categories of foods that stimulate the gastrocolic reflex more than anything else. (1) Fats and (2) Insoluble fibers... It's actually very easy to work around this."* Alcohol, caffeine, chocolate, artificial sweeteners, foods which produce gas and/or high acid foods can also be troublesome. Sounds a lot like the IC diet, doesn't it?

But when you're struggling with constipation, well meaning family members and physicians suggest loading up on high, insoluble fiber foods (i.e. bran, granola, greens, roughage, psyllium products etc.). The challenge, of course, is that these "insoluble fibers" are notoriously challenging to the more tender IBS gut. Heather said *"Insoluble fiber is a huge GI stimulant. It sends the gastrocolic reflex out of control and can trigger spasms, cramps, and diarrhea.. and can also exacerbate constipation. If you don't have IBS, insoluble fiber is great for constipation. If you do have IBS, it can make your gut spasm and make those contractions so irregular that it interferes with motility and worsens constipation."*

It's the starchy, soluble fiber found oatmeal, pasta, rice, potatoes, tapioca, bananas that is more soothing for the bowel and gut of a typical IBS patient. According to Heather, soluble fiber regulates the gastrocolic reflex, thus calming painful muscle contractions of the gut. Soluble fiber also regulates water content in the bowel and can help with both diarrhea and constipation. She said *"People get so confused. I spend my life telling people with*

constipation that soluble fibers won't make them worse and that they aren't "binding." She cautioned *"Never have insoluble fiber alone, on an empty stomach, or in large quantities all at once. Always have insoluble fibers with soluble fibers. Make yourself fried rice and add some veggies to that or a put vegetable sauce on pasta. Try cooking some fresh fruit in your oatmeal. Cooking breaks down insoluble fiber and so does cutting it up and pureeing it in the blender, which makes it a lot more tolerable. Cooked veggies are safer than raw. A fresh fruit smoothie is safer than a big, raw fruit salad."*

Many patients have also experienced IBS attacks after eating salad greens. Greens (i.e. lettuce, spinach, kale, chard) also contain insoluble fibers which can stimulate the gut. Heather advises patients to make soluble fiber the foundation of their meals and/or the first thing that they eat in a given meal, saving the insoluble fiber for the end of the meal. Want a salad? Eat it after you eat the bread!

For protein, focus on lean meats such as skinless chicken, turkey breasts, seafood or egg whites. Fatty red meats are a well known IBS trigger because they are high in fat and the proteins are hard to digest. Dairy products high in fat and protein can also be a trigger.

High acid fruits and veggies can trigger discomfort for both IC and IBS. It can help to remove the skins because that contains most of the insoluble fiber. Bananas, pears, mild sweet apples, some melon are reasonable to try. Water intake is also important. Soluble fiber needs water in the gut to work, especially for patients who struggle with constipation. You can find many more diet ideas and strategies on Heather's website: www.helpforibs.com

Treatments

The treatments for IBS are quite similar to the treatments for IC in that they are designed to calm and soothe nerves though, in this case, the nerves of the gut rather than the nerves in the bladder.

• Fiber Supplements

Many physicians recommend using a fiber supplement to ease constipation. Surprisingly, psyllium products are not the first choice for IBS because they contain some insoluble fiber. Soluble fiber products, such as Acacia Fiber, seem to be better tolerated.

• Laxatives

Several types of laxatives are available to ease constipation, including bulk-forming laxatives, stimulants, osmotics, stool softeners, lubricants, calcium channel acitvators and saline laxatives. Please talk with your doctor about which form of

laxative would be best for you depending upon your specific condition.

- **Antidiarrheals**

Antidiarrheals (i.e. Loperamide) can help reduce diarrhea by slowing the movement of stool through the colon.

- **Antispasmodics**

Antispasmodics (i.e. hyoscine, cimetropium, pinaverium) can help control colon spasms.

- **Antidepressants**

Both tricyclic antidepressants (TCA's) and selective serotonin reuptake inhibitors (SSRIs) in low doses can help relieve IBS symptoms including abdominal pain. In theory, TCAs should be better for people with IBS-D and SSRIs should be better for people with IBS-C due to the effect on colon transit, but this has not been confirmed in clinical studies. TCAs work in people with IBS by reducing sensitivity to pain in the GI tract as well as normalizing GI motility and secretion.

- **Lubiprostone (Amitiza).**

Lubiprostone is prescribed for people who have IBS-C. The medication has been found to improve symptoms of abdominal pain or discomfort, stool consistency, straining, and constipation severity.

- **Probiotics**

Probiotics are live microorganisms, usually bacteria, that are similar to microorganisms normally found in the GI tract. Studies have found that probiotics, specifically Bifidobacteria and certain probiotic combinations, improve symptoms of IBS when taken in large enough amounts. But more research is needed. Probiotics can be found in dietary supplements, such as capsules, tablets, and powders, and in some foods, such as yogurt. A health care provider can give information about the right kind and right amount of probiotics to take to improve IBS symptoms.

- **Managing Stress & Talk Therapy**

Talking with a therapist may reduce stress and improve IBS symptoms. Two types of talk therapy used to treat IBS are cognitive behavioral therapy and psychodynamic, or interpersonal, therapy. Cognitive behavioral therapy focuses on the person's thoughts and actions. Psychodynamic therapy focuses on how emotions affect IBS symptoms. This type of therapy often involves relaxation and stress management techniques.

- **Hypnotherapy**

In hypnotherapy, the therapist uses hypnosis to help the person relax into a trancelike state. This type of therapy may help the person relax the muscles in the colon.

- **Mindfulness training**

People practicing this type of meditation are taught to focus their attention on sensations occurring at the moment and to avoid worrying about the meaning of those sensations, also called catastrophizing. It's important to remember that IBS isn't considered a disease. It is a functional disorder and your job is to learn what works best in your gut. If stress is an issue that provokes frequent IBS attacks, then you must work on and build your stress management skills. If your diet is out of control and you're eating foods notorious for triggering diarrhea, then it's worth trying some of the diet suggestions offered in The First Year: IBS – An Essential Guide for the Newly Diagnosed.

If your symptoms are not improving, look for a medical care provider, such as a gastroenterologist, that specializes in functional disorders. They may find that missing piece to your puzzle! It's worth the effort.

References

1. Pezzone M. Chronic Pelvic Pain and the Overlap of Chronic Pelvic Pain Disorders. International Foundation for Functional Gastrointestinal Disorders. 2007
2. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis, and treatment: an update for health-care practitioners. Journal of Gastroenterology and Hepatology. 2010;25:691–699.
3. Owyang C. Irritable bowel syndrome. In: Yamada T, ed. Textbook of Gastroenterology. 5th ed. Vol. 1. West Sussex, UK: John Wiley & Sons Ltd.; 2009: 1536–1573.
4. Irritable Bowel Syndrome. National Digestive Diseases Information Clearinghouse. NIH Publication No. 12-693. July 2, 2012
5. Irritable Bowel Syndrome and IC: Practical Suggestions to Help IC/IBS Patients Manage Their Bowel Syndromes. 2006 IC & PBS On-Line Patient Conference – June 20, 2006

Resources

- irritable Bowel Syndrome – National Digestive Diseases Information Clearinghouse. NIH Pub No 12-693, July 2012. digestive.niddk.nih.gov
- The First Year: IBS – An Essential Guide for the Newly Diagnosed – Heather Van Vorous and David Posner – 2001
- Heather's Tummy Fiber – Organic Acacia Fiber

- Helpforibs.com – Heather Van Vorous's IBS support website.
- American Neurogastroenterology and Motility Society
- International Foundation for Functional Gastrointestinal
- Rome Foundation

Author: Jill H. Osborne MA
Created: Feb. 2013
Updated: Jan 2017

ICNetwork
YOU ARE NOT ALONE

info@ic-network.com

> The Fall 2018 IC Optimist Is Now Available

> IC Vision & Eyesight Survey Launched Today

> Self Help Tip – Don't Let Fear of Physical Therapy Stop You

> Butternut Squash & Pear Soup

> A Popular Allergy Medicine May Help IC Symptoms

About Us Contact Us
ICN Sponsors & Advertisers
ICN Medical Advisory Board
Privacy Policy Disclaimer
ICN Editorial Policy
ICN Awards
ICN Donation & Giving Guide

BY BECOMING AN MEMBER

SECTION D

Harvard Women's Health Watch

Diagnosing and treating interstitial cystitis

Updated: May 1, 2018 Published: August, 2011

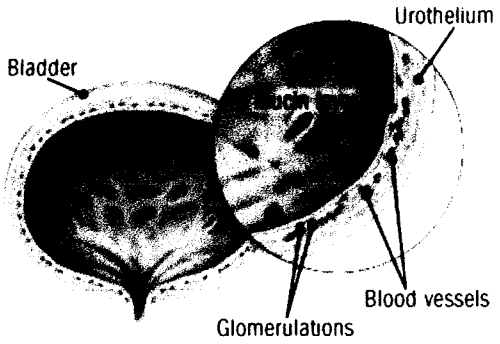
Also called painful bladder syndrome, this frustrating disorder disproportionately affects women.

Interstitial cystitis is a chronic bladder condition that causes recurring bouts of pain and pressure in the bladder and pelvic area, often accompanied by an urgent and frequent need to urinate — sometimes as often as 40, 50, or 60 times a day, around the clock. Discomfort associated with interstitial cystitis can be so excruciating that, according to surveys, only about half of people with the disorder work full-time. Because symptoms are so variable, experts today describe interstitial cystitis as a member of a group of disorders collectively referred to as interstitial cystitis/painful bladder syndrome. (In this article, we'll call it interstitial cystitis, or IC.)

Among the one to two million Americans with IC, women outnumber men by as much as eight to one, and most are diagnosed in their early 40s. Several other disorders are associated with IC, including allergies, migraine, irritable bowel syndrome, fibromyalgia (a condition causing muscle pain), chronic fatigue syndrome, and vulvodynia (pain or burning in the vulvar area that isn't caused by infection or skin disease).

There's no cure for IC, but many treatments offer some relief, either singly or in combination. Figuring out what works can be hit-or-miss; there's no way to predict who will respond best to which treatment.

Glomerulations and interstitial cystitis



A defect in the layer of mucus (mucin layer) that protects the cells lining the bladder (the urothelium) may permit toxic substances from urine to seep through and inflame tissues. Irritated blood vessels produce tiny areas of bleeding in the bladder lining called glomerulations. Most people with interstitial cystitis have glomerulations.

Possible causes

No one knows the exact cause of IC; more than one mechanism is probably involved. Biopsies of the bladder wall in people with IC indicate various abnormalities, but it's not clear whether these are the cause of the condition or the result of some other underlying process. Some research has focused on defects in the glycosaminoglycan (GAG) layer, part of the layer of mucus that lines and protects the bladder. Defects in the GAG layer may allow toxins in the urine to leak through and damage underlying nerve and muscle tissues; this in turn may trigger pain and hypersensitivity.

Another line of research centers on antiproliferative factor (APF), a substance that's found only in the urine of people with IC. APF appears to block the normal growth of cells that line the bladder and may hinder the healing process that follows any damage or irritation to bladder tissues. Scientists seeking a diagnostic test for IC are considering APF as a possible biomarker.

There are several other theories about the cause of IC. It may be an infection with an unknown agent, such as a virus. Or it may be an autoimmune disorder set in motion by a bladder infection. It's possible that mast cells normally involved in allergic responses are releasing histamine into the bladder. Another idea is that sensory nerves in the bladder somehow "turn on" and spur the release of substances that contribute to symptoms. Because interstitial cystitis is mainly a woman's disease, many researchers think that hormones play a role.

Variable symptoms

The onset of IC is usually gradual, with bladder pain and urinary urgency and frequency developing over a period of months. The course of the disorder and its symptoms can vary greatly from woman to woman and even in the same woman. Symptoms may change from day to day or week to week, or they may remain constant for months or years and then go away, only to return several months later. Pain ranges from dull and achy to acute and stabbing; discomfort while urinating fluctuates from mild stinging to burning. But virtually everyone with IC has pain associated with bladder filling and emptying. Some women with IC have a constant need to urinate, because urinating helps relieve the pain.

In women who also have chronic abdominal or pelvic pain from other causes, such as irritable bowel syndrome or endometriosis, IC may flare up when those symptoms are at their worst. Sexual intercourse can trigger pain lasting several days, and symptoms may worsen with menstruation. On the other hand, some women experience complete relief during the second and third trimesters of pregnancy. Some find that their symptoms are worse after consuming certain foods or drinks, including strawberries, oranges, tomatoes, chocolate, spices, caffeine, alcohol, and beverages that acidify the urine, such as cranberry juice.

Diagnosis of exclusion

IC is not a urinary tract infection, and it can't be identified by a simple urinalysis or urine culture. Rather, it's a diagnosis of exclusion, which means that it's diagnosed only after a number of other conditions have been ruled out. A clinician — usually a urologist or a gynecologist — will first take a thorough history, then conduct a physical exam (including a pelvic exam, if it's not too uncomfortable) and perform tests for infection, bladder stones, bladder cancer, kidney disease, multiple sclerosis, endometriosis, sexually transmitted diseases, and other disorders. The AUA guidelines also recommend an early assessment of pain, urinary frequency, and urine volume, to help evaluate the effectiveness of later treatments.

If a diagnosis is uncertain or there are symptoms (such as blood in the urine) that suggest other problems, the next step is usually cystoscopy, which involves inserting a fiber-optic tube through the urethra to look at the bladder wall. During the procedure, a tissue sample may be taken to rule out bladder cancer. Some clinicians favor hydrodistention under local or regional anesthesia, which involves filling the bladder during cystoscopy with a liquid that stretches it, providing a closer view of the bladder wall. However, AUA guidelines do not recommend hydrodistention for either diagnosis or treatment. In people with IC, glomerulations — tiny pinpoint spots of blood — are usually visible on the bladder wall during cystoscopy with hydrodistention, but these lesions are often seen within the normal bladder as well.

One finding from cystoscopy that can help in making an IC diagnosis is the presence of reddened patches or lesions called Hunner's ulcers, which can stiffen tissue and cause reduced bladder capacity. However, Hunner's ulcers, which occur in 10% to 15% of cases, aren't required to make an IC diagnosis.

Selected resources

American Urological Association Foundation
800-828-7866 (toll-free)
www.urologyhealth.org

Interstitial Cystitis Association
800-435-7422 (toll-free)
www.ichelp.org

Managing IC

There's little consensus on the best way to treat IC, but treatment generally starts with conservative measures and proceeds to more invasive ones if symptoms don't improve. Usually a combination of approaches is needed, including these:

Psychosocial support. Chronic pain can be an isolating experience, so it may help to be in touch with others who feel your pain and understand what you're going through. Local pain support groups or national support groups like the Interstitial Cystitis Association (see "Selected resources") can serve that purpose. Learning as much as you can about IC may also give you a greater sense of control over your condition.

Chronic pain can cause depression, so don't hesitate to consult a mental health professional if you're feeling overwhelmed. (Support groups can usually refer you to counselors.) You may also want to talk to someone who specializes in stress reduction techniques, such as guided imagery, which was shown in one controlled study to improve IC patients' response to therapy. Some people say they've been helped by biofeedback, which trains people to use their minds to control physiological processes, such as muscle tension, that may be contributing to symptoms.

Behavior changes. Avoid anything that appears to cause flare-ups, whether that's a certain kind of exercise, sexual activity, constipation, tight clothing, or a specific food. (Because high-acid foods seem to cause flare-ups, some clinicians suggest taking an antacid with meals.) Expanding your bladder capacity is also important (constantly succumbing to the urge to go all the time can shrink bladder capacity). For example, if you're urinating every 30 minutes, try holding off for 45 minutes; if you manage that for a week, increase the interval to 60 minutes the second week, and so forth.

Medications. Various medications may help relieve pain and reduce inflammation. (See "Medications for the treatment of interstitial cystitis.") Some are taken orally; others are bladder instillations — drugs that are introduced into the bladder by catheter and held for a few seconds up to 10 or 15 minutes. Instillation usually takes place in a clinician's office, although in some cases, these drugs can be self-administered at home.

Medications for the treatment of interstitial cystitis

Treatment	Comment
Oral drugs	
Tricyclic antidepressants	Taken at low doses, tricyclic antidepressants relax the bladder and hinder the release of neurochemicals that can cause bladder pain and inflammation. They may also improve sleep. Amitriptyline (Elavil) is the medication most commonly prescribed for interstitial cystitis. Side effects include sleepiness, dry mouth, and weight gain.
Pentosan polysulfate sodium (Elmiron)	The only oral medication approved by the FDA specifically for the treatment of IC, Elmiron is thought to help repair defects in the bladder lining. It can take several months to reduce pain and urinary frequency, and the effect may be modest. Serious side effects are rare. If Elmiron doesn't work in six months, stop taking it.
Antihistamines	The antihistamine hydroxyzine (Atarax, Rezine, Vistaril, others) is thought to block mast cells' release of histamine in the bladder. It helps in relieving pain, urinary frequency, and (because it's sedating) nighttime urination. Some clinicians recommend cimetidine (Tagamet) and ranitidine (Zantac), which are a different type of antihistamine, but there's little evidence to support their use.
Painkillers	Nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen, naproxen sodium) and acetaminophen can help relieve pain.
Cyclosporine A	In early studies, this immunosuppressant drug helped relieve symptoms, but its use is limited by serious side effects — including uncontrollable trembling, muscle or joint pain, and enlarged gums.
Bladder instillations	
Dimethyl sulfoxide (DMSO)	DMSO instilled in the bladder was FDA-approved for the treatment of IC in the 1970s. It helps relax the bladder and alleviate pain. Treatment involves weekly instillations for six to eight weeks and then every two weeks for three or more months.
Heparin and lidocaine	Some clinicians combine one or both of these drugs with Elmiron (as a bladder instillation) and other medications in "rescue instillations" administered to quickly reduce pain and inflammation and help restore the mucus in the bladder.

Specialized physical therapy. Working with a physical therapist trained in pelvic soft tissue manipulation and rehabilitation may help to release scars and other sources of pelvic pain. Exercises that relax the pelvic floor are okay, but the AUA recommends that people with IC avoid exercises that strengthen pelvic floor muscles (Kegels).

Additional options. If standard treatments don't work, your clinician may suggest a trial of an implantable device called InterStim, which stimulates the sacral nerve in the lower back and may help alleviate urinary urgency and frequency in some women. If the device helps, it can be permanently implanted. Researchers are also studying the instillation of botulinum toxin into the bladder, but so far, the side effects and complications have been too serious to recommend its general use.

What doesn't work. The AUA found no evidence that the following therapies help relieve IC symptoms, and some evidence they may be harmful: long-term oral antibiotics, bladder instillation of bacillus Calmette-Guerin (BCG), and bladder instillation of resiniferatoxin (RTX).

ICNetwork
YOU ARE NOT ALONE
Patient-to-Patient Bladder & Pelvic Pain Support

Is It Time To Consider Medical Marijuana for Bladder & Pelvic Pain?

There are few more hotly debated discussions in the USA than the use of medical marijuana. With the common and often ugly image of drug addicts smoking joints, it's easy to think of marijuana as just a street drug. Yet, if we could remove that image from the American psyche and replace it with that of a medication that reduces pain with far fewer side effects than other pain medications, would it be more well received?

A Spring 2010 legislative report produced by the University of California San Diego (UCSD) Center for Medicinal Cannabis Research shared the results of five scientific clinical trials that *"showed that cannabis can be helpful in easing pain in selected syndromes caused by injury or diseases of the nervous system and possibly for painful muscle spasms due to multiple sclerosis." (1)* I found this report compelling. These aren't guesses made by people desperately hoping to legalize marijuana. These are valid, scientific studies that show that it has the potential of helping pain patients who may have found little relief from traditional medications.

New research has since emerged which, yet again, shows the pain fighting properties. On July 1st, 2010, the International Anesthesia Research Society (IARS) released a paper discussing a marijuana derivative (MDA19) that helps to fight neuropathic pain yet does not trigger the typical physical and emotional side effects associated marijuana use. (2) Isn't that interesting? If research can take out the components of marijuana that help patients "get high" and keep the components that fight pain, wouldn't that be a credible use of MJ? Could medicinal marijuana help with bladder pain?? It might be worth considering.

Patients Debate the Issue

I was curious about how patients would respond to this research report and posted a link to it on my Facebook page. The first, somewhat angry, response set the tone for a vibrant debate. She said *"I believe medical marijuana is just an excuse for people to do drugs."* Another offered a thoughtful counterpoint. *"We should all keep an open mind about treatment options out there. Marijuana has a bad rap because people label it 'recreational.' What about the 'recreational' use of prescription meds in this*

country? It's not like prescription pain killers don't come with a huge list of side effects, including dependency..."

Most patients were receptive to the possibility that medical marijuana could offer new treatment options. *"I would have no problem with this at all. I don't see how this could possibly be worse than using stronger, more damaging drugs. It has the possibility of really helping some people and that's what matters to me. I see no difference between using this and using any other drug for a medical purpose. I'm not going to get hung up in preconceived notions of what is a 'good drug' and what is a 'bad drug'."*

"I would not begrudge anyone legal pain relief and it is legal in some states." —IC Patient on Facebook

Two key issues were legality and professional responsibility. One patient said *"I would try it if it was legal here. I would much rather go to that than narcotics. But I live in the one state it will never be legal in."* Another offered *"As I am a school librarian, I could never use marijuana (I could lose my job) but I would not begrudge anyone legal pain relief and it is legal in some states."*

And the conservative parents of an IC patient spoke out *"I've seen my daughter suffer all her life beginning with kidney surgery at the age of 2 weeks of coming into this world. Believe me she has tried so many things and she has yet to find anything that will reduce the intensity of the pain she suffers every single day. Along with IC, she also has developed a number of additional health issues. Coming from a very old fashioned strict family background I never considered MJ until this illness intensified over the years. Now I, along with her extremely old fashioned grandparents, fully support medicinal MJ. I would prefer to find ways to improve my daughter's quality of life than label it as an excuse."*

Survey Studies Marijuana Use in IC Patients

It dawned on me that this is such a politically sensitive topic that no researcher had, up to this point, asked IC patients if they did use marijuana to help reduce their symptoms and, if so, did it help. So, last July, I created an online survey to ask these questions. As of press time, 118 IC patients had participated. 67.5% of patients reported that they have used medical marijuana in the past six months to help improve their pain with different levels of success. For a fortunate 18.2% of survey respondents, marijuana made their symptoms go away completely. The majority of patients (63.6%) reported that medical marijuana reduced their symptoms by 50%. 14.8% reported that their symptoms reduced 25%. Two patients reported that it did not help their symptoms and one reported that marijuana made their symptoms worse.

Pain

The survey demonstrated that patients use marijuana primarily for its pain fighting properties. 31.8% of patients reported a complete resolution of their pain with another 55.7% reporting that their pain was

reduced by 50%. Only 3.4% of patients reported that it did not reduce their pain. Like the research suggests, marijuana does seem to target neuropathic pain. One patient said "The nerve pain was almost gone for 2 to 3 hours." One man reported that it "reduced his testicular pain, perineal pain and ano/rectal pain." Others found that it helped their back pain and migraines.

Muscle Tension & Spasms

Given the research that found that medical marijuana could help reduce the muscle tension in patients struggling with multiple sclerosis, we were curious to see if it could help with pelvic floor dysfunction and the data suggests that it does. 31.3% of patients reported that their muscle tension completely improved with one patient offering *"It reduced the continuous spasm that comes with IC by 70%. This resulted in a reduction in pain – so less medicine has to be taken."* Another 43.4% reported that their muscle tension improved by 50%. It did not improve the muscle tension in 12% of patients participating in the survey. Several patients reported that marijuana reduced the pain that they had experienced with intimacy. One patient noted that it *"changed my perception of pain. I was able to eat due to the lack of pain. Sexual relations were normal and pain free after many years of suffering."*

"It reduced the continuous spasm that comes with IC by 70%. This resulted in a reduction in pain – so less medicine has to be taken."—survey participant

Frequency & Urgency

Patients also reported similar relief with their frequency and urgency. Roughly 56% of patients reported that their frequency improved at least 50% while 52% reported a similar improvement with urgency.

Sleep Quality

Marijuana substantially improved sleep quality in 78.2% of patients. One patient reported *"The sleeping part helped a lot, I did not wake up to urinate at all. It numbed my bladder, a very awesome feeling."* 27.6% of patients reported that they could sleep through the night without getting up to use the restroom. 50.6% of patients reported that they can sleep normally and get up only once or twice a night after using medical marijuana.

Anxiety

Several patients reported that marijuana helped reduce their panic and anxiety levels dramatically. One patient said that it *"greatly reduced panic, anxiety, IBS, GERD, depression and fibromyalgia."* Another said that it reduced *"anxiety about how the flare was going to impact my life."*

Stomach & Bowel

Several patients noted that it improved nausea, stomach and bowel problems. One found relief for her painful bowel movements. She said *"when smoking marijuana I would have total comfort, almost no flank or pelvic pain. I would be able to have comfortable bowel movements with no spasms."* Another said *"I get terrible stomach cramps from my IC. Marijuana can help reduce or sometimes completely eliminate all of the cramping. It also helps with some of the bladder spasms and spasms I feel in the urethra."* Another noted that it helped reduce the nausea she experienced as a side effect from various medications.
As has been widely reported in chemotherapy patients, marijuana also helps patients eat. One IC patient offered that marijuana did not help her bladder symptoms but it did improve her appetite. She said *"It stimulated my appetite and helped me eat more. I have accidentally lost 10 pounds since my diagnosis 7 months ago due to my extreme diet change and being afraid to eat. Medical marijuana encourages me to eat!"*

Flares & Flare Management

We were curious to see if marijuana actually worsened any IC symptoms. Of the 45 people who answered that question, less than five reported that it triggered symptoms. One said *"It did make the urine burn more than usual."* Another said *"It can increase my urinary frequency but it reduces pain." Others reported diet induced flares "I didn't pay attention to what I was eating (pizza, chocolate, pop)."*
The far more frequent response was "no" or "Just the opposite. It can stop a flare before it builds up steam." One said *"Medical marijuana helps me in an immediate flare-up. If I use it soon enough after I feel a flare building, it numbs the pain and the urgency much sooner than were I to take some OTC Pyridium or get an emergency instill from my urologist. It does not cut down the pain of urination but it does stop the stabbing radial pain in my pelvic and abdominal area."*

Smoked or Ingested

As I cited in the introduction to this story, some companies are developing cannabinoid analogues that may be delivered in pill form. But, for now, the most popular method of ingesting marijuana is clearly by smoking it with 97% of our survey respondents reporting that that's how they have used it. Like cigarette smoke, marijuana smoke has chemical by-products that can irritate the bladder. Medical researchers in Europe are currently testing a new, more promising way to deliver marijuana through an inhaled vapor.

Conclusion

I have mixed feelings about marijuana. I think the perception of drug addicts using marijuana is valid. I worry about teens becoming addicted to recreational drugs and that marijuana is a natural starting point in drug use. Yet, I stand 100% against suffering. Some IC patients, myself included, have had extreme pain that required emergency room visits and hospitalizations. If there's a chance that medicinal marijuana can reduce that suffering, then I think it deserves careful consideration.

I start with the research. The new UCSD report caught my attention. It's credible, scientific and gives both patients and policy makers a chance to look at the evidence available. I strongly encourage you to read it. If we had no studies that showed that marijuana could reduce pain, then I wouldn't be writing this article. The ICN Survey on Medical Marijuana and IC is very preliminary but also a fascinating glimpse into this controversial topic. Clearly, some patients have found medicinal marijuana to be helpful in the reduction of their pain, their pelvic floor dysfunction, bladder spasms, night time sleep quality, etc. However, we must do more work to further understand how it might help pelvic pain patients.

In the next article, Stacey Shannon shares new research about cannabinoid receptors in the bladder and a possible new bladder instillation using marijuana under study. How's that for shocking? And, of course, legality is the most important issue of all. I don't want patients to read this article (and the next) and assume that they should try marijuana if it's illegal in their state. There is a serious, real risk of criminal prosecution. You should explore the pain management options that are legally available to you.

If medicinal marijuana is approved in your state and you struggle with pain and/or using strong pain medications that limit your life due to side effects, I think it's worth discussing it with your doctor. That's one benefit that might be underestimated. Traditional pain medication is notorious for causing side effects, particularly severe constipation. If using marijuana can resolve that issue, that's also worth considering.

I encourage you to be sensitive to the impact of marijuana on your family and friends as well. Second hand smoke has health risks that are
undeniable to family members, pets, and adjoining neighbors. Remember, marijuana smoke is really pungent, districtive and hard to hide. You might not smell it, but others do, and may find it very offensive. Marijuana use is, ultimately, a matter of personal choice and
responsibility.

References
1. Center for Medicinal Cannabis Research: Report to the California Legislature (2010)http://www.cmcr.ucsd.edu/
2. Xu J, Diaz P, Astruc-Diaz F, Craig S, Munoz E, Naguib M. Pharmacological Characterization of a Novel Cannabinoid Ligand, MDA19, for Treatment of Neuropathic Pain. Anesthesia & Analgesia July 2010 Vol. 111 N. 1 99-109

by Jill Osborne, MA – Originally published in the Summer/Fall 2010 IC Optimist Magazine

By Jill Osborne|November 1st, 2013|Editorial, Interstitial Cystitis Network Blog, Must Reads, Pain Care, Self-Help Tips for IC, Bladder & Pelvic Pain|Comments Offon Is It Time To Consider Medical Marijuana for Bladder & Pelvic Pain?

About the Author: Jill Osborne

My Google Profile+ Jill Heidi Osborne is the president and founder of the Interstitial Cystitis Network, a health education company dedicated to interstitial cystitis, bladder pain syndrome and other pelvic pain disorders. An IC support group leader and national spokesperson for the past 20 years, she has represented the IC community on radio, TV shows, at medical conferences and as a member of the US Army administered CDMRP research program. She has written hundreds of articles on IC and its related condition. She is the publisher & editor of the IC Network website, rated the top patient website in research studies offered by Harvard Medical School (2011) and the University of London (2013). She also edits and writes much of the IC Optimist quarterly magazine. With a Bachelors Degree in Pharmacology and a Masters in Psychology, Jill spends the majority of her time providing WELLNESS COACHING for patients in need and developing new, internet based educational and support tools for IC patients, including the "Living with IC" video series currently on YouTubeand the ICN Food List smartphone app! Jill was diagnosed with IC at the age of 32 but first showed symptoms at the age of 12.

CRESCOlabs

IRRITABLE BOWEL SYNDROME

A Brief Description

Irritable bowel syndrome (IBS), or spastic colon, ranks as the most common gastrointestinal disorder, affecting 35 million Americans. As a chronic disorder affecting the colon, IBS is diagnosed based on the symptoms experienced by the patient. IBS is classified as a functional gastrointestinal disorder, meaning that it is apparently of spontaneous origin because the biological mechanism which leads to the diseased state is unknown. First documented in the Rocky Mountain Medical Journal in 1950, research recognizes that painful cramping, nausea, chronic diarrhea or constipation. IBS commonly leads to stomach pain, gassiness, bloating, constipation, diarrhea or both.

How Can Cannabis Help?

Although the exact cause of IBS remains unknown, it is known that, like many physiological processes, the gastrointestinal tract is controlled by the body's endocannabinoid system. Experts report that the colon muscle of an IBS sufferer is overly sensitive, causing it to spasm after even the most mild stimulation because of a disruption in the communication pathway between the brain and the gastrointestinal tract. Cannabis provides significant medical efficacy in the treatment of IBS because it is made up of hundreds of organic chemical compounds, known as cannabinoids, which are able to bind to the same receptors in the brain as the body's own gastrointestinal tract regulating endocannabinoids. Medical cannabis is able to fill in the missing pieces of the homeostasis puzzle when the body fails to regulate its own endocannabinoid production.

The most abundant psychoactive cannabinoid known for producing the feeling of being high, THC, is also known for being an effective reliever of pain and nausea, which are two of the most common symptoms of irritable bowel syndrome. CBD, the most abundant non-psychoactive cannabinoid works is a powerful anti-spasmodic that also produces calming effects in patients. Experts report that, in the treatment of IBS and many other conditions, the medical efficacy of each individual cannabinoid found in medical cannabis increases dramatically when they work together in a process known as the entourage effect. For example, CBC works synergistically with THC to increase the amount of the gastrointestinal regulating endocannabinoid, anandamide, that is in the body at any given time. More anandamide in the system equates to reduced pain because it prevents excessive spasms in the gut wall.

What Does The Research Say?

The effectiveness of cannabis and its derivatives for treating IBS and other gastrointestinal disorders has been known for centuries. Many of those suffering from IBS report that symptoms of the condition, like abdominal pain, nausea, cramping and irregularity of bowel movements are more manageable or even alleviated with the use of medical cannabis. The experiences reported by IBS patients shows that medical cannabis is ideal for broad-spectrum relief, and is often an effective treatment even when the condition has been non-responsive to more commonly prescribed treatment options.

Medical research demonstrates that this interaction between medical cannabis and the colon can result in improved motility, calmed spasms, and pain relief. Recent research has shown that endogenous cannabinoids play crucial neuromodulatory roles in controlling the operation of the gastrointestinal system, and can control gastrointestinal motility and inflammation. A study [http://informahealthcare.com/doi/abs/10.1517/13543784.12.1.39] conducted in Italy in 2003 found that THC, the most common cannabinoid known for its strong psychoactive properties, reduced intestinal motility, thereby alleviating colonic spasms and abdominal pain.

Links To Research

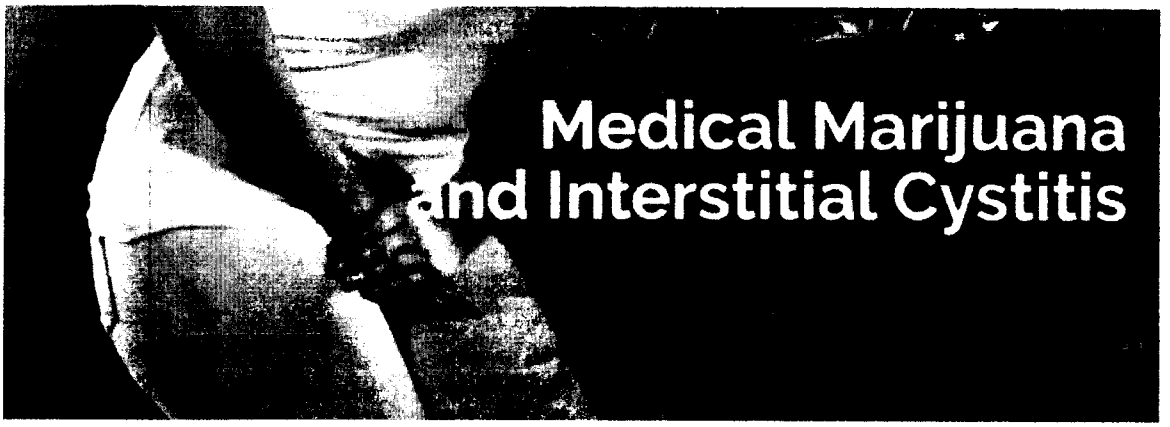
Cannabinoids for gastrointestinal diseases: potential therapeutic applications.

Selective inhibition of FAAH produces antidiarrheal and antinociceptive effect mediated by endocannabinoids and cannabinoid-like fatty acid amides.

Acute activation of cannabinoid receptors by anandamide reduces gastrointestinal motility and improves postprandial glycemia in mice.

Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

SECTION G



Medical Marijuana and Interstitial Cystitis

Unlike urinary tract infections, a bacterial infection does not cause interstitial cystitis, meaning antibiotics are of no help. While there is no known cure for the disease, there are, however, some options available for those hoping to relieve their chronic symptoms. One of these beneficial options would be medicinal marijuana.

Interstitial cystitis, also known as painful bladder syndrome, is a chronic condition. It causes feelings of pain and pressure in the bladder. In some cases, it can also cause pelvic pain.

History of Interstitial Cystitis

Although there may have been cases earlier in human history, the first record of interstitial cystitis dates to the early 1800s. Dr. Philip Syng Physick, a surgeon in Philadelphia, recorded a description of a bladder that had what he called an ulcer. The bladder had symptoms similar to one with a bladder stone. The patient with the condition also had pain in the area and an urgent, frequent need to urinate.

According to a surgeon in Philadelphia, Dr. Joseph Parrish, Dr. Physick called the illness, "tic douloureux of the bladder." "Tic douloureux" is also the name of a condition that causes sharp, stabbing pain in one or more areas of the face.

It wasn't until 1876 that the condition got the name it's known by today — interstitial cystitis. The condition was described in a book published by Samuel D. Gross.

A few years later, in 1878, Dr. Alexander Skene published the book, "Diseases of the Bladder and Urethra in Women," and noted that the illness seemed to be connected to inflammation in the bladder. Throughout the 19th century, interstitial cystitis was used as a catch-all phrase to describe a variety of problems that could be linked to bladder inflammation. It wasn't until later that the name was used to describe one specific condition.

The development of the cystoscope in the early 1900s changed the way that doctors diagnosed the condition. A Dr. Guy Hunner used a cystoscope to examine the bladders of patients and made the discovery that many of those bladders had what appeared to be ulcers.

These "ulcers" were lesions on the bladder wall, but the name "Hunner's Ulcers" caught on. It would be several more decades before doctors realized that many patients with painful bladder syndrome didn't have

ulcers or lesions.

While the earliest patients with interstitial cystitis were women, the condition also occurs in men and children. One study in the early 1940s examined interstitial cystitis in males.

Understanding of interstitial cystitis continued to evolve throughout the 20th century. In the late 1940s, a Dr. J.R. Hand established a grading system for the lesions found in the ulcers. He also noted several, "dot-like bleeding points," in the bladders he examined.

Dr. Hand's grading system is as follows:

Grade 1 — Very small submucosal hemorrhages on the bladder wall, dot-like bleeding points and single parallel streaks. At this stage, the capacity of the bladder isn't affected.

Grade 2 — Lesions are large, and the bladder's capacity is noticeably diminished.

Grade 3 — Many lesions and scarring from old lesions are present, as well as fissuring on the bladder wall. The bladder is considerably smaller.

After years of confusion over the disease's name and confusion over what it was, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) created a definition for interstitial cystitis in 1987. The definition of the disease was meant to be used for study and research — not to diagnose patients.

The focus of the NIDDK's definition was on lesions and bladder wall findings. Interestingly enough, patients under the age of 18 couldn't have the condition, based on the NIDDK's original definition. People with symptoms that lasted for less than nine months also didn't qualify as having interstitial cystitis.

In 2002, a new name for interstitial cystitis, painful bladder syndrome, was introduced by the International Continence Society. The name change was meant to acknowledge the fact that not every individual with the condition has damage to the bladder wall. The American Urological Association suggested a combined name, interstitial cystitis/painful bladder syndrome, in 2011.

Living with Interstitial Cystitis

The good news about interstitial cystitis is that it's not a common condition. When stricter diagnostic criteria were in place, only about 0.1 percent of people had it. That percentage has increased to two percent of women worldwide as the definition of the condition has changed.

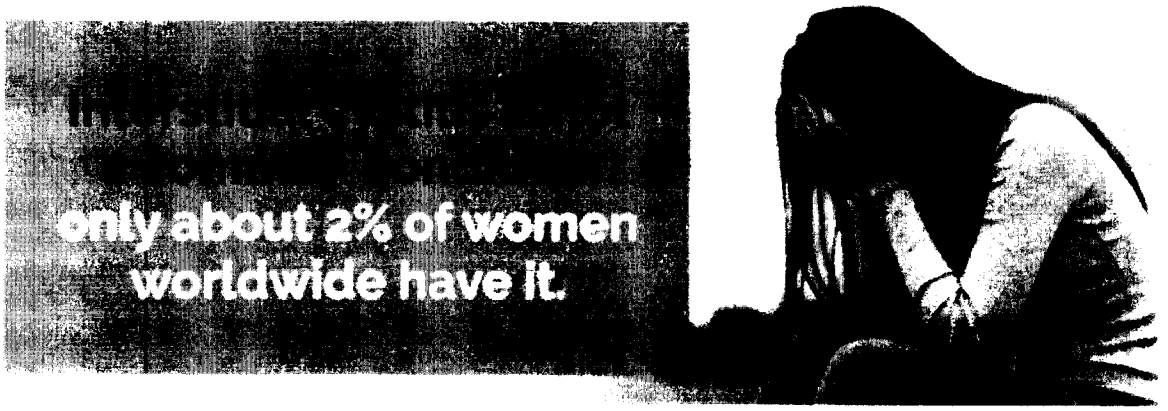
In the US, anywhere from three to eight million women have painful bladder syndrome. The condition is far more common in women than in men. It might also be more common in Caucasian women than in other races or ethnicities.

Whether the condition affects your quality of life depends on several factors. Some people with painful bladder syndrome might not have severe symptoms. It's also possible for symptoms to only flare up at certain times, such as during menstruation or after sex.

In more serious cases, the condition can have a substantial effect on a person's quality of life. For example, some people with painful bladder syndrome might get up a lot at night to urinate or have a constant urge to

urinate. They might not get a full night's sleep on a regular basis as a result.

The constant pain can also affect a person's mental health. Some individuals with interstitial cystitis report feeling depressed, as there is an occasional connection between constant pain and depression.



Risk Factors for and Causes of Interstitial Cystitis

Many theories and hypotheses exist about the cause of painful bladder syndrome, but no known cause exists. Some people, such as women over 30 years of age, have a higher risk than others for developing interstitial cystitis. Additional factors that raise your risk of interstitial cystitis include:

Fair skin

Red hair

History of urinary tract infections

Family history of interstitial cystitis

Damage to the wall of the bladder

Chronic pain conditions like irritable bowel syndrome (IBS), allergies, endometriosis, chronic fatigue syndrome or fibromyalgia.

Injury to the pelvic floor due to childbirth or a sports-related injury.

Painful bladder syndrome may have an autoimmune disease nature according to studies. When a person has an autoimmune disease, the immune system gets confused and attacks healthy cells in the body. Interstitial cystitis' relation to an autoimmune disorder is its tendency to coexist with other autoimmune diseases and develop in families with a history of painful bladder syndrome.

Symptoms of Interstitial Cystitis

The symptoms of interstitial cystitis vary from patient to patient. While some people may not notice their symptoms, other can find their symptoms very debilitating.

Symptoms of the condition fall into three categories:

1. Pain

The pain a person experiences due to interstitial cystitis can take many forms. For example, some people feel pain in their bladder as it fills up while others only feel a slight discomfort. The pain is markedly different from the discomfort you might feel when your bladder is full, and you need to pee.

After urinating, the pain in the bladder usually subsides for a while. Some people don't feel pain all the time, but rather have occasional flare-ups.

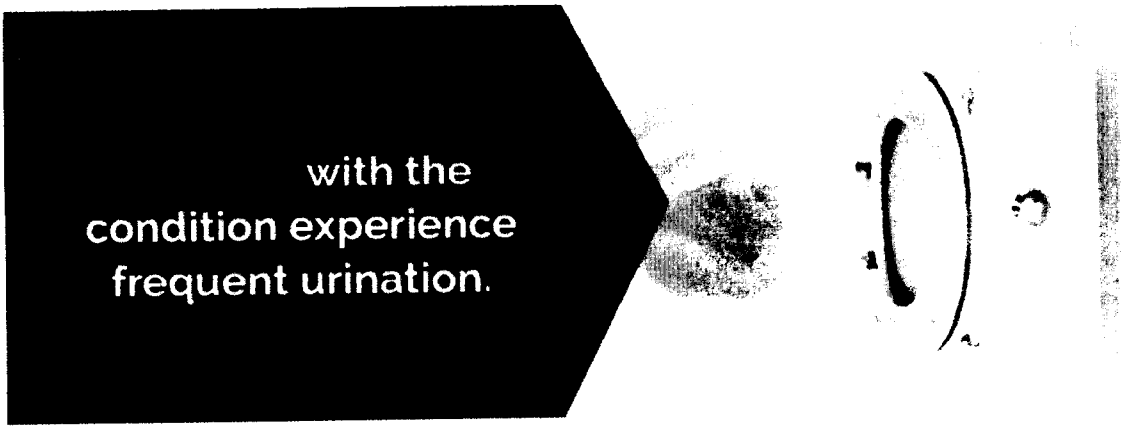
It's also possible to feel pain in other areas due to interstitial cystitis. For example, women and men might feel spasms of pain in the perineum or pelvic area. The pain can become worse during sex for women.

2. Frequent Urination

The need to urinate often is another common symptom of painful bladder syndrome. More than 90 percent of patients with the condition experience frequent urination. Although the exact frequency can vary, some people may have to pee 60 times over the course of a single day.

3. Urgent Urination

Urgent urination is the sudden need to go. It occurs in about 84 percent of people with interstitial cystitis. In some cases, the need to urinate occurs at night and can cause a person to get up and go to the bathroom every 30 or 15 minutes.



Current Treatments Available

Treating interstitial cystitis can be tricky, as there's no magic cure or one effective treatment option for everybody. Usually, treatment takes several forms, ranging from making changes to your habits to physical therapy, medication, and surgery.

Your treatment depends on the severity of your condition and whether a less invasive option has been

effective or not. Treatments include:

Making lifestyle changes. In some cases, making lifestyle changes is all a person needs to do to experience relief from the pain and discomfort of interstitial cystitis. One common lifestyle change is to adjust your diet.

Certain foods can trigger the symptoms of interstitial cystitis in some patients. Often called the "four C's" these items include carbonated drinks, foods and drinks with caffeine, foods with a high amount of vitamin C and citrus fruits. Similarly, foods that are acidic, such as pickles and tomatoes, can also trigger attacks for some people.

If you think that your symptoms are connected to what you eat, try keeping a diary and recording everything you eat and drink daily to see if there is a connection.

Training the bladder. Bladder training can also help reduce certain symptoms of interstitial cystitis, such as increased and urgent urination. Your doctor can assist you through the process, but it usually involves urinating on a set schedule, such as every 30 minutes, instead of when you feel the need to go.

Going to physical therapy. In some instances, working with a physical therapist and performing certain pelvic floor exercises can help relieve the pain of interstitial cystitis.

Taking oral medications. If the pain you experience from painful bladder syndrome is mild, your doctor might recommend taking an over-the-counter pain reliever. In cases where the pain is severe, your physician might prescribe a stronger pain reliever, but those carry a risk of addiction and other side effects.

In cases where lifestyle changes, over-the-counter medicines and therapy haven't helped, a doctor might prescribe something stronger, such as an antidepressant to relax the bladder or an antihistamine to reduce the activity in the bladder wall. The side effects from antidepressants can include dry mouth, weight gain, heart problems and, in some instances, cognitive decline.

One medicine is FDA approved for treating interstitial cystitis. Pentosan polysulfate might help relieve pain and other symptoms by restoring the bladder wall's coating. The prescription drug can take up to six months to improve symptoms. Side effects can include sleep problems, moodiness, hair loss and stomach pain.

Treating the bladder. In some instances, treatment of painful bladder syndrome might go straight to the source of the problem — the bladder.

A doctor might perform something known as bladder instillation. During it, they thread a catheter into the bladder and wash the inside of the bladder with a medication that can reduce irritation and inflammation. Treatment takes about 15 minutes and is usually every week or so for about two months. Many people see an improvement after the third or fourth treatment session.

In the US, anywhere from three to eight million women have painful bladder syndrome.

In US 3 to 8 million women have painful bladder syndrome

Another way to treat the bladder is to stretch it. During this treatment, your doctor will expand your bladder by filling it with liquid. While it can help ease the pain in some people, the treatment can also make pain worse several days later.

Undergoing bladder surgery. Invasive surgery is rarely used to treat painful bladder syndrome for two reasons. One, it may not improve your condition. Two, it can cause complications, such as infections, kidney damage and perforation. Surgical options can include augmenting the bladder, removing ulcers and in extreme cases, removing the bladder.

Because treating interstitial cystitis is a lifelong challenge for patients, many have sought alternative treatments that can ease their discomfort, such as medical marijuana.

Medical Cannabis for Interstitial Cystitis

Few studies are available that examine the role medical marijuana can play in helping individuals with interstitial cystitis. It's thought that cannabis can help ease the pain in people with the condition though.

Marijuana helps trigger the activation of the CB2 receptors which are seemingly the primary inhabitants of inflammation. Marijuana may also reduce swelling and bladder weight. When considering that phytocannabinoids like tetrahydrocannabinol (THC) and cannabidiol (CBD) are known to activate the CB2 receptors, one can conclude that medical marijuana could be of benefit in the treatment of chronic bladder diseases.

One study, published in 2014 in the "Journal of Urology," examined the effect of a cannabinoid receptor two on a group of mice with established cystitis. The mice were treated with GP1a, a cannabinoid receptor two agonist. The researchers concluded that GP1a could be potentially therapeutic for the treatment of interstitial cystitis because the mice had a decrease in inflammation and their cystitis after treatment.

An earlier study, from 2003, examined the effect of cannabis on interstitial cystitis in a woman. The 31-year-old woman was given two synthetic cannabinoid medications, nabilone and dronabinol. After the nabilone had caused unpleasant side effects, such as hallucinations, the patient switched to the dronabinol. The dronabinol helped to ease her pain and didn't produce the same side effects.

Strains that may help alleviate your interstitial cystitis include:

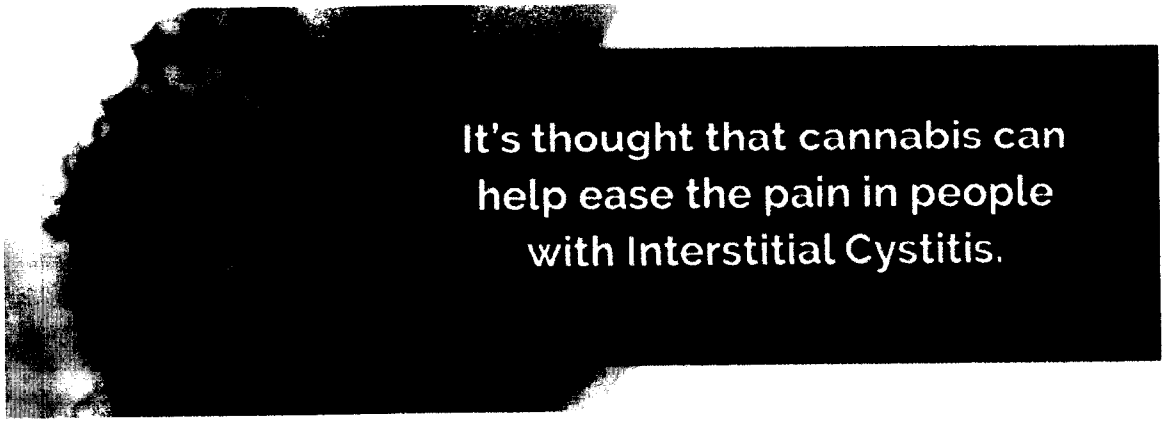
Cannatonic

Critical Mass

Snowcap

LA Confidential

Side effects from medical cannabis use are minimal and include nausea or headaches, both of which are minor and temporary. Medical marijuana could help ease the pain and inflammation people with interstitial cystitis experience. If you are one of the millions of people in the US who is dealing with the pain and other symptoms of painful bladder syndrome, medical cannabis is worth looking into.



Find a Medical Marijuana Doctor Near You

Medical cannabis can also be prescribed to treat chronic pain or other bladder symptoms, which interstitial cystitis may qualify as, depending on your severity of painful bladder syndrome. You don't have to live with the pain or feeling that you have to go all the time. Search our site to find a compassionate and educated medical marijuana doctor in your state.

Resources:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4708563/#r3

https://www.womenshealth.gov/a-z-topics/bladder-pain

https://www.nature.com/nrurol/journal/v4/n9/pdf/ncpuro0874.pdf?origin=ppub

https://www.ic-network.com/interstitial-cystitis-symptoms/

MARIJUANA DOCTORS

A NEW KIND OF HEALTHCARE

https://www.marijuanadoctors.com/conditions/interstitial-cystitis/

SECTION H

Indian J Urol. 2010 Jan-Mar; 26(1): 26–35.
doi: [10.4103/0970-1591.60440]
PMCID: PMC2878434
PMID: 20535281

Functional role of cannabinoid receptors in urinary bladder

Pradeep Tyagi, Vikas Tyagi, Naoki Yoshimura,[1] and Michael Chancellor

Departments of Urology, William Beaumont Hospital, MI 48073
[1]University of Pittsburgh, PA 15213, USA
For correspondence: Dr. Pradeep Tyagi, Department of Urology, William Beaumont Hospital, MI 48073. E-mail: pradeep.tyagi@beaumont.edu

Abstract

Cannabinoids, the active components of Cannabis sativa (maijuana), and their derivatives produce a wide spectrum of central and peripheral effects, some of which may have clinical applications. The discovery of specific cannabinoid receptors and a family of endogenous ligands of those receptors has attracted much attention to the general cannabinoid pharmacology. In recent years, studies on the functional role of cannabinoid receptors in bladder have been motivated by the therapeutic effects of cannabinoids on voiding dysfunction in multiple sclerosis patients. In this review, we shall summarize the literature on the expression of cannabinoid receptors in urinary bladder and the peripheral influence of locally and systemically administered cannabinoids in the bladder. The ongoing search for cannabinoid-based therapeutic strategies devoid of psychotropic effects can be complemented with local delivery into bladder by the intravesical route. A greater understanding of the role of the peripheral CB_1 and CB_2 receptor system in lower urinary tract is necessary to allow the development of new treatment for pelvic disorders.

Keywords: Bladder, cannabinoids, irritation, protein-coupled receptor, receptor expression

PHARMACOLOGY OF PHYTOCANNABINOIDS GUIDING RECEPTOR DISCOVERY

For many centuries, phytocannabinoids obtained from cannabis plant (mar?uana) have been consumed for their analgesic, anxiolytic, antiemetic and antispasmodic properties especially in the oriental culture.[1] However, therapeutic utility of cannabis plant or its products in the evidence based medicine continues to remain a lightning rod for controversy on social, legal and medical fronts. Pharmacological and chemical investigation on cannabis plant found more than 50 compounds, of which the main psychoactive principal was identified as Δ^9-tetrahydrocannabinol, (Δ^9-THC) [Figure 1] apart from two other bioactive cannabinoids, cannabidiol (CBD) and cannabinol (CBN).[2] Further studies dealing with the search of biological targets for the Δ^9-THC led to the cloning and identification of two CB_1 and CB_2 receptors belonging to the heptahelical G protein-coupled receptor (GPCR) superfamily.[3]

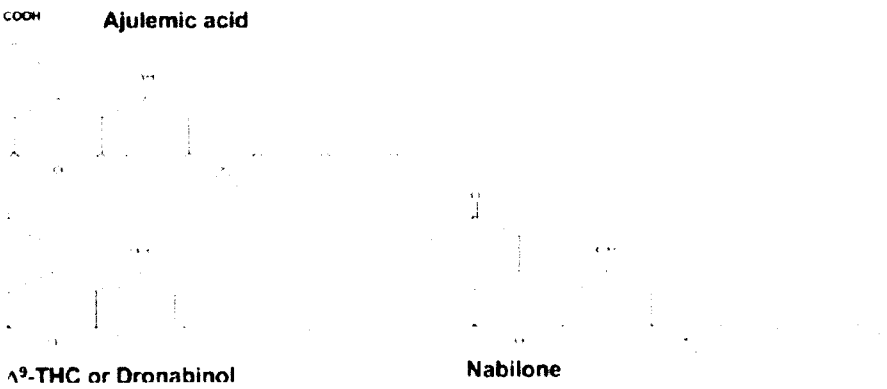


Figure 1

Chemical Structures of classical synthetic cannabinoids, with a basic tricyclic dibenzopyran structure, which is also shared by the psychoactive principle (-) Δ^9-THC from cannabis. Synthetic analog of (-) Δ^9-THC is the drug known as dronabinol. Two other drugs nabilone and ajulemic acid are synthetic derivatives of a phase I metabolite of (-) Δ^9-THC. They differ from (-) Δ^9-THC in terms of the extra methyl groups and a ketonic or carboxyl group in place of methyl group at the ninth carbon position

The receptor CB_1 is the most abundant of all receptor types in the brain and other CNS regions involved with pain transmission and modulation, specifically in the spinal dorsal horn and periaqueductal gray.[4,5] CB_1 receptors are also located peripherally in both neuron and non-neuronal tissue, while CB_2 receptors are mainly found in immune cells and brain glial cells.[4,6] These receptors have been found to have many physiological and patho-physiological functions, including mood alteration, control of feeding and appetite, motor and co-ordination activities, analgesia, immune modulation and gut motility.[1]

Given the ubiquitous expression of CB_1 and CB_2 receptors, cannabinoids have been shown to produce wide spectrum of effects including induction of proliferation, growth arrest, or apoptosis in a number of cells, including neurons, lymphocytes, and various neural and non neural cells.[7] Alterations in the reproductive system produced by cannabis motivated the studies leading up to the discovery [8] CB_1 receptors have been detected in the testis, prostate and vas deferens.[9–11] In addition, expression of functional CB_1 receptors on sperm and presence of the archetypal endocannabinoid anandamide in reproductive secretions have also been detected [12] It can be said therefore that discovery of cannabinoid receptors in bladder lagged behind the discovery of these metabotropic receptors in other organs lining the genitourinary tract.

CB_1 and CB_2 receptors and signaling

Cannabinoids elicit their well known diverse effects by activating numerous signaling pathways. CB_1 and CB_2 receptors exhibit 48% amino acid sequence identity and both of them are negatively coupled to adenylase cyclase to inhibit cyclic AMP and mitogen-activated protein kinase [Figure 2].[13] In addition, CB_1 receptors couple via pertussis toxin -sensitive $G_{ig/o}$ proteins to inhibit L-, N-, and P/Q-type calcium channels and activate potassium channels.[14] The endogenous ligands for these receptors are called as endocannabinoids (ECB), which are namely anandamide, 2-arachidonoylglycerol, virodhamine, and noladin ether (2-arachidonylglyceryl ether).

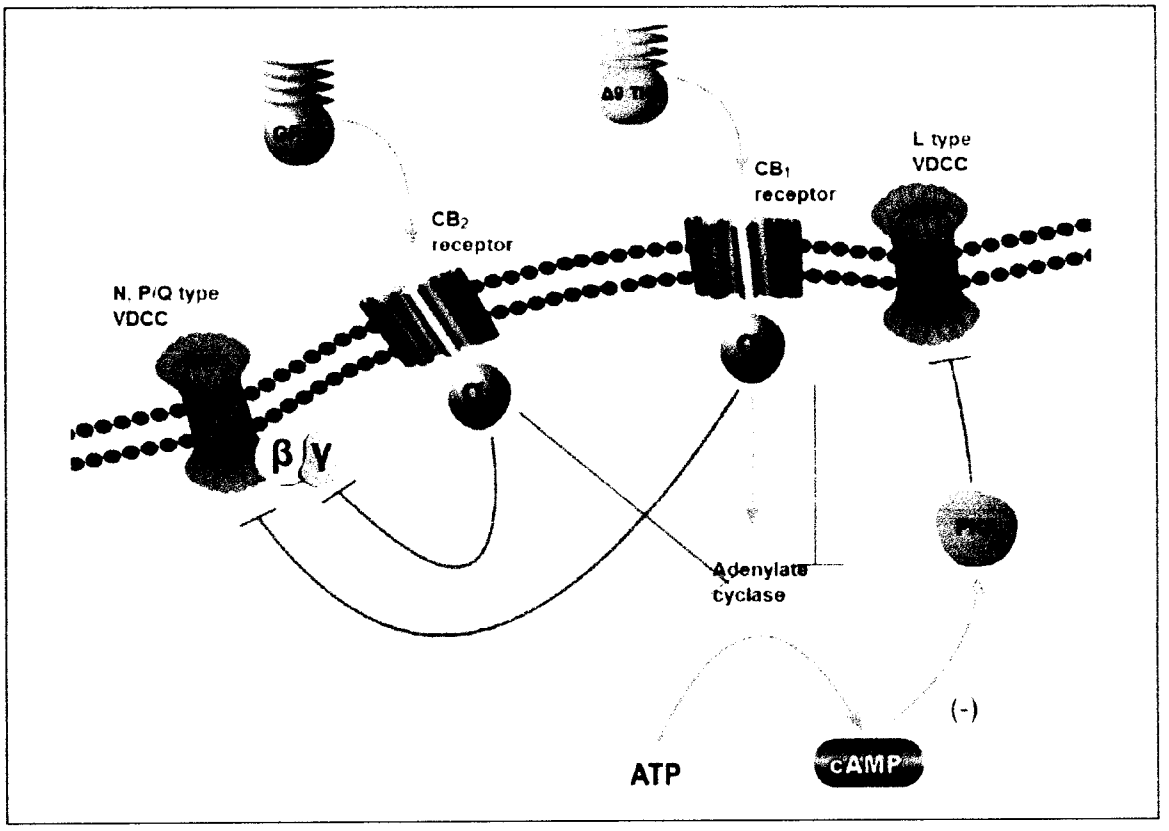


Figure 2

The metabotropic CB_1 receptor exhibit 48% amino acid sequence identity with CB_2 receptors and both of them are negatively coupled to adenylyl cyclase to inhibit cyclic AMP that indirectly inhibit L-type Ca^{2+} channel. CB_1 receptors couple via pertussis toxin -sensitive Gi/o proteins to inhibit N^-, and P/Qtype Ca^{2+} channels and K−channels. The inhibitory effects of cannabinoids on Ca^{2-} channels in nerve terminals are similar to other endogenous anti-nociceptive agents such as opioids.[14] GP1a (N-(Piperidin-1-yl)-1-(2,4-dichlorophenyl)-1,4- dihydro-6-methylindeno[1,2-c]pyrazole-3-carboxamide) is a highly selective CB_2 agonist with Ki values of 0.037 and 363 nM for CB_2 and CB_1, respectively. The Δ^9-THC mimics the action of endocannabinoids and acts non-selectively on both CB_2 and CB_1 receptors

These ECBs structurally resemble eicosanoids as they are derived from arachidonic acid; a polyunsaturated fatty acid that serves as precursor for a plethora of other bioactive metabolites such as prostaglandins, thromboxanes, leukotrienes etc. In animal studies, the pharmacological action of Δ^9-THC was mimicked by endocannabinoids.[15] Most of the ECBs derived from arachidonic acid act in a receptor-dependent manner and have the ability to act as retrograde inhibitors of synaptic neurotransmission in GABAergic and glutamatergic synapses, as well as modulators of post-synaptic transmission, involving norepinephrine and dopamine.[14] These ECBs are transported into cells by a specifi c uptake system and degraded by two well-characterized enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase.[16] The ECBs are synthesized on demand and have short-lived effects due to effective metabolic pathways.[17]

ECBs, like anandamide, are different from classical neurotransmitters in the sense that they are not stored in and released from nerve vesicles, but rather released on demand from the nerve cell membrane during inflammation.[18] The anandamide released from post-synaptic cells could mediate its inhibitory effect by acting on presynaptic CB_1 receptor. The inhibition of transmitter release from nociceptive afferents by anandamide may indicate a mechanism for modulating the spinal nociceptive pathways.[19] The growing knowledge of the broad physiological roles of the ECBs including biosynthesis and catabolism is providing insight into potentially novel therapeutic targets.[20]

Expression of cannabinoid receptors in bladder

The results of a recently completed large randomized, controlled, multicenter clinical trial known as the cannabinoids in multiple sclerosis study (CAMS) sparked the interest in studying the expression of cannabinoid receptors in resident bladder tissue of urothelium and detrusor.[21] The multi-center CAMS study randomized 630 patients to receive either oral administration of cannabis extract, Δ^9-THC or a matching placebo. Patients completed incontinence diaries throughout the study. Significant reduction in urge incontinence episodes and improvement in bladder control from baseline were noted at the end of the study with the use of cannabis extract (38%) or Δ^9-THC (33% reduction).[21] The small increase in efficacy of cannabis extract over pure Δ^9-THC seems to suggest that ingredients other than Δ^9-THC in cannabis extract such as CBD and CBN may antagonize some of the undesirable effects of Δ^9-THC and contribute positively to bladder symptoms.[22] The placebo arm of the trial only showed 18% decrease in incontinent episodes relative to baseline to further suggest a distinct clinical effect of cannabinoids on bladder symptoms.

Cannabinoid receptors in rodent bladder

In earlier studies, the presence of CB_1 receptors has been indirectly demonstrated in the rodent bladder using specific [23] Results from an isolated bladder strip study suggested that these receptors are located in the prejunctional neuron. Further, systemic administration of CB agonist and antagonists in spinal cord injured rats with detrusor overactivity demonstrated the role of a tonically active ECB system in pathological voiding.[24]

Previously, the expression of muscarinic, neurokinin and beta 3 adrenoceptors in bladder have been successfully demonstrated using molecular and pharmacological techniques.[25] Literature accounts on the expression of CB_1 and CB_2 receptors in different organs have relied on differentapproaches, such as autoradiography, in situ hybridization of receptor messenger RNA[26] or functional assays.[27] A recent study determined the localization of CB_1 and CB_2 receptors in rat bladder by immunohistochemistry and a functional assay.[28]

Hayn *et al.*, positively identified the expression of CB_1 receptors in rat bladder by the immunoreactivity of CB_1 bladder comparable to that in cerebellum. Similarly, the presence of immunoreactivity for CB_2 in spleen was used as positive control for the positive localization of CB_2 receptors in bladder by the same antibody.[28] The known ability of peripheral cannabinoid receptors to modulate afferent transmission by modulating the stimulus-evoked neuropeptide release was used to design a functional assay.[29] Studies show that quantification of released calcitonin gene related peptide (CGRP) can be a suitable marker for measuring afferent neuronal activity in rat bladder.[30] The bladder of adult female rats receives approximately 16,000 axons (i.e., is the target of that many ganglion neurons) of which at least half are sensory.[31] Virtually all bladder sensory fibers that originate from dorsal root ganglia are immunoreactive for capsaicin receptor transient receptor potential vanilloid (TRPV1) and CGRP.[32] The role of TRPV1 in voiding has been well established[33] but the potential role of CB_1 and CB_2 receptors in micturition and pain originating from bladder is yet to be completely investigated.

The presumed expression of CB receptors on capsaicin- sensitive sensory nerves,[34] being coupled to inhibition of neurotransmitter release, was demonstrated in an isolated rat bladder model. Application of the mixed CB_1/CB_2 receptor agonist, ajulemic acid (AJA) inhibited the evoked release of CGRP from afferent nerve terminals in isolated rat bladder. Sensory afferent axons in the bladder are the only structures in the bladder that contain high levels of CGRP released upon nerve depolarization or chemical stimulation by capsaicin [Figure 3].[35] Pharmacological specificity of the inhibitory effect of AJA on sensory neuronal activity originating from the bladder through CB_1 and CB_2 receptors was demonstrated using selective receptor antagonists.

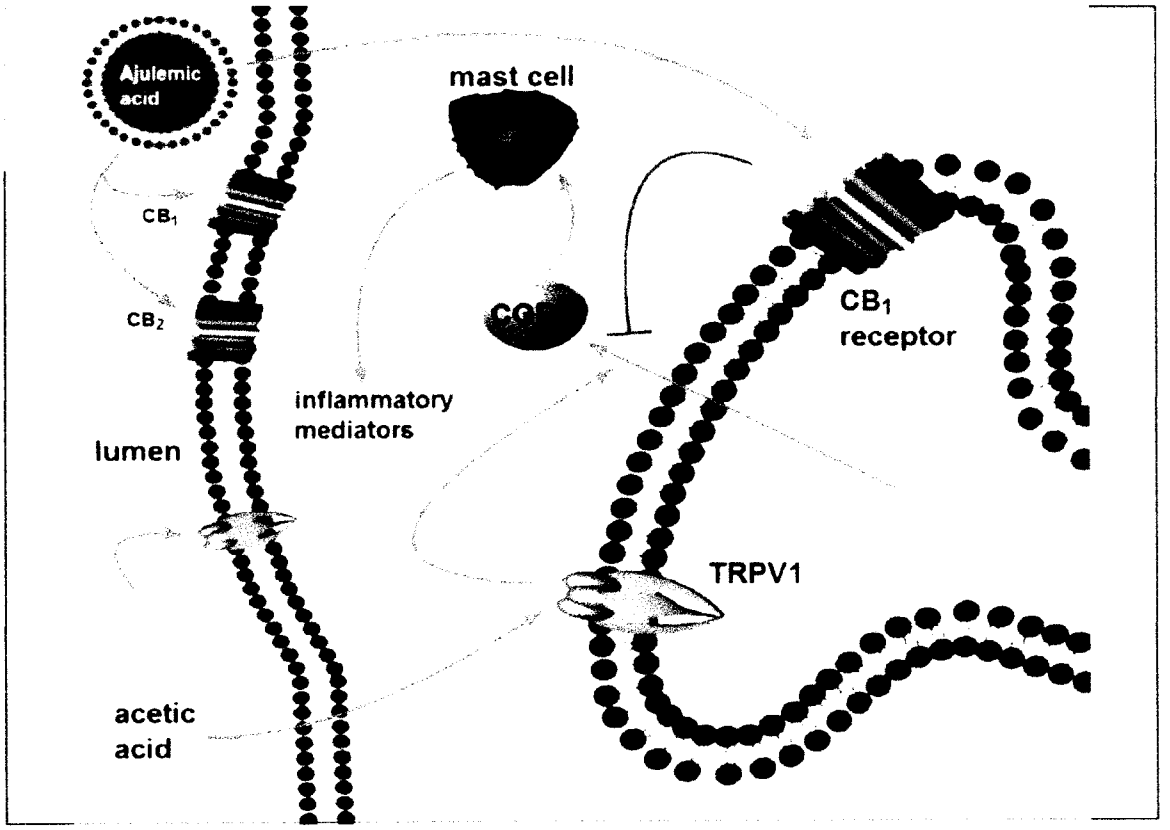


Figure 3

Proposed mechanism of locally administered cannabinoid agonist in irritated bladder. Bladder irritated by acetic acid, in the animal model, activates TRPV1 on urothelium and adjoining nerves to release CGRP. Irritation evoked release of CGRP is blocked by mixed CB_1/CB_2 agonist ajulemic acid entrapped into liposome that activates CB_1 and CB_2 receptors on bladder surface and nerves

Cannabinoid receptors in human and primate bladder

Encouraged by expression in rat bladder, the expression of CB_1/CB_2 receptors in bladder obtained from human cadavers was recently investigated using different techniques.[36] Expression of functional CB_1 and CB_2 receptors in human detrusor and urothelium was demonstrated using real-time quantitative polymerase chain reaction QPCR and protein expression using immunohistochemistry and Western blot. QPCR was done using customized CB_1 and CB_2 primers which amplified gene products from the open reading frame of single exon human CB_1 and CB_2 genes [Figure 4]. Expression of CB_1 and CB_2 receptors was demonstrated in the detrusor and urothelium, with the expression for both receptors approximately two fold higher in the urothelium than in the detrusor ($P < 0.05$). The mRNA expression of the CB_1 receptor was significantly higher than that of the CB_2 receptor in both tissue types ($P < 0.05$). Immunofluorescence results show that expression of CB_1 and CB_2 is specific to bladder and not contributed by infiltrating cells.

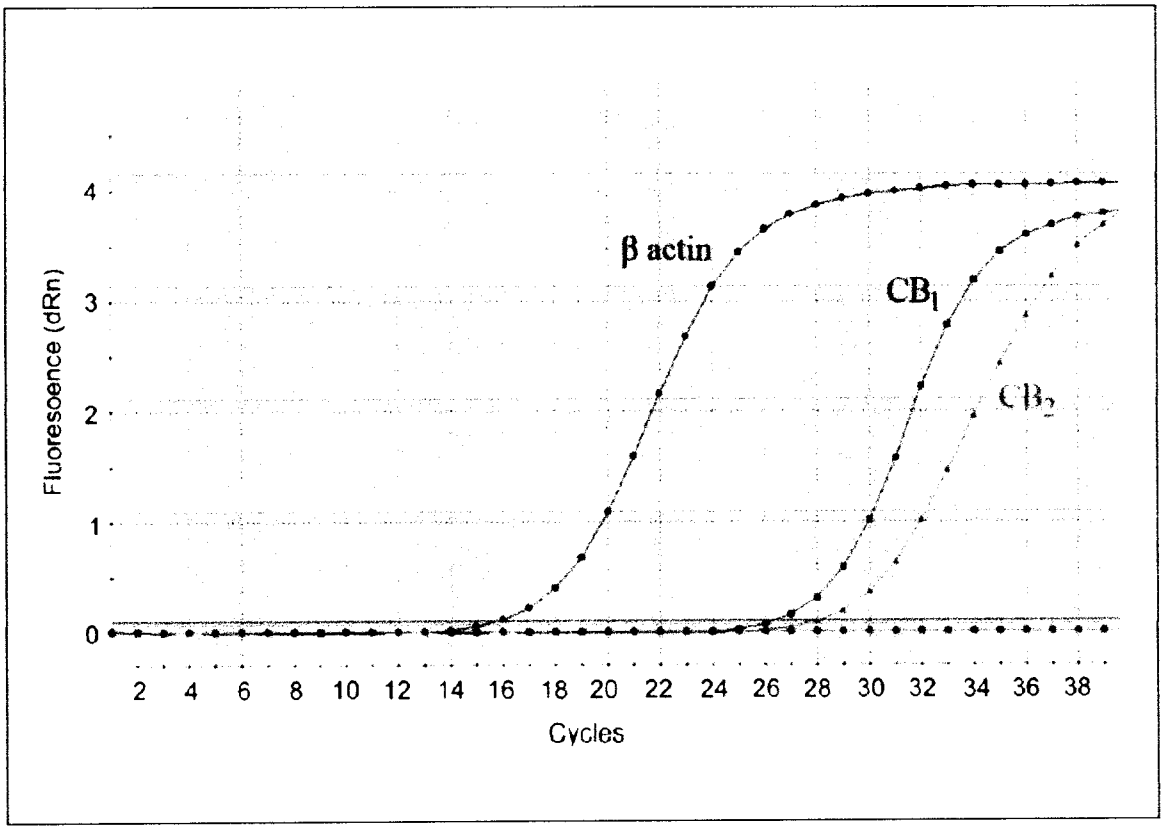


Figure 4

Amplification plot from a typical real time PCR experiment to detect expression of CB receptors in human urothelium relative to housekeeping gene β- actin. The urothelium specimens were obtained from organ donors. M3000P instrument measures the fl uorescence of dsDNA intercalating dye SYBR Green twice in each PCR cycle. This infl ection point is called the cycle number (Ct) at which fl uorescent signal generated passes over threshold baseline. The Ct value was determined for each specimen to measure receptor expression

Expression of CB_1 and CB_2 receptors detected at the mRNA level by QPCR was confirmed at the protein level by immunoreactivity and Western blot analysis. Activation of CB_1 and CB_2 receptors attenuated the electrically evoked contraction of detrusor strips. These inhibitory effects of cannabinoid receptor agonists were suggested to be attributable to prejunctional CB_1 receptors that decrease contractile transmitter release.[36] It is well accepted that endogenous cannabinoids and CB_1 receptors are involved in the regulation of smooth muscle contractility, through a mechanism mainly related to reduction of acetylcholine release from cholinergic nerve endings.[37] The modulatory action of the cannabinoid agents on the non-adrenergic non-cholinergic neurotransmission operating in the bladder is yet to be studied.

Using similar techniques of Western blot and immuno histochemistry, similar results on expression of CB_1/CB_2 receptors in human bladder were also reported by Gratzke et al., 2009.[34] Apart from humans, this group also investigated the distribution of CB_1 and CB_2 receptors in the rat and monkey species. Higher expression of CB_2 receptor, but not CB_1, was noted in the urothelium relative to detrusor. Expression of CB_2 receptors in urothelium was localized to the sensory and cholinergic nerves in the bladder obtained from humans as well as other species of rats and rhesus monkeys. Co-localization of CB_2 receptor antibody stain with the stain for CGRP, TRPV1, and vesicular acetylcholine transporter (VAChT) protein specific for cholinergic nerves further confirmed the expression of CB_2 receptor by bladder afferents. Nerve fibers containing CB_2 and VAChT were also located in the detrusor. The co-expression of VAChT and CB receptor, and effects by CP55940, on nerve mediated contractions suggest a CB_2 receptor mediated modulatory effect on cholinergic nerve activity in bladder.[34]

The localization of CB_2 receptor with nerves argues for a role of CB_2 in bladder afferent signals which can be best demonstrated by cystometric studies. These *in vivo* effects of CP55940 (CB_1/CB_2 receptor agonist) on urodynamic parameters. MI and TP may be considered parameters that indirectly represent sensory functions during cystometry. Lack of a direct effect of CB_1/CB_2 agonist CP55,940 and the nonselective agonist anandamide on carbachol induced contractions indicated the absence of direct CB mediated functions of isolated detrusor smooth muscle.[34]

Recent studies demonstrated the modulatory effects of CB_1/CB_2 agonists on nerve induced contractions in detrusor preparations obtained from most mammalian species.[23,28,34,36] In contrast, according to a previous report CB_1/CB_2 agonists fail to show any effect on the electrically evoked contractions of bladder preparations isolated from dogs, pigs, cynomolgus monkeys and humans.[27] However, the same report was able to reproduce the inhibition of neuronally evoked contractions in isolated rat and mouse bladders by CB_1/CB_2 agonists. Definitive characterization of CB receptor in tissues depends on the availability of selective agonists and antagonists and difference in the selectivity of agents used in different studies may explain the different results. In addition, there may be differences in the age and associated pathology of organ donors who donated the bladder for the muscle strip studies. Previously published studies in the spinal cord injured rat revealed that peripheral CB receptors are involved in detrusor over activity.[24] The inhibitory effect of CB agonists on detrusor pressure observed by Blyweert *et al.*, further corroborates the inhibitory effects of CB agonists on isolated human detrusor strips in organ bath.

Unique pharmacology of anandamide in bladder

One of the interesting aspects of study reported by Gratzke et al., 2009.[34] is the difference in the pharmacology of a synthetic CB_1/CB_2 receptor agonist and ECBs such as anandamide. The difference was best illustrated by anandamide led 26% increase in the TP and 19% decrease of MI in cystometric studies relative to increase of 124% (TP) and 46% (MI) by CP55940 ($P < 0.05$ and < 0.01, respectively). Furthermore, nerve mediated contractions were enhanced by anandamide and decreased by CP55940 ($P < 0.05$).[34]

The unique pharmacology of anandamide have been explained in the past by its ability to elicit effects by acting on both via G protein-coupled CB_1 receptors and transient receptor potential (TRP) channels (chiefly TRPV1 receptors). The pre-synaptic inhibitory effect of anandamide is evident at low concentration and at higher concentrations the activation of TRPV1 counters the effect on CB_1/CB_2 receptors.[19] The activation of TRPV1 channels can lead to desensitization and loss of pre-synaptic inhibition observed in various studies.[28]

Anandamide has also been noted to aggravate cyclo phosphamide induced cystitis in rodents through its activation of TRPV1 ion channels and thereby causing detrusor overactivity and hyperalgesia.[38] In contrast, anandamide have been also shown to mediate attenuation of detrusor overactivity induced by nerve growth factor instillation in bladder.[39] The attenuation of detrusor overactivity by anandamide unmasked the role of CB_2 receptors expressed in bladder in controlling the pain initiated locally in bladder. [40] Concentration and time of exposure may be critical in determining which of these opposite effects of anandamide ultimately prevails.

Most TRPV1 receptor-expressing cells are also known to co-express the CB_1 receptors as well. [41] The close proximity of CB_1 and TRPV1 may facilitate the dual, concentration- dependent effect of anandamide observed in different studies.[38] Dual dose dependent effect of cannabinoids have also been previously noted in relation to immune system where low doses of cannabinoids may enhance cell proliferation and high doses of cannabinoids may induce growth arrest or apoptosis.[7] The ability of same ligands to activate both metabotropic CB_1/CB_2 receptors and ionotropic TRPV1 receptors suggest possible interactions between the two signaling systems.[38] Stimulation of CB_1 and desensitization of TRPV1 could be a strategy to protect against inflammation in bladder.

To further confound the pharmacology of anandamide in bladder, the responses to anandamide as reported by Gratzke et al., (2009) were attenuated but not abolished after desensitization by capsaicin. Further, anandamide response were partially attenuated by an prostaglandin receptor EP1 antagonist and almost abolished by indomethacin, a cyclooxygenase inhibitor.[34] Neither the CB_1 antagonist AM251 nor the CB_2 antagonist AM630 had any effect on the response to anandamide, to suggest possible role of EP1 receptor.

Cannabinoid receptors fueling drug discovery

The distribution of these CB_1/CB_2 receptors at key sites involved in nociceptive processing is instrumental in the analgesic effects of phytocannabinoids (plant source) or synthetic cannabinoids developed in last 30 years.[13] Synthetic cannabinoids are chemicals having action similar to cannabis on their cognate receptors. Studies have

shown that synthetic and semi-synthetic cannabinoids that lack psychotropic effects are effective against severe pain states refractory to even opioids.[42] The activation of nociceptive sensory neurons leads to nociception. However, CB_1/CB_2 agonists are capable of altering nociceptor activity without producing nociceptive behavior.[13,43] CB_1/CB_2 agonists have been able to suppress the nociceptive transmission and inhibit pain-related behavior in animal models of acute and persistent nociception by their activity at spinal, supraspinal and peripheral sites.[44]

The new drugs based on pharmacology of cannabinoids can be classified into two categories: Direct and indirect agonists. Direct agonists selectively activate either CB_1 or CB_2 receptor. CB_2 receptor agonists are not associated with the adverse side-effects of CB_1-selective agonists and therefore may provide an alternative analgesic target.[45] Indirect agonists work on the principle that metabolic degradation is the rate-limiting step in the therapeutic effects of ECB and the efficacy can be magnified by blocking the ECB metabolism either through cellular reuptake or enzymatic hydrolysis. Such compounds can theoretically act selectively on tissues with ongoing synthesis and degradation of ECB, thus producing fewer unwanted effects than direct agonists. By acting through up-regulation of ECB, another advantage of indirect agonists is that they may produce beneficial actions through actions on other receptors as well such as CB_1, CB_2 or TRPV1 receptors.

The drug discovery of synthetic cannabinoids is also fuelled by the notorious toxicity of cannabis or phytocannabinoids. Some synthetic cannabinoids with limited side effects and abuse liability have already been approved for clinical use in Canada. Nabilone and dronabinol are classical synthetic cannabinoids, with chemical structure based on Δ^9-THC, approved for treating severe nausea and vomiting associated with cancer chemotherapy[15] [Figure 1]. A plethora of preclinical reports on analgesic effect of cannabinoids[44] has motivated the off-label use of nabilone and dronabinol in chronic pain management in a few clinical trials, case reports or case series.[46,47] To avoid the possible risk of abuse of these drugs by patients, experts in the field have put guidelines for clinical use of these agents.[48]

These peripherally acting agents could evoke profound pain relief in animal models as well as in a few small clinical studies, but the underlying mechanism and signaling pathways mediating these effects are yet to be completely understood.[44] A major challenge facing the biomedical research community is the identifi cation of compounds that are safe and effective in treating pain, particularly chronic pain such as painful bladder syndrome (PBS) or interstitial cystitis (IC). Various methods, medicines, and devices are available to IC/PBS patients to reduce their pain and symptoms but many of these conventional therapies have significant limitations.[30] Based on the known effects of cannabinoids, in preclinical and clinical studies, it can expected that peripherally acting cannabinoid receptor agonists can modulate bladder sensory pathways by acting on nociceptive pathways originating from bladder.

Route of administration affects bioavailability and toxicity of cannabinoids

As described in earlier sections here, experimental factors such as drug concentration, timing of drug delivery and location of drug administration can influence the therapeutic and adverse response of cannabinoids. The acute adverse effects reported with the consumption of cannabis by smoking or by oral route includes increased food intake, tachycardia, orthostatic hypotension, pulmonary irritation, impaired motor coordination, cognitive impairment, anxiety, paranoia, and psychosis.[49] In addition, the bioavailability of CBs from the oral route is uncertain as illustrated by unpredictable pharmacokinetics of (Δ^9- THC) after oral administration.[50] This has generated a lot of interest in alternative routes for delivering cannabinoids. It was recently shown that topical application of 30 μg of Δ^9-THC reduced allergic inflammation in mouse ear model of allergic dermatitis.[51] The activation of cutaneous CBs lead to attenuation of nociceptor excitation, pain and itch perception,[52] and decreased the release of neuropeptides, particularly CGRP, from terminal afferents

It is definitely more logical to develop local CB delivery with predictable bioavailability that rules out central side effects. Route of inhalation is also a distinct possibility for the therapeutic delivery of cannabinoids, as shown by the recent approval of an oromucosal (sublingual) spray standardized for the Δ^9-THC and CBD (1:1 ratio) in Canada, as adjunctive treatment for neuropathic pain of multiple sclerosis patients. (53) The rationale for the combination of CBD and Δ^9-THC is that CBD can antagonize some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic properties.[22] This is because Δ^9-THC can activate cannabinoid CB_1 and CB_2 receptors but CBD possesses no, or very weak affinity for these receptors. The spray is administered with a device equipped with an electronic tool to facilitate accurate dosing.

In an open-label pilot study on advanced MS patients, daily inhalation from the oromucosal spray (Sativex®) for 16 weeks improved the refractory lower urinary tract symptoms of these patients.[54] The spray also reduced neuropathic pain, spasticity, muscle spasms and sleep disturbances. Most common adverse events reported were dizziness, sleepiness, fatigue, feeling of intoxication and a bad taste.[55]

Local administration of cannabinoids inside bladder

Studies done on other tissues such as ear and paw have already shown that locally administered CB agonists act on peripheral receptors and attenuate the pain behavior induced by localized tissue damage or irritation.[40,51,56] Local administration of anandamide via intraplantar injection suppressed neuropathic pain in rats.[57] These observations lend support to the concept that CB receptors in the periphery participate in the intrinsic control of pain initiation and locally generated endocannabinoid such as anandamide and may mediate this effect.[40] Recent studies indicate a possible antinociceptive synergy from cannabinoid action on peripheral receptors with that on spinal sites.[56]

Intravesical drug delivery offers an attractive opportunity to focus the potency of potentially toxic drugs only on site of action as demonstrated by clinical management of PBS/ IC with intravesical DMSO.[58] In recent years, considerable effort has been expended into developing formulation suitable for intravesical administration of antimuscarinics, capsaicin, resiniferatoxin and local anesthetics.[58,59] The success of delivering antimuscarinics, capsaicin and botulinum toxin into the bladder,[60,61] encouraged intravesical delivery of cannabinoids using liposomes.[62–64] Phytocannabinoids and synthetic cannabinoids are generally not soluble in water and formulation of these agents into liposomes can overcome the aqueous solubility of these agents.[62–64]

Guided by the results of CGRP experiments in isolated bladder, selective CB_1/CB_2 agonist AJA was loaded inside the liposomes and instilled into bladder to unmask the role of peripheral cannabinoid receptors in bladder. AJA is a synthetic derivative of nabilone that is currently approved in Canada for chemotherapy induced emesis. AJA has been efficacious in animal models of chronic pain by activation of the CB_1 receptor with a superior therapeutic index compared to other CB compounds.[65] AJA binds to human CB_1/CB_2 receptors *in vitro*, with high affinity at human CB_1 (Ki 6nM) as well as h CB_2 (Ki 56 nM) receptors.[65] In a previous study, by our group, on systemic administration of AJA, the role of CB_1/CB_2 receptors in micturition was more evident in the irritated condition of bladder than in normal condition.[66]

Female rats were pretreated with AJA (0.5 ml of liposomal for 30 min) prior to irritation with acetic acid [Figure 5]. First, baseline cystometric parameters were derived through transurethral open cystometry (CMG) under urethane anesthesia (dose1.0 g/kg body weight), with saline infusion at the rate of 0.04 ml/min. Bladder irritation was induced by infusing acetic acid (0.125% v/v) in saline into the bladder.[64] As shown in the CMG tracing of Figure 5, infusion of acetic acid in bladder reduces the micturition interval MI of rats instilled with saline previously, because acetic acid irritates the afferents in the bladder to induce hyperexcitability.

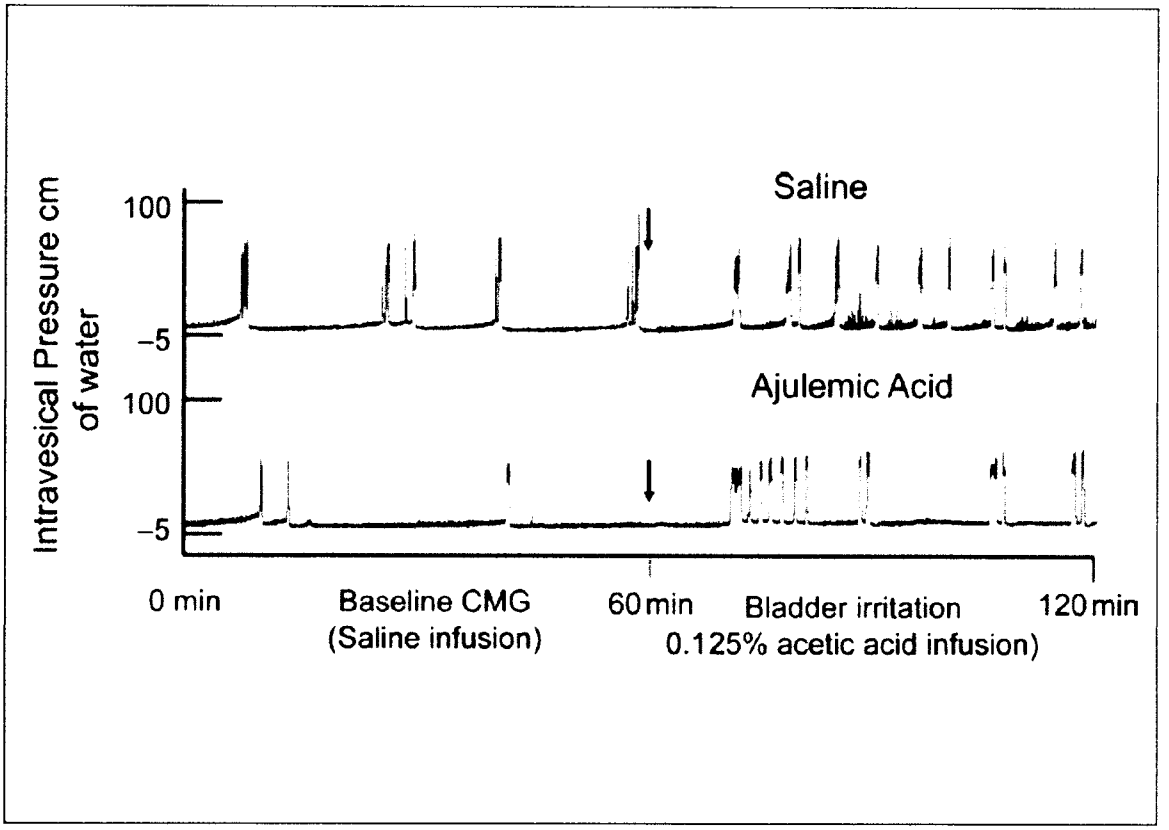


Figure 5

Cystometric effect of mixed CB_1/CB_2 receptor agonist, ajulemic acid on bladder irritation induced by infusion of acetic acid (0.125%). Rats were pretreated with either saline or ajulemic acid entrapped in liposomes. Baseline cystometry (CMG) was done under saline infusion prior to bladder irritation induced by acetic acid. Activation of local cannabinoid receptors in the bladder blunted the decrease in micturition interval MI induced by acetic acid. Decrease in MI is evident from reduced time interval between the peaks of cystometrogram of saline treated rat relative to rat treated with ajulemic acid. The urodynamic parameter, MI, indirectly represents sensory functions and reduced MI is an integrated response of irritated bladder

As revealed by cystometric parameters, local activation of cannabinoid system in bladder by intravesical administration can blunt the pain initiated in the bladder by acid infusion. The therapeutic effect of instilled drugs was assessed by the per cent reduction in MI after infusion of acetic acid. Cystometric data supported the hypothesis that instilled CB_1/CB_2 agonist can buffer the pain signals emerging from bladder following acetic acid infusion. Local action of CB_1 on sub agonist in the bladder may involve action at CB_1 receptors on sub urothelial nerve plexus to reduce afferent excitability induced by acetic acid [Figure 4].

Local action of CB agonist in the bladder may involve action at receptors on peripheral nerves or an indirect modulation of immune cell responses decreasing peripheral nerve excitability [Figure 5]. Similar pharmacological studies in gut have shown that activation of CB_1 receptor inhibits intestinal motility by reducing the acetylcholine release from enteric nerves.[67] Possibility of a similar action of CB_1 agonists in bladder, to explain higher MI, cannot be ruled out. Locally administered cannabinoids can also inhibit NF-kB activation to suppress hyperalgesia. [68] These findings support the notion that cannabinoid system participates in buffering the pain signals emerging from the peripheral sites.

The beneficial effects of direct agonists of CB_2 receptor instilled locally in the bladder can also be explained by action on bladder mast cells that make important contribution to the visceral hyperalgesia initiated by local irritation. [69] Expression of CB_2 receptor have previously been documented in mast cells and local injection of CB_2 receptor agonist JWH-133 provided analgesic effect in models of acute, inflammatory and neuropathic pain.[70] Release of

inflammatory mediators from inflamed tissue is purported to be suppressed by activation of CB_2 on non neuronal cells.[69] Alternative mechanisms that may explain these observations include attenuation of NGF-induced mast cell degranulation and neutrophil accumulation in bladder cannot be ruled out.

The property of CB_1 agonists to evoke desensitization without nociception has unrealized potential. Studies have indicated that opioids and cannabinoids act at different systemic or peripheral sites to produce antinociception through independent mechanisms. No evidence of any cross-tolerance between the antinociceptive effects of opioids and cannabinoids was seen in animals.[44] It is well recognized that the opioids, a powerful class of analgesics which have been long utilized in clinical pain management, are not effective against neuropathic pain and are amenable to tolerance development.[71] Chronic pain may induce changes in gene expression at the site of inflammation that makes the pain more responsive to local treatment, just as local administration of opioids could only evoke dose-dependent naloxone-reversible analgesia in patients suffering from chronic pain but not from acute inflammatory pain.[72]

Studies on intravesical administration of CB agonists demonstrate that it is ideally suited to best maximize the beneficial effects of cannabinoid agents and avoid the possibility of dysphoric and psychotropic side effects. The studies demonstrating the presence of CB_1 and CB_2 receptor subtypes in the human bladder may open up the possibility of deriving therapeutic benefit in patients with IC/PBS by activating these receptors. Given their role in pain transmission, we surmise that CB_1 and CB_2 receptors are expressed at higher levels in the bladder of patients with IC/ PBS. Future studies using bladder tissue from human subjects with IC/PBS could be performed to test this hypothesis and further validate the use of CB agents for genitourinary pain. CB based drugs acting through novel therapeutic target and mechanism can be a new approach for managing pain associated with IC/PBS.

Knockout mice of cannabinoids receptors

It can be a challenge to determine the *in vivo* mechanism of CB agonists administered systemically or intravesically[73]given the ability of CB ligands to activate other receptors, namely TRPV1, at varying concentrations. This can also explain the difficulty faced by researchers engaged in investigating the role of CB_1 and CB_2 receptors using pharmacological antagonists and agonists. For example, SR-141716, a CB_1 receptor antagonist, can also show agonist property because of its other effects.[74] Therefore, the use of a genetic approach has gained favor among scientists to complement the pharmacological analysis of the cannabinoid system, and mice with targeted deletions in the cannabinoid receptor genes have been generated to study role of of the endocannabinoid system in addiction research.[75] The pharmacological specificity of CB_1/CB_2 agents administered systemically or intravesically can be easily determined by comparing results in knockout mice with wild type littermates. The development of transgenic $CB_1^{-/-}$ and $CB_2^{-/-}$ receptor knockout mice using homologous recombination has opened up the opportunity to study the role of the CB_1 and CB_2 receptor system in lower urinary tract. The concerns of global deficit of CB_1 and CB_2 receptors, in the survival of these mice, can be ameliorated using time-dependent and bladder specific deletion of CB_1 and CB_2 receptors.

Take home message and important points

1. Expression of CB_1 and CB_2 receptor in lower urinary tract is relevant to effects of cannabinoids on voiding dysfunction.
2. Expression of CB_1 and CB_2 receptor in bladder demonstrated by molecular, immunofluorescence, detrusor strip contraction and cystometric studies.
3. Pharmacology of ECBs is complex due to their ability to act on multiple receptors.
4. Route of administration have a drastic influence on therapeutic index of of cannabinoids.

CONCLUSIONS

The diverse effects of CB_1 and CB_2 receptor system in lower urinary tract may be novel targets for therapies designed to treat diseases afflicting lower urinary tract. The growth-inhibiting action of cannabinoids acting on these receptors expressed on transformed cells might be useful for the management of malignancy in bladder. Recently published pre-clinical studies have demonstrated that cannabinoids appear to act principally as prejunctional modulators of neurotransmission to affect the micturition process indirectly by affecting the nociceptive responses pathways. It is likely that CB_1 and CB_2 receptors located in periphery such as in bladder participate in the intrinsic

Endocannabinoids

control of initiation of afferent stimulus. Emerging studies show that ECBs are mediators of spinal activity-dependent pain sensitization to create a future role for pharmacological antagonists CB_1 and CB_2 receptors in control of neuropathic pain.

Historically, products from cannabis or its synthetic analogues have faced many obstacles in getting investment from the pharmaceutical industry and acceptance from regulatory agencies. Currently, opioids are the most effective prescription-based analgesics for the painful symptom emanating from the lower urinary tract with limited efficacy and serious toxicity, such as tolerance development, physical dependence, sedation, respiratory depression and gastrointestinal symptoms. The assurance of safety, from ongoing search, of cannabinoid-based therapeutic strategies devoid of psychotropic effects can be complemented with local delivery into bladder by intravesical route. A greater understanding of the role of the peripheral CB_1 and CB_2 receptor system in lower urinary tract is necessary to allow the development of new treatments.

Footnotes

Source of Support: Nil

Conflict of Interest: None declared.

REFERENCES

1. Zuardi AW. History of cannabis as a medicine: A review. Rev Bras Psiquiatr. 2006;28:153–7. [PubMed]

2. Khiabani HZ, Bramness JG, Bjorneboe A, Morland J. Relationship between THC concentration in blood and impairment in apprehended drivers. Traffic Inj Prev. 2006;7:111–6. [PubMed]

3. Felder CC, Dickason-Chesterfield AK, Moore SA. Cannabinoids biology: The search for new therapeutic targets. Mol Interv. 2006;6:149–61. [PubMed]

4. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, et al. International Union of Pharmacology. XXVII. Classification of Cannabinoid Receptors 10.1124/pr.54.2.161. Pharmacol Rev. 2002;54:161–202. [PubMed]

5. Ahluwalia J, Urban L, Bevan S, Capogna M, Nagy I. Cannabinoid 1 receptors are expressed by nerve growth factor- and glial cell-derived neurotrophic factor-responsive primary sensory neurones. Neuroscience. 2002;110:747–53. [PubMed]

6. Pertwee RG, Ross RA. Cannabinoid receptors and their ligands. Prostaglandins Leukot Essent Fatty Acids. 2002;66:101–21. [PubMed]

7. Guzman M, Sanchez C, Galve-Roperh I. Control of the cell survival/ death decision by cannabinoids. J Mol Med. 2001;78:613–25. [PubMed]

8. Kumar AM, Solomon J, Patel V, Kream RM, Drieze JM, Millard WJ. Early exposure to delta 9-tetrahydrocannabinol influences neuroendocrine and reproductive functions in female rats. Neuroendocrinology. 1986;44:260–4. [PubMed]

9. Gye MC, Kang HH, Kang HJ. Expression of cannabinoid receptor 1 in mouse testes. Arch Androl. 2005;51:247–55. [PubMed]

10. Pertwee RG, Ross RA, Craib SJ, Thomas A. Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens. Eur J Pharmacol. 2002;456:99–106. [PubMed]

11. Ruiz-Llorente L, Sanchez MG, Carmena MJ, Prieto JC, Sanchez-Chapado M, Izquierdo A, et al. Expression of functionally active cannabinoid receptor CB_1 in the human prostate gland. Prostate. 2003;54:95–102. [PubMed]

12. Aquila S, Guido C, Laezza C, Santoro A, Pezzi V, Panza S, et al. A new role of anandamide in human sperm: Focus on metabolism. J Cell Physiol. 2009;221:147–53. [PubMed]

13. Cabral GA. Localization of cannabinoid receptors using immune peroxidase methods. Methods Mol Med. 2006;123:41–69. [PubMed]

14. Mackie K, Stella N. Cannabinoid receptors and endocannabinoids: Evidence for new players. Aaps J. 2006;8:E298–306. [PMC free article] [PubMed]

15. Mechoulam R, Hanu L. The cannabinoids: An overview. Therapeutic implications in vomiting and nausea after cancer chemotherapy, in appetite promotion, in multiple sclerosis and in neuroprotection. Pain Res Manag. 2001;6:67–73. [PubMed]

16. Stella N. Cannabinoid signaling in glial cells. Glia. 2004;48:267–77. [PubMed]

17. Hohmann AG, Suplita RL, Bolton NM, Neely MH, Fegley D, Mangieri R, et al. An endocannabinoid mechanism for stress-induced analgesia. Nature. 2005;435:1108–12. [PubMed]

18. D'Argenio G, Valenti M, Scaglione G, Cosenza V, Sorrentini I, Di Marzo V. Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation. Faseb J. 2006;20:568–70. [PubMed]

19. Ahluwalia J, Urban L, Bevan S, Nagy I. Anandamide regulates neuropeptide release from capsaicin-sensitive primary sensory neurons by activating both the cannabinoid 1 receptor and the vanilloid receptor 1 *in vitro*. Eur J Neurosci. 2003;17:2611–8. [PubMed]

20. Massa F, Storr M, Lutz B. The endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract. J Mol Med. 2005;83:944–54. [PubMed]

21. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: A multicentre, randomised placebo-controlled trial (CAMS-LUTS) Int Urogynecol J Pelvic Floor Dysfunct. 2006;17:636–41. [PubMed]

22. Russo E, Guy GW. A tale oftwo cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66:234–46. [PubMed]

23. Pertwee RG, Fernando SR. Evidence for the presence of cannabinoid CB_1 receptors in mouse urinary bladder. Br J Pharmacol. 1996;118:2053–8. [PMC free article] [PubMed]

24. Blyweert W, Van der Aa F, Ost D, Stagnaro M, De Ridder D. Interstitial cells of the bladder: The missing link? BJOG. 2005;111:57. [PubMed]

25. Tyagi P, Thomas CA, Yoshimura N, Chancellor MB. Investigations into the presence of functional Beta1, Beta2 and Beta3-adrenoceptors in urothelium and detrusor of human bladder. Int Braz J Urol. 2009;35:76–83. [PubMed]

26. Onaivi ES. Neuropsychobiological evidence for the functional presence and expression of cannabinoid CB_2 receptors in the brain. Neuropsychobiology. 2006;54:231–46. [PubMed]

27. Martin RS, Luong LA, Welsh NJ, Eglen RM, Martin GR, MacLennan SJ. Effects of cannabinoid receptor agonists on neuronally-evoked contractions of urinary bladder tissues isolated from rat, mouse, pig, dog, monkey and human. Br J Pharmacol. 2000;129:1707–15. [PMC free article] [PubMed]

28. Hayn MH, Ballesteros I, de Miguel F, Coyle CH, Tyagi S, Yoshimura N, et al. Functional and immunohistochemical characterization of CB_1 and CB_2 receptors in rat bladder. Urology. 2008;72:1174–8. [PubMed]

29. Ellington HC, Cotter MA, Cameron NE, Ross RA. The effect of cannabinoids on capsaicin-evoked calcitonin gene-related peptide (CGRP) release from the isolated paw skin of diabetic and non-diabetic rats. Neuropharmacology. 2002;42:966–75. [PubMed]

30. Chancellor MB, Yoshimura N. Treatment of interstitial cystitis. Urology. 2004;63:85–92. [PubMed]

31. Gabella G. Structure of the intramural nerves of the rat bladder. J Neurocytol. 1999;28:615–37. [PubMed]

32. Avelino A, Cruz F. TRPV1 (vanilloid receptor) in the urinary tract: Expression, function and clinical applications. Naunyn Schmiedebergs Arch Pharmacol. 2006;373:287–99. [PubMed]

33. Kalsi V, Fowler CJ. Therapy Insight: Bladder dysfunction associated with multiple sclerosis. Nat Clin Pract Urol. 2005;2:492–501. [PubMed]

34. Gratzke C, Streng T, Park A, Christ G, Stief CG, Hedlund P, et al. Distribution and function of cannabinoid receptors 1 and 2 in the rat, monkey and human bladder. J Urol. 2009;181:1939–48. [PubMed]

35. Su HC, Wharton J, Polak JM, Mulderry PK, Ghatei MA, Gibson SJ, et al. Calcitonin gene-related peptide immunoreactivity in afferent neurons supplying the urinary tract: Combined retrograde tracing and immunohistochemistry. Neuroscience. 1986;18:727–47. [PubMed]

36. Tyagi V, Philips BJ, Su R, Smaldone MC, Erickson VL, Chancellor MB, et al. Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium. J Urol. 2009;181:1932–8. [PubMed]

37. Ghasemi M, Sadeghipour H, Shafaroodi H, Nezami BG, Gholipour T, Hajrasouliha AR, et al. Role of the nitric oxide pathway and the endocannabinoid system in neurogenic relaxation of corpus cavernosum from biliary cirrhotic rats. Br J Pharmacol. 2007;151:591–601. [PMC free article] [PubMed]

38. Dinis P, Charrua A, Avelino A, Yaqoob M, Bevan S, Nagy I, et al. Anandamide-evoked activation of vanilloid receptor 1 contributes to the development of bladder hyperreflexia and nociceptive transmission to spinal dorsal horn neurons in cystitis. J Neurosci. 2004;24:11253–63. [PubMed]

39. Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB_2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. Pain. 1998;76:189–99. [PubMed]

40. Calignano A, La Rana G, Giuffrida A, Piomelli D. Control of pain initiation by endogenous cannabinoids. Nature. 1998;394:277–81. [PubMed]

41. Morisset V, Ahluwalia J, Nagy I, Urban L. Possible mechanisms of cannabinoid-induced antinociception in the spinal cord. Eur J Pharmacol. 2001;429:93–100. [PubMed]

42. Costa B, Siniscalco D, Trovato AE, Comelli F, Sotgiu ML, Colleoni M, et al. AM404, an inhibitor of anandamide uptake, prevents pain behaviour and modulates cytokine and apoptotic pathways in a rat model of neuropathic pain. Br J Pharmacol. 2006;148:1022–32. [PMC free article] [PubMed]

43. Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: An overview. Int J Obes (Lond) 2006;30:S13–8. [PubMed]

44. Yesilyurt O, Dogrul A. Lack of cross-tolerance to the antinociceptive effects of systemic and topical cannabinoids in morphine-tolerant mice. Neurosci Lett. 2004;371:122–7. [PubMed]

45. Malan J, Philip T, Ibrahim MM, Lai J, Vanderah TW, Makriyannis A, Porreca F. CB_2 cannabinoid receptor agonists: Pain relief without psychoactive effects? Current Opinion in Pharmacology. 2003;3:62–7. [PubMed]

46. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain: [Les effets de la nabilone, un cannabinoide synthetique, sur la douleur postoperatoire] Can J Anaesth. 2006;53:769–75. [PubMed]

47. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med. 2006;7:25–9. [PubMed]

48. Clark AJ, Lynch ME, Ware M, Beaulieu P, McGilveray IJ, Gourlay D. Guidelines for the use of cannabinoid compounds in chronic pain. Pain Res Manag. 2005;10:44A–6. [PubMed]

49. Fisher BA, Ghuran A, Vadamalai V, Antonios TF. Cardiovascular complications induced by cannabis smoking: A case report and review of the literature. Emerg Med J. 2005;22:679–80. [PMC free article] [PubMed]

50. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet. 2003;42:327–60. [PubMed]

51. Karsak M, Gaffal E, Date R, Wang-Eckhardt L, Rehnelt J, Petrosino S, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. Science. 2007;316:1494–7. [PubMed]

52. Maekawa T, Nojima H, Kuraishi Y, Aisaka K. The cannabinoid CB_2 receptor inverse agonist JTE-907 suppresses spontaneous itch-associated responses of NC mice, a model of atopic dermatitis. Eur J Pharmacol. 2006;542:179–83. [PubMed]

53. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. Ann Pharmacother. 2006;40:251–60. [PubMed]

54. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler. 2004;10:425–33. [PubMed]

55. Barnes MP. Sativex: Clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opin Pharmacother. 2006;7:607–15. [PubMed]

56. Dogrul A, Gul H, Akar A, Yildiz O, Bilgin F, Guzeldemir E. Topical canna binoid antinociception: Synergy with spinal sites. Pain. 2003;105:11–6. [PubMed]

57. Sokal DM, Elmes SJ, Kendall DA, Chapman V. Intraplantar injection of anandamide inhibits mechanically-evoked responses of spinal neurones via activation of CB_2 receptors in anaesthetised rats. Neuropharmacology. 2003;45:404–11. [PubMed]

58. Tyagi P, Tyagi S, Kaufman J, Huang L, de Miguel F. Local drug delivery to bladder using technology innovations. Urol Clin North Am. 2006;33:519–30. [PubMed]

59. Tyagi P, Chancellor MB, Li Z, De Groat WC, Yoshimura N, Fraser MO, et al. Urodynamic and immunohistochemical evaluation of intravesical capsaicin delivery using thermosensitive hydrogel and liposomes. J Urol. 2004;171:483–9. [PubMed]

60. Chuang YC, Thomas CA, Tyagi S, Yoshimura N, Tyagi P, Chancellor MB. Human urine with solifenacin intake but not tolterodine or darifenacin intake blocks detrusor overactivity. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:1353–7. [PubMed]

61. Chuang YC, Tyagi P, Huang CC, Yoshimura N, Wu M, Kaufman J, et al. Urodynamic and Immunohistochemical Evaluation of Intravesical Botulinum Toxin A Delivery Using Liposomes. J Urol. 2009;182:786–92. [PubMed]

62. Tyagi V, Yoshimura N, Chancellor MB, Tyagi P. Local Activation Of Cannabinoid CB_1 Receptors Bladder Suppresses Acetic Acid Induced Bladder Irritation. J Urol. 2008;179:539–54.

63. Tyagi V, Yoshimura N, Chancellor MB, Tyagi P. Instillation of Selective CB_2 Agonist Protects Against Bladder Irritation J Urol. 2008;179:352.

64. Ganabathi R, Tyagi P, de Miguel F, Tyagi S, Yoshimura N, Chancellor MB. Effect of IP-751, Ajulemic Acid. against Acetic Acid Induced Bladder Pain Responses in Rats 24h After Intravesical Administration J Urol. 2006;176:93–4.

65. Dyson A, Peacock M, Chen A, Courade JP, Yaqoob M, Groarke A, et al. Antihyperalgesic properties of the cannabinoid CT-3 in chronic neuropathic and inflammatory pain states in the rat. Pain. 2005;116:129–37. [PubMed]

66. Hiragata S, Ogawa T, Hayashi Y, Tyagi P, Seki S, Nishizawa O, et al. Effects of IP-751, ajulemic acid, on bladder overactivity induced by bladder irritation in rats. Urology. 2007;70:202–8. [PubMed]

67. Izzo AA, Coutts AA. Cannabinoids and the digestive tract. Handb Exp Pharmacol. 2005;168:573–98. [PubMed]

68. Gutierrez T, Farthing JN, Zvonok AM, Makriyannis A, Hohmann AG. Activation of peripheral cannabinoid CB_1 and CB_2 receptors suppresses the maintenance of inflammatory nociception: A comparative analysis. Br J Pharmacol. 2007;150:153–63. [PMC free article] [PubMed]

69. Mazzari S, Canella R, Petrelli L, Marcolongo G, Leon A. N-(2-hydroxyethyl) hexadecanamide is orally active in reducing edema formation and inflammatory hyperalgesia by down-modulating mast cell activation. Eur J Pharmacol. 1996;300:227–36. [PubMed]

70. Rahn EJ, Makriyannis A, Hohmann AG. Activation of cannabinoid CB(1) and CB(2) receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. Br J Pharmacol. 2007;152:765–77. [PMC free article] [PubMed]

71. Ossipov MH, Porreca F. Challenges in the development of novel treatment strategies for neuropathic pain. NeuroRx. 2005;2:650–61. [PMC free article] [PubMed]

72. Dionne RA, Lepinski AM, Gordon SM, Jaber L, Brahim JS, Hargreaves KM. Analgesic effects of peripherally administered opioids in clinical models of acute and chronic inflammation. Clin Pharmacol Ther. 2001;70:66–73. [PubMed]

73. Di Marzo V, Griffin G, De Petrocellis L, Brandi I, Bisogno T, Williams W, et al. A structure/activity relationship study on arvanil, an endocannabinoid and vanilloid hybrid. J Pharmacol Exp Ther. 2002;300:984–91. [PubMed]

74. Shire D, Calandra B, Bouaboula M, Barth F, Rinaldi-Carmona M, Casellas P, et al. Cannabinoid receptor interactions with the antagonists SR 141716A and SR 144528. Life Sci. 1999;65:627–35. [PubMed]

75. Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB_1 receptor knockout mice. Science. 1999;283:401–4. [PubMed]

SECTION H

GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

Gastroenterol Hepatol (N Y). 2016 Nov; 12(11): 668–679.

PMCID: PMC5193087
PMID: 28035196

Therapeutic Use of Cannabis in Inflammatory Bowel Disease

Waseem Ahmed, MD✉ and Seymour Katz, MD

Dr Ahmed is an internal medicine resident at the New York University Medical Center in New York, New York. Dr Katz is a clinical professor in the Division of Gastroenterology at the New York University Medical Center and an associate director of the Inflammatory Bowel Disease Program at the Tisch Hospital and Ambulatory Care Center in New York, New York.
✉Corresponding author.
Address correspondence to: Dr Waseem Ahmed Department of Internal Medicine New York University Medical Center 550 First Avenue New York, NY 10016 Tel: 646-501-2316 Fax: 646-754-9653 E-mail: Waseem.Ahmed@nyumc.org

Abstract

The marijuana plant *Cannabis sativa* and its derivatives, cannabinoids, have grown increasingly popular as a potential therapy for inflammatory bowel disease (IBD). Studies have shown that modulation of the endocannabinoid system, which regulates various functions in the body and has been shown to play a key role in the pathogenesis of IBD, has a therapeutic effect in mouse colitis. Epidemiologic data and human therapy studies reveal a possible role for cannabinoids in the symptomatic treatment of IBD, although it has yet to be determined in human populations whether cannabinoids have therapeutic anti-inflammatory effects in IBD or are simply masking its many debilitating symptoms. Large, double-blind, randomized, placebo-controlled trials using serial inflammatory markers, biopsy findings, and endoscopic disease severity to demonstrate objective improvement in IBD are necessary before cannabis can be empirically accepted and recommended as an IBD treatment option. Questions concerning its safety profile and adverse effects prompt the need for further research, particularly in regard to dosing and route of administration to maximize benefits and limit potential harms. Cannabis use should be reserved for symptomatic control in patients with severe IBD refractory to the currently available standard-of-care and complementary and alternative medicines.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, cannabis

The use of cannabis, commonly referred to as marijuana, is increasingly popular; in North America, roughly 10.7% of people ages 15 to 64 years reported cannabis use in 2009.[1] In the United States, cannabis is a Schedule I substance and its use for recreational or medicinal means is illegal according to federal law. However, contrary to federal policy, individual state laws have allowed for medical use of marijuana in 24 states and recreational use in 4 states; additionally, use of marijuana is now decriminalized in 21 states.[2] Given the evolving policies regarding the medical use of cannabis, physicians are increasingly prompted with questions about its therapeutic role for a variety of disorders.

In the United States, cannabis use is legalized state-to-state for the medical treatment of several chronic, debilitating disorders, including cancer, HIV/AIDS, multiple sclerosis, chronic pain, nausea, hepatitis C virus, posttraumatic stress disorder, amyotrophic lateral sclerosis, cachexia, glaucoma, and epilepsy.[3,4] Data on the efficacy of cannabis use for the treatment of many of these conditions are often scarce and inconsistent, yet medical use of cannabis is increasing as patients choose complementary and alternative medicine (CAM) over more conventional, proven therapies.[5]

The plant *Cannabis sativa* has been used in medicinal practice for thousands of years.[6] The pharmacologically active constituents of the plant are termed cannabinoids, of which at least 70 are known today. Phytocannabinoids (cannabinoids derived from the plant), synthetic cannabinoids (artificial compounds with cannabinomimetic effects),

and endocannabinoids (endogenous compounds with cannabinomimetic effects) act together on the endocannabinoid system (ECS), which regulates various functions in the body.[7]

Among the phytocannabinoids, delta-9-tetra-hydrocannabinol (THC) is thought to be the most pharmacologically active, with various central and peripheral effects. THC is also considered the most active psychotropic agent among the phytocannabinoids and is largely the most studied. Other phytocannabinoids include cannabidiol, cannabigerol, and cannabichromene, all mostly devoid of central effects.[8] Formulations related to these compounds include nabilone (Cesamet, Meda Pharmaceuticals), dronabinol, and nabiximols. Nabilone is approved by the US Food and Drug Administration (FDA) for chemotherapy-induced nausea and vomiting unresponsive to typical antiemetics, and dronabinol is FDA-approved for chemotherapy-induced nausea and vomiting and AIDS-associated anorexia. Nabiximols is approved outside of the United States for patients with cancer-associated pain, neuropathic pain, and spasticity in association with multiple sclerosis.[3]

Inflammatory bowel disease (IBD) is a chronic inflammatory condition comprised of ulcerative colitis (UC) and Crohn's disease (CD) and characterized by relapsing and remitting episodes of inflammation primarily involving the gastrointestinal tract. The pathophysiology of IBD has yet to be fully established and appears to involve an inappropriate inflammatory response with a dysregulated immune system in the appropriate environmental and genetic background. Conventional therapies aimed at induction and remission of IBD mainly work through immune suppression and consist of aminosalicylates, antibiotics, corticosteroids, immunomodulators, and biologic therapies. Given the limited therapy options and known adverse side effects with chronic use, physicians often manage patients with disease refractory to conventional methods, prompting surgical resection of the diseased bowel.[9] Patients are commonly attracted to the use of CAM for management of their IBD, and physicians should be familiar with these various therapies in order to advise patients on safe use.[5]

Anecdotal reports have suggested a therapeutic role for cannabis in the treatment of IBD for hundreds of years. A case report from 1990 describes patients with IBD maintaining remission of disease via cannabis use.[10] The use of medical marijuana preceded the discovery of the ECS, prompting further research of cannabis as a treatment option for IBD. As the therapeutic use of cannabis gains more attention in the press, there is growing recognition of a fraction of IBD patients who are using cannabis for symptomatic control of their IBD, reportedly with successful management of abdominal pain, joint pain, cramping, diarrhea, poor appetite, weight loss, and nausea.[11,12] Physicians are often unaware of the therapeutic role and adverse effects of marijuana use amid concerns of federal prosecution and the changing political status of the drug, yet its use cannot be ignored.[3] This article reviews the ECS and its role in gastrointestinal physiology, population studies regarding the use of medical cannabis in IBD patients and its perceived effectiveness, results and potential pitfalls of therapy trials in the use of cannabis for treatment of IBD, and general safety concerns regarding acute and chronic cannabis use.

The Endocannabinoid System and Its Role in Gastrointestinal Physiology

The ECS consists of endogenous cannabinoids, the receptors on which they act, and the enzymes involved in their biosynthesis and degradation (Figure 1). The 2 primary endocannabinoids are N-arachidonoylethanolamine, or anandamide, and 2-arachidonoylglycerol (2-AG). These ligands are synthesized from cellular membrane phospholipids and bind to presynaptic receptors, namely the G protein—coupled receptors cannabinoid 1 and 2 receptors (CB1 and CB2). Anandamide acts as a partial agonist of CB1 and CB2, with a slightly higher affinity to CB2; 2-AG binds to both receptors equally well with greater potency. 2-AG is found in higher levels in the gastrointestinal tract.[8]

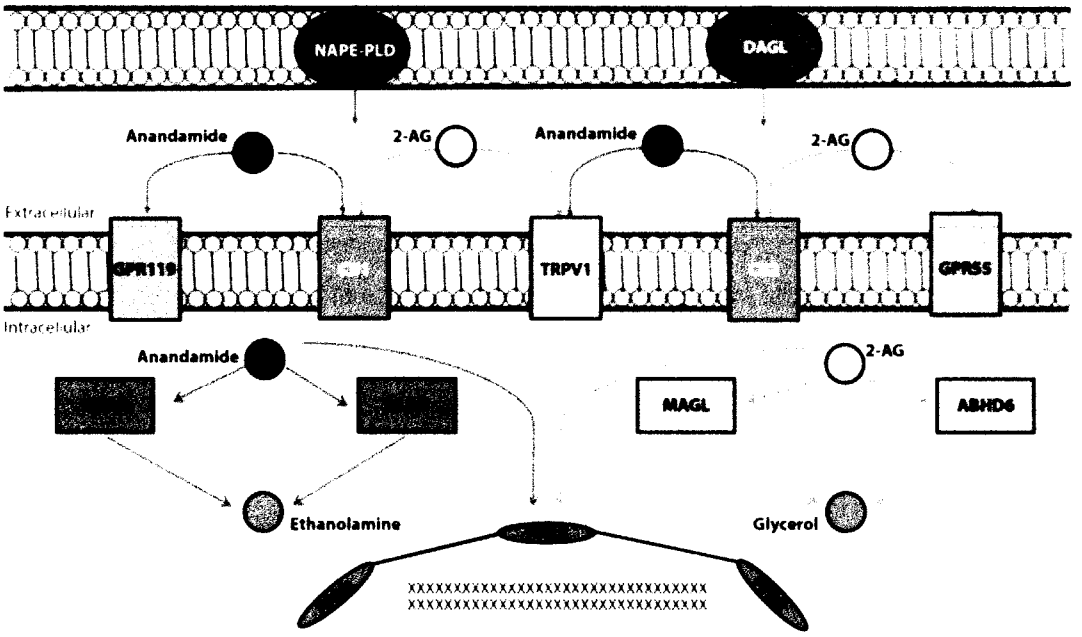


Figure 1.

Anandamide and 2-arachidonoylglycerol (2-AG) are formed via phospholipid precursors by the enzymes N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL). These active lipids interact with membrane and intracellular receptors, including the G protein–coupled receptors 119 and 55 (GPR119 and GPR55), the cannabinoid 1 and 2 receptors (CB1 and CB2), the transient receptor potential vanilloid subtype 1 receptor (TRPV1), and the peroxisome proliferator-activated receptors (PPARs), among others. Anandamide is hydrolyzed intracellularly by N-acylethanolamine-hydrolyzing acid amidase (NAAA) and fatty acid amide hydrolase (FAAH), and 2-AG is hydrolyzed intracellularly by monoacylglycerol lipase (MAGL) and alpha/beta-hydrolase domain 6 (ABHD6).[8]

The phytocannabinoids THC and cannabidiol act via similar pathways as anandamide and 2-AG. THC is a partial agonist of both CB1 and CB2, also acting on noncannabinoid receptors. The actions of THC on CB1 make it largely responsible for the psychoactive effects of cannabis use. Cannabidiol binds to both CB1 and CB2 with poor affinity and primarily exerts its effects via additional pathways.[8]

The ECS is found in all vertebrates and humans and is distributed among organs and tissues. CB1 is mostly expressed in neurons of the central, peripheral, and enteric nervous systems, while CB2 is found mainly in immune cells. In the gastrointestinal system, CB1 and CB2 are found in all layers of intestinal sections, including the myenteric and submucosal plexi and the epithelium.[13,14] Numerous mouse models have demonstrated a relationship between the ECS, intact gastrointestinal physiology, and regulation of gut inflammation (Figure 2).[13-20] Expression of cannabinoid receptors is most abundant on B cells, followed by natural killer cells, monocytes, neutrophils, and CD8 and CD4 leukocytes.[13] Overall, endocannabinoids acting on CB2 result in attenuation of inflammatory response, yet other data suggest that cannabinoids have proinflammatory effects and that their immunomodulatory effect is based on the frequency of cannabis use, the dose administered, the specific type of cannabinoid used, and the cells on which they act.[13]

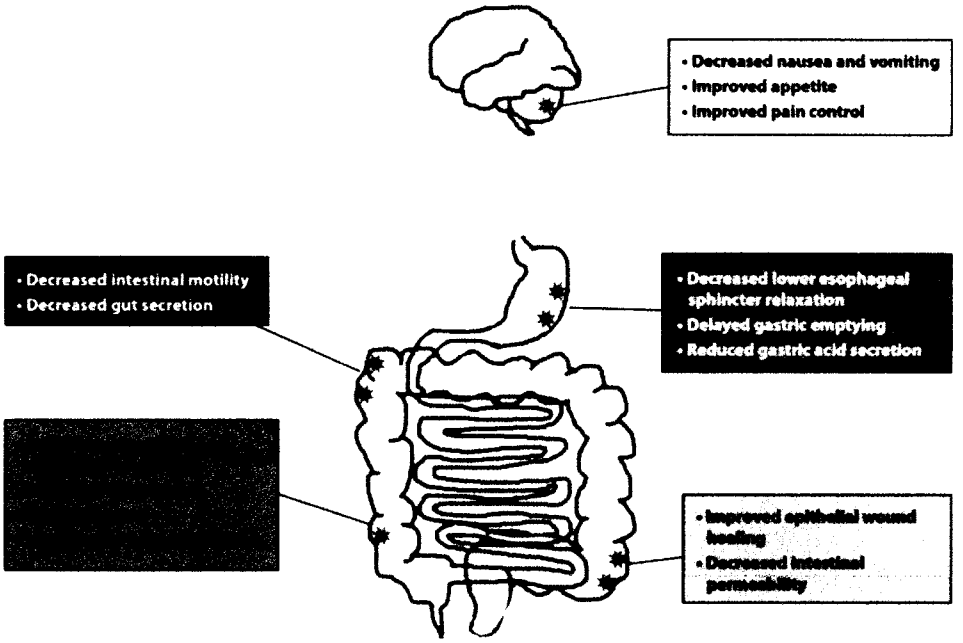


Figure 2.

Natural and synthetic cannabinoids act primarily via cannabinoid 1 receptors (CB1; green stars) and cannabinoid 2 receptors (CB2; blue stars) located in the central, peripheral, and enteric nervous systems. Cannabinoids predominately mediate inhibitory pathways in the gastrointestinal tract through reduction of vagal cholinergic tone. CB2 modulate inflammation, whereas CB1 control central functions, including pain control, satiety, nausea, and vomiting. The distribution and concentration of the endocannabinoid system in specific tissues demonstrate the physiology of cannabinoids in the gastrointestinal tract and offer possible drug targets for the management of inflammatory bowel disease. The majority of the above functions are demonstrated in mouse models; it is yet unclear if all effects mirror those seen in humans.[13-20]

Alteration of the Endocannabinoid System in Inflammatory Bowel Disease

The role of the ECS in gut homeostasis and its ability to modulate inflammatory responses demonstrate its part in preserving gastrointestinal function. Alterations of the ECS may predispose patients to pathologic disorders, including IBD. This has been demonstrated in both murine models[8,20,21] (Table 1) and human models, described below.

Table 1.

Results of Modulation of the Endocannabinoid System in Murine Models With Inflammatory Bowel Disease

Study	Results
Massa et al[20]	$CB1^{-/-}$ mice have an increased risk of colitis vs wild mice after induction with DNBS and dextran sulfate sodium. In $CB2^{-/-}$ mouse models, the effect is similar, suggesting that these cannabinoid receptors together maintain intestinal homeostasis.
Engel et al[21]	Double-knockout mice, $CB1^{-/-}$ and $CB2^{-/-}$, do not show increased relative susceptibility to TNBS-induced colitis compared with single-knockout models, suggesting additional compensatory mechanisms accounting for a more robust inflammatory response. In FAAH—knockout mice with increased endocannabinoid levels, there is less response to DNBS-induced colitis.
Alhouayek and Muccioli[8]	Levels of anandamide are increased in the colons of DNBS- and TNBS-rats, whereas levels of 2-arachidonoylglycerol appear unchanged. Expression of FAAH mRNA (precursors to the enzyme involved in degradation of anandamide) has shown to be decreased in inflamed colons; however, this does not seem to correlate with changes in FAAH activity.

CB1, cannabinoid 1 receptor; CB2, cannabinoid 2 receptor; DNBS, dinitrobenzene sulfonic acid; FAAH, fatty acid amide hydrolase; TNBS, trinitrobenzene sulfonic acid.

Di Sabatino and colleagues described modulation of the ECS in 2011 using endoscopic biopsy specimens from 41 patients with CD and 33 patients with UC.[22] Biopsies were analyzed for endocannabinoid levels, expression of cannabinoid receptors, and activity of enzymes involved in endocannabinoid synthesis and degradation. Levels of anandamide were significantly decreased in inflamed IBD mucosa, which correlated with a decrease in expression of N-acyl-phosphatidylethanolamine-phospholipase D (NAPE-PLD) and an increase in expression of fatty acid amide hydrolase (FAAH). CB1 was also found to have increased expression in inflamed areas of both CD and UC; however, CB2 levels seemed to be unaltered.[22]

Marquéz and colleagues studied expression of the ECS in 24 patients with UC vs rectal samples from control patients after colonic resection for colorectal tumors.[23] Results showed increases of CB2 and the diacylglycerol lipase (DAGL) and monoacylglycerol lipase (MAGL) enzymes in mild to moderate pancolitis. Severe pancolitis showed a decrease in expression of NAPE-PLD. In quiescent colitis, patients treated with aminosalicylates and corticosteroids experienced decreases in expressions of CB1, CB2, and DAGL, whereas NAPE-PLD levels rose. In patients with acute pancolitis, lamina propria immune cells showed increased amounts of MAGL and FAAH; however, this level of expression dropped after appropriate treatment.[23]

These studies show different levels of elements of the ECS in murine and human IBD models. Further delineation of mechanism of action is needed to determine whether these results are pathologic or reactive effects to inflammation. However, cannabinoids appear to have a clear role in gut pathology and offer a potential target for drug intervention in the treatment of IBD.

Increased Cannabis Use in Patients With Inflammatory Bowel Disease

A significant proportion of patients with IBD use CAM for additional management of symptoms. Motives for using CAM include ineffectiveness of current therapies, fewer side effects, and a sense of gaining control over the disease.[5,24,25] As public awareness of medical cannabis use increases, population studies have reinforced the use of medical cannabis for symptom relief in IBD patients (Table 2) [5,12,24,26,27]

Table 2.

Population Studies Evaluating Cannabis Use in Patients With IBD

Study	Number of Subjects	Evet Used Cannabis (%)	Actively Used Cannabis (%)	Used Cannabis for IBD (%)	Used Cannabis for Abdominal Pain Relief (%)	Used Cannabis for Diarrhea Relief (%)	Weight Gain or Improved Appetite (%)
García-Planella et al[5]	214	N/A	10	N/A	N/A	N/A	N/A
Lal et al[24]	291	49	14.4	43.9	94.4	33.3	74.1
Ravikoff Allegretti et al[26]	292	51.3	12.3	32	89.5	41.6	72.9
Storr et al[12]	319	44.2	N/A	17.6	83.9	28.6	N/A
Weiss and Friedenberg[27]	2,084,895	67.3	15.7	N/A	N/A	N/A	N/A

IBD, inflammatory bowel disease.

In 2007, García-Planella and colleagues surveyed 214 patients with IBD in Spain and found that nearly 10% of patients actively used cannabis or its derivatives.[5] In 2011, Lal and colleagues polled 291 patients with IBD at a tertiary care center in Ontario, Canada.[24] UC patients reported a 50.5% lifetime and 11.6% active use of cannabis, and CD patients reported a 48.1% lifetime and 15.9% current use of cannabis. Interestingly, 33% and 50% of UC and CD lifetime users, respectively, reported use of medical cannabis specifically for symptom relief of IBD. A notable proportion of patients found symptomatic relief of abdominal pain, diarrhea, and poor appetite. Patients with a history of abdominal surgery, chronic analgesic use, CAM use, and a lower Short Inflammatory Bowel Disease Questionnaire score were more likely to use cannabis for symptom relief. Forty-seven percent of patients overall reported using CAM for IBD management. More than 50% of patients expressed interest in participating in a clinical trial of cannabis for IBD.[24]

Ravikoff Allegretti and colleagues performed the first survey regarding patterns of cannabis use in the US population.[26] A total of 292 patients (a significant proportion of whom were using standard-of-care therapies) at a specialized IBD center were enrolled in a prospective cohort survey study. A 94% response rate showed a 12.3% rate of active marijuana use among IBD patients, higher than the rate of use among the general population. Thirty-two percent of lifetime users reported using marijuana for control of IBD symptoms. Multivariate analysis revealed that age and chronic abdominal pain were associated with marijuana use. A substantial proportion of patients perceived cannabis as effective for relief of abdominal pain, poor appetite, and nausea, and less successful for relief of diarrhea. The authors discuss whether these results suggest a central-mediated mechanism for cannabis relief rather than an improvement in mucosal inflammation. Similar to the study by Lal and colleagues,[24] nearly half of nonusers expressed interest in cannabis use if medically legal.[26]

A 2014 Canadian population study noted a worse disease prognosis in patients with CD using cannabis.[12] In a study of 319 patients with IBD, 17.6% reported lifetime use of cannabis for IBD, especially among patients with self-reported severe IBD, patients recently hospitalized, and patients with surgical history. Ninety-one percent of patients indicated improvement of IBD symptoms with cannabis use; 83.9% reported improved abdominal pain, 76.8% indicated improved abdominal cramping, 48.2% had improved joint pain, and 28.6% reported improved diarrhea.[12] Patients also believed that cannabis improved their general well-being, stress level, and sense of control over IBD. Surprisingly, 35.7% of patients believed that cannabis worked better than corticosteroids, and nearly 43% reported fewer side effects with cannabis use compared with corticosteroids. In addition, 82.1% of users planned to continue using cannabis for their IBD and 87.5% would recommend cannabis to other patients for management of IBD. When asked why they used cannabis for IBD, 46.4% of patients said they heard that cannabis would help, followed by being frustrated with their disease, wanting to try a different approach, and feeling that medications prescribed by doctors did not help. Only 39% of patients discussed their use of cannabis with their physician, and 82% of physicians were indifferent or not supportive of marijuana use for IBD management. Overall, 64.3% of nonusers felt that cannabis should be legalized for medical use.[12] However, in patients with CD, regression analysis linked prolonged cannabis use to an increased history of surgery (odds ratio, 5.03). Storr and colleagues acknowledged that it was not possible to associate the time of cannabis use with surgeries, making any association between temporal relationships or causality from their methods impossible.[12] Research has suggested that cannabis use may be associated with an increased risk for surgery based on prior studies showing increased rates of liver fibrosis with marijuana use.[28] Similar effects could be responsible for the fibrostenotic sequelae complicating CD and requiring surgical intervention. Furthermore, cannabis use may mask ongoing inflammation. Because of improved symptom control, patients may perceive their disease to be in remission and thus not present to physicians for routine care, resulting in adverse consequences in a young population.[12]

The first large population-based survey, which was conducted by Weiss and Friedenberg using the National Health and Nutrition Examination Survey in 2015, reviewed more than 2 million IBD patients vs age- and sex-matched controls in regard to patterns of cannabis use.[27] Results showed that patients with IBD had a higher incidence of having used marijuana or its resin form hashish vs the matched control subjects (67.3% vs 60.0%). Patients with IBD were more likely to use a higher amount of marijuana or hashish per day, but were less likely to use marijuana or hashish every month for a year. Multivariable logistic regression analyses identified IBD, male sex, and age over 40 years as predictors of marijuana or hashish use. Patients with IBD tended to score higher on the Median Depression Score, were more likely to have alcohol-use patterns concerning for dependence and abuse, had a higher prevalence of smoking, and had higher levels of C-reactive protein (CRP).[27] Results of this survey mirror those of previous smaller studies, allowing for more defined generalizations of marijuana use and its perceived benefits among IBD patients.

The aforementioned studies share several themes. Cannabis use is common among patients with IBD and often specifically for symptomatic relief. Patients report substantial therapeutic effects of cannabis in the management of abdominal pain, nausea, and diarrhea, and a significant number of patients are interested in using cannabis for management of their IBD. Additionally, patients infrequently report use of cannabis to their physicians, emphasizing the need to question patients on use. Lastly, most studied patients received treatment at specialized or dedicated IBD tertiary care centers, suggesting poor control of abdominal pain, nausea, and diarrhea in patients with severe IBD despite use of the most up-to-date therapies. Cannabis seems to be of symptomatic benefit to patients often refractory to conventional medicines; however, none of the above studies delineate whether this is a central subjective effect masking active disease or an actual treatment of inflammation.

Symptomatic Improvement With Cannabis Use in Patients With Inflammatory Bowel Disease

Following the promising results of cannabinoids in murine models of colitis (Table 3),[29-32] Naftali and colleagues in 2011 presented the first study examining the response of patients with CD to cannabis use (Table 4).[33] The authors conducted a retrospective, observational study of 30 CD patients in Israel who were legally using cannabis due to a lack of response to conventional treatments and chronic intractable pain. Disease activity before and after cannabis use was estimated using the Harvey-Bradshaw index for CD, and patients assessed their general medical well-being before and after use. Patients' hospital records were obtained to monitor disease activity, rate of hospital admission, use of additional drugs, and need for surgical intervention.[33] All 30 patients rated their general medical well-being as improved after cannabis use via a visual analog scale. Twenty-one patients had a notable improvement after treatment with cannabis use, and the average Harvey-Bradshaw index for all patients improved from 14 to 4.7

(P<.001). Only 2 patients required surgery during a period of 3 years of cannabis use, a rate that Naftali and colleagues claimed is a significant improvement for the normal operative rate in patients with CD.[33] The mean number of bowel movements decreased from 8 to 5. Whereas 26 patients required corticosteroid therapy prior to cannabis use, only 4 patients were still maintained on corticosteroids after cannabis use, suggesting a possible corticosteroidsparing effect of cannabis. There was also a substantial drop in use of aminosalicylates, thiopurines, methotrexate, and tumor necrosis factor antagonists. The authors cited these data as objective benefits of cannabis use and advocated for more placebo-controlled studies for further evaluation of therapeutic effects of cannabis use.[33]

Table 3.

Results of Murine Colitis Models Treated With Cannabinoids

Study	Results
Borrelli et al[29]	In DNBS-induced colitis, cannabidiol reduced colon injury, decreased expression of inflammatory markers and inducible nitric oxide synthase, and decreased reactive oxygen species production.
Jamontt et al[30]	TNBS-induced colitis treated with THC, cannabidiol, THC combined with cannabidiol, and sulphasalazine compared with controls showed decreased inflammation and functional disturbances after treatment with THC and cannabidiol. THC alone or with cannabidiol improved the function of cholinergic motor neurons, results not seen with sulphasalazine use.
Cluny et al[31]	A peripherally restricted CB1/CB2 agonist was ineffective in dextran sodium sulfate—induced colitis and did not significantly reduce colitis in a TNBS-colitis model.
D'Argenio et al[32]	Use of VDM11, an inhibitor of fatty acid amide hydrolase, increases anandamide tone, which improves TNBS- and DNBS-induced rat colitis.

CB1, cannabinoid 1 receptor; CB2, cannabinoid 2 receptor; DNBS, dinitrobenzene sulfonic acid; THC, tetrahydrocannabinol; TNBS, trinitrobenzene sulfonic acid; VDM11, N-(-4-hydroxy-2-methylphenyl) arachidonoyl amide.

Table 4.

Therapy Studies Evaluating Clinical Response in Patients With IBD

Study	Study Design	Subjects	Treatment	Outcomes
Naftali et al[33]	Retrospective, observational	30 patients with Crohn's disease	Retrospective inhalational or oral cannabis use	Significant clinical response but need for other drugs and surgery with cannabis
Lahat et al[34]	Prospective, observational without controls	13 patients with IBD	50 g of cannabis cigarette per month (3 months total)	Significant improvement in quality of life, disease activity, and weight gain
Naftali et al[35]	Prospective, randomized, double-blind, placebo-controlled	21 patients with Crohn's disease	*Cannabis sativa* cigarette (23% THC, 0.5% cannabidiol)	Significant clinical response with cannabis but no objective decrease in inflammation

IBD, inflammatory bowel disease; THC, tetrahydrocannabinol.

The first prospective, observational, single-arm trial was published by Lahat and colleagues.[34] Thirteen patients with longstanding IBD refractory to conventional therapies and on a stable IBD medical regimen prior to inclusion were provided a total dose of 50 g of processed cannabis plant in the form of prepared cigarettes. Patients were instructed to use inhaled cannabis whenever they felt pain for a total of 3 months. Patients completed 2 quality-of-life questionnaires (the 36-Item Short Form Health Survey [SF-36] and the EuroQol 5 dimensions questionnaire [EQ-5D]), and physicians measured patient body weights and calculated Harvey-Bradshaw indexes and partial Mayo scores (excluding mucosal endoscopic appearance) before and after cannabis treatment. All patients used the entire amount of inhaled cannabis supplied each month; no cannabis usage was reported prior to study initiation. Using the SF-36, patients reported a statistically significant improvement in 12 of 14 daily activities and a notable improvement in pain after 3 months of treatment. Patients noted improvement in health perception, social functioning, ability to work, and depression. They had an average weight gain of 4.3 kg during treatment (P=.00002) and an average increase in body mass index of 1.4 (P=.002). The average Harvey-Bradshaw index was reduced from 11.36 to 2.68 (P=.001); reductions were mainly seen in general well-being and abdominal pain. The average number of daily liquid stools decreased from 5.54 to 3.18. Owing to a limited number of patients with UC, statistical analysis was unable to be performed on this subset. Lahat and colleagues were able to provide CRP levels for only 6 patients before and during treatment, and this trended toward a decrease in CRP levels during treatment with cannabis.[34]The authors concluded that cannabis use improves quality of life in patients with IBD, results in a statistically significant increase in patient weight and body mass index, and improves clinical disease activity index in patients with CD, and postulated that such effects were related to the analgesic, anti-inflammatory, antimotility, and additional effects of cannabinoids.[34]

After performing retrospective research,[33] Naftali and colleagues completed the first prospective, randomized, double-blind, placebo-controlled trial by evaluating 21 patients with CD refractory to aminosalicylates, corticosteroids, immunomodulators, or biologic agents.[35] The primary objective of the study was induction of remission of CD as defined by a Crohn's Disease Activity Index (CDAI) score of less than 150 after 8 weeks of treatment. Secondary objectives were rate of response, defined by the authors as a 100-point decrease in the CDAI score, reduction of at least 0.5 mg in CRP levels, or improvement in quality of life by at least 50 points as measured by the SF-36. Patients in the treatment group were instructed to smoke 2 marijuana cigarettes containing 115 mg of THC, whereas patients in the placebo group smoked placebo cannabis flowers extracted of all THC content for a total of 8 weeks of treatment. Patients were on stable doses of medications prior to the initiation of treatment and had an average CDAI score of greater than 200. Previous cannabis use was an excluding factor. Patients were evaluated at 0, 2, 8, and 10 weeks, and evaluated parameters included CDAI score, CRP levels, and the SF-36. The primary objective was not met, as 5 of 11 patients in the treatment group achieved remission compared with 1 of 10 patients in the placebo group (P=.43). The authors suggested that the primary objective may not have been reached due to low sample size. Following 8 weeks of treatment, the secondary objective response rate via reduction of the CDAI score by 100 points was reached in 90% (10/11) of patients in the treatment group, from an average of 330 to 152, and in 40% (4/10) of patients in the placebo group, from an average of 373 to 306 (P=.028). Two weeks after cannabis treatment was stopped, the mean CDAI score in treatment and placebo groups was 331 and 280, respectively. Naftali and colleagues noted that 3 corticosteroid-dependent patients in the treatment group stopped corticosteroid use during the study and that at the end of the study, no patients in the treatment group required corticosteroids.[35] They also noted that 2 patients in the treatment group using opiates for management of chronic pain stopped opiate use during the study. A significant increase in quality of life via the SF-36 was observed in the treatment group compared with the placebo group. Levels of CRP did not show any significant changes after treatment with cannabis. Endoscopic inflammation was not assessed. Naftali and colleagues reported that THC-rich cannabis produced significant clinical, corticosteroid-free benefits in patients with active CD compared with placebo and advocated for further trials to be conducted with a larger sample size.[35] Given that their patients had longstanding CD with high rates of nonresponse or intolerance to biologic agents, the authors claimed such findings as impressive, yet recognized that further data are necessary and that the current role of cannabis in IBD should only be for compassionate management.[35]

Flaws in Human Studies

Findings from human studies have resulted in an increase in publicity regarding the efficacy of cannabis use in IBD therapy; however, the flaws of these studies are rarely mentioned.[11,19,36] The population studies discussed in this article lack objective parameters showing improvement in IBD activity with cannabis use. For example, the large, population-based survey by Weiss and Friedenberg provides CRP levels for patients, but not for the full duration of

the study period.[27] The other studies lack measurements of sedimentation rate, fecal calprotectin levels, endoscopic inflammation, or histologic evidence of active disease. Although each of these studies reports improved levels of abdominal pain, nausea, and appetite, significant prior data have shown that cannabis use via central effects can be responsible for such benefits; the fact that fewer patients reported relief of diarrhea argues that cannabis may not have a role in mediating inflammation and instead masks active disease with symptomatic improvement and overexaggerates treatment effect, as suggested by Storr and colleagues.[12] The majority of these trials occurred in specialized IBD centers with a largely white, homogeneous population that does not match the typical demographic seen in IBD patients today. Patients presented with severe, complex forms of IBD and represented a potential referral bias, demonstrating that cannabis use may be limited only to refractory cases.

Data have shown that cannabis use is often underreported among users; therefore, its use may be even higher in the general IBD population.[5] However, there is still a significant effect of a recall bias, as patients whose IBD symptoms improved are more likely to search for causal events (such as cannabis use) as potential triggers.

Human trials share many of the same weaknesses as population studies, such as a small sample size of patients, a short period of study, and a limited or absent follow-up period. The retrospective trial by Naftali and colleagues studied only 30 patients, 26 of whom were male, relying on subjective measures of well-being and the Harvey-Bradshaw index to demonstrate treatment efficacy, with a clear recall bias.[33] Subjective reported values of the Harvey-Bradshaw index include sense of well-being, abdominal pain, and liquid stools, and the authors only provided scores for bowel movements; objective data were limited.[33] Patients also used cannabis via different routes, in different doses, and in unstandardized preparations without any reporting of additional CAM or recreational drug use.

Naftali and colleagues' subsequent placebo-controlled trial[35] generated significant media attention regarding the therapeutic use of cannabis in IBD; however, the study was met with an equal amount of criticism in the scientific community.[37-39] Critics claimed the trial was underpowered, with only 21 subjects studied over 8 weeks with a 2-week follow-up. The authors measured disease activity using the CDAI, an accepted score system for disease activity in literature, although without specific variable results. The CDAI, similar to the Harvey-Bradshaw index, has subjective parameters, including stool pattern, abdominal pain, and general well-being; a patient with poorly controlled irritable bowel syndrome could appear as a poorly controlled IBD patient via CDAI measurement, as these parameters are the main drivers of the score.[37] Two weeks after cannabis treatment was stopped, the mean CDAI score in the treatment group increased. Naftali and colleagues argued that these results demonstrate a therapeutic role of cannabis; however, it may be that subjects were experiencing central effects of cannabis treatment, ameliorating symptoms during the study rather than actual treatment of inflammation, or were experiencing withdrawal symptoms after completion (although the authors noted that patients denied having withdrawal symptoms after discontinuation of cannabis). Importantly, there were no significant changes in CRP levels during the study; thus, the only parameter of objective treatment efficacy was inconclusive. Endoscopic studies to correlate treatment effect were not performed. While the study attempted to be double-blinded, the authors mentioned that the psychotropic effects of the drug made blinding difficult; at the end of the study, all participants except 2 in the placebo group were able to correctly differentiate whether they had received cannabis or placebo. Critics also noted that patients in remission, defined by a CDAI score of less than 150, can still have significant inflammation on endoscopy. Vu and colleagues suggested that although the authors tried to standardize treatment via distribution of similar quantities of cannabis, the lack of testing of blood levels of cannabis is an additional flaw and hypothesized that unreported additional drug use such as alcohol may affect intrinsic THC levels.[39] The studies by Naftali and colleagues[33,35] were supported, and researchers were employed, by the Tikun Olam Organization, the largest and foremost supplier of medical cannabis in Israel, which openly advocates for use of medical marijuana in many medical conditions and whose website contains data regarding the beneficial effect of medical cannabis.

The prospective trial by Lahat and colleagues was observational rather than a blinded, placebo-controlled study and enrolled only 13 patients for a brief period of 3 months without subsequent follow-up.[34] The authors relied on subjective health questionnaires and health indexes (SF-36, EQ-5D, and the Harvey-Bradshaw index), and were unable to provide endoscopic data, with only limited use of CRP measurements. This trial lacked use of a placebo control, and it is therefore impossible to rule out a placebo effect, as prior data have shown can be quite significant in therapy trials for IBD. Further, Lahat and colleagues were unable to standardize the actual cannabis used in the trial or demonstrate cannabinoid levels.[34] Although the weight of the drug consumed was equivalent, the actual active levels of cannabinoids in the product were not measured, resulting in an absence of data of a possible dose-effect of cannabis use.

Critics share concern that cannabis may simply be masking symptoms without affecting intestinal inflammation. Larger, standardized, placebo-controlled, and blinded trials showing objective improvement in disease are needed. Further demonstration of a low adverse-effect profile prior to the widespread use of cannabis for IBD is also advised.[37]

Concerns Regarding Acute and Chronic Cannabis Use

The safety profile of cannabis is not well established, and use is associated with psychosocial disease and acknowledged physiologic effects. Whereas cannabis use in the United States is illegal by federal law, its legality for medical or recreational use varies by state law, allowing for poor regulation in its preparation, potency, ratio of contents, and route of usage, with variations in requirements for product labeling and testing.[3] Furthermore, Storr and colleagues reported that 36% of patients with IBD who did not use cannabis were worried about side effects of its use.[12]

Many of the psychotropic effects of cannabis are seen in centrally acting cannabinoids, namely THC. Adverse effects of acute use include anxiety, panic, psychosis, tachycardia, and increased appetite with dry mouth.[3] Long-term use also raises concerns regarding development of dependence, tolerance, and withdrawal upon discontinuation. Symptoms of withdrawal include increased irritability, sleep disturbance, anorexia, and depression, yet it is estimated that only approximately 10% of cannabis users ever develop dependency, which is comparatively less than what is seen in tobacco, alcohol, cocaine, or heroin use. No deaths have been solely attributed to marijuana.[15,40]

Chronic use of marijuana has been responsible for an increased risk of motor vehicle crashes, development of amotivational syndrome, altered adolescent neuropsychological development, cannabis hyperemesis syndrome, gynecomastia, impaired immune function, and decreased fertility.[41-43] Diffusion-weighted magnetic resonance imaging of the brain showed impaired axonal connectivity among chronic cannabis users, although subsequent analyses have reported mixed results by linking cannabis with cognitive decline.[44-46] In a systematic review of cannabinoid adverse effects, Wang and colleagues reported nearly 5000 adverse events, approximately 97% of which were not considered to be serious.[43] Among the nearly 150 serious events were vomiting, urinary tract infection, and relapse of treated conditions.

Physiologic studies of cannabis have demonstrated impairment of lung function and development of bronchial inflammation with chronic use. However, this effect is inconclusive in subsequent studies.[47,48] Cannabis use has not been associated with development of cancer, although it has been implicated in cardiovascular disease.[49,50] A recent study by Williams and colleagues revealed that the proinflammatory effects of THC enhance expression of tissue factors with resultant elevated procoagulant activity.[51] This finding suggests that cannabis use could potentiate coagulopathies, especially in individuals with chronic immune activation (eg, IBD patients known to have an increased risk of thrombotic events).

Naftali and colleagues also raise concern of the ideal preparation, drug content, and route of cannabis use if medically legalized.[41] In one study, 45% of patients not using cannabis for IBD treatment declined use because they did not want to smoke drugs.[12] The issue of smoking is of further concern in IBD patients given the detrimental role that smoking cigarettes has shown to have in patients with CD, and thus it would be paramount that any preparations of cannabis lacked both tobacco and nicotine.[52] However, the bioavailability of cannabis is significantly decreased when ingested orally as opposed to inhaled, with significant differences in time to effect, time to peak, and time to elimination, leading to difficulty in regulating a therapeutic dosage.[3,41] Furthermore, once THC enters the bloodstream, it is lipophilic and quickly absorbed in fat tissues, which raises concern of a lasting effect from slow elimination.[41]

In the study by Lal and colleagues, nearly one-third of patients reported significant side effects ranging from feelings of euphoria and heightened awareness to dry mouth, paranoia, palpitations, anxiety, and memory loss.[24] More than 75% of cannabis users in the population study by Storr and colleagues experienced side effects of increased appetite, anxiety, dry mouth, and drowsiness, all largely rated as mild.[12] However, other studies did not report significant side effects or did not include adverse events as a studied parameter.[5,24,26,27]

Recent data by Gubatan and colleagues linked cannabis abuse as an independent risk factor to emergency department visits in gastroenterology patients.[53] Although it was not possible to establish a temporal relationship of cannabis use to emergency department visits or determine that cannabis use has detrimental effects on the primary gastrointestinal

disorder in studied patients, it is important for providers to acknowledge cannabis abuse as a probable marker of disease severity.

Storr and colleagues raised the possibility that cannabis use may result in worsening severity of IBD by promotion of fibrostenosis with increased rates of surgery.[12] While significant research has been published regarding cannabis therapy for IBD over the last decade, equal attention has also been focused on its role in liver disease. Studies suggest cannabis as having a proinflammatory effect on chronic liver disease, resulting in worsening rates of fibrosis.[28,54] Antagonism of the ECS has been proposed as a potential treatment target for chronic hepatitis.[55] However, cannabis has also been theorized to have a protective effect on cardiac fibrosis and has been implicated as protective to end-organ dysfunction in other models.[56,57] It is critical for further studies to not only demonstrate the role of cannabis on inflammation in IBD patients, but also to ensure the lack of progression in the rate of complications.

It is important for future studies to establish a drug preparation that is readily orally bioavailable, demonstrates additive central and peripheral dose effects with a predictive time to effect, and optimizes the risk-to-benefit ratio in a standardized form of production.

Conclusion

A significant portion of IBD patients, particularly those with severe disease, use cannabis to relieve symptoms of pain, nausea, and appetite and to improve their overall mood. The significant morbidity seen in patients with severe disease emphasizes the limited number of conventional therapies for symptomatic control of IBD, a disorder still poorly understood. Patients with IBD have increased rates of psychiatric disease, pain, and malnutrition, and thus the use of adjunctive therapies or CAM to treat poorly controlled symptoms may improve patient morbidity. However, cannabis use, as discussed above, raises concerns of legality, side effects, and preparation, and its use in human trials has failed to provide objective evidence of therapeutic efficacy on endoscopy, biopsy, and inflammatory marker levels.[58] Concerns regarding the possible profibrotic effects of cannabis need further study, as such possible side effects could have consequences in patients with stricturing disease.

The safety profile of cannabis is still not established despite acknowledged detrimental effects. However, current options for IBD management, including corticosteroids, immunomodulators, and biologic agents, carry risks for long-term side effects such as malignancy and infection.[8] Large, randomized, double-blind, placebo- and standard-of-care—controlled trials using standardized, oral preparations of cannabis with long-term follow-up and safety profiles are justified prior to acceptance of medical cannabis as a therapeutic drug.

Footnotes

The authors have no relevant conflicts of interest to disclose.

References

1. Substance Abuse and Mental Health Services Administration. Results From the 2011 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012. NSDUH Series H-44, HHS Publication No. (SMA) 12-4713.

2. Legal issues. NORML. [Accessed October 10, 2016]. www.norml.org/legal

3. Gerich ME, Isfort RW, Brimhall B, Siegel CA. Medical marijuana for digestive disorders: high time to prescribe? Am J Gastroenterol. 2015;110(2):208–214. [PubMed]

4. Belendiuk KA, Baldini LL, Bonn-Miller MO. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. Addict Sci Clin Pract. 2015;10:10. [PMC free article] [PubMed]

5. García-Planella E, Marín L, Domènech E, et al. Use of complementary and alternative medicine and drug abuse in patients with inflammatory bowel disease [in Spanish] Med Clin (Bare). 2007;128(2):45–48. [PubMed]

6. Russo EB, Jiang HE, Li X, et al. Phytochemical and genetic analyses of ancient cannabis from Central Asia. J Exp Bot. 2008;59(15):4171–4182. [PMC free article] [PubMed]

7. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002;54(2):161–202. [PubMed]

8. Alhouayek M, Muccioli GG. The endocannabinoid system in inflammatory bowel diseases: from pathophysiology to therapeutic opportunity. Trends Mol Med. 2012;18(10):615–625. [PubMed]

9. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol. 2006;4(5):621–630. [PubMed]

10. Baron JA, Folan RD, Kelley ML., Jr Ulcerative colitis and marijuana. Ann Intern Med. 1990;112(6):471. [PubMed]

11. Eisenstein M. Medical marijuana: showdown at the cannabis corral. Nature. 2015;525(7570):S15–S17. [PubMed]

12. Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflamm Bowel Dis. 2014;20(3):472–480. [PubMed]

13. Katchan V, David P, Shoenfeld Y. Cannabinoids and autoimmune diseases: a systematic review. Autoimmun Rev. 2016;15(6):513–528. [PubMed]

14. Massa F, Storr M, Lutz B. The endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract. J Mol Med (Berl). 2005;83(12):944–954. [PubMed]

15. Bashashati M, McCallum RW. Cannabis in gastrointestinal disorders. Pract Gastroenterol. 2014;12(4):36–46.

16. Izzo AA, Fezza F, Capasso R, et al. Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. Br J Pharmacol. 2001;134(3):563–570. [PMC free article] [PubMed]

17. Wright KL, Duncan M, Sharkey KA. Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in states of inflammation. Br J Pharmacol. 2008;153(2):263–270. [PMC free article] [PubMed]

18. Wright K, Rooney N, Feeney M, et al. Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. Gastroenterology. 2005;129(2):437–453. [PubMed]

19. Schicho R, Storr M. Cannabis finds its way into treatment of Crohn's disease. Pharmacology. 2014;93(1-2):1–3. [PMC free article] [PubMed]

20. Massa F, Marsicano G, Hermann H, et al. The endogenous cannabinoid system protects against colonic inflammation. J Clin Invest. 2004;113(8):1202–1209. [PMC free article] [PubMed]

21. Engel MA, Kellermann CA, Burnat G, Hahn EG, Rau T, Konturek PC. Mice lacking cannabinoid CB1-, CB2-receptors or both receptors show increased susceptibility to trinitrobenzene sulfonic acid (TNBS)-induced colitis. J Physiol Pharmacol. 2010;61(1):89–97. [PubMed]

22. Di Sabatino A, Battista N, Biancheri P, et al. The endogenous cannabinoid system in the gut of patients with inflammatory bowel disease. Mucosal Immunol. 2011;4(5):574–583. [PubMed]

23. Marquez L, Suárez J, Iglesias M, Bermudez-Silva FJ, Rodríguez de Fonseca F, Andreu M. Ulcerative colitis induces changes on the expression of the endocannabinoid system in the human colonic tissue. PLoS One. 2009;4(9):e6893. [PMC free article] [PubMed]

24. Lal S, Prasad N, Ryan M, et al. Cannabis use amongst patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2011;23(10):891–896. [PubMed]

25. Rawsthorne P, Shanahan F, Cronin NC, et al. An international survey of the use and attitudes regarding alternative medicine by patients with inflammatory bowel disease. Am J Gastroenterol. 1999;94(5):1298–1303. [PubMed]

26. Ravikoff Allegretti J, Courtwright A, Lucci M, Korzenik JR, Levine J. Marijuana use patterns among patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(13):2809–2814. [PMC free article] [PubMed]

27. Weiss A, Friedenberg F. Patterns of cannabis use in patients with inflammatory bowel disease: a population based analysis. Drug Alcohol Depend. 2015;156:84–89. [PubMed]

28. Ishida JH, Peters MG, Jin C, et al. Influence of cannabis use on severity of hepatitis C disease. Clin Gastroenterol Hepatol. 2008;6(1):69–75. [PMC free article] [PubMed]

29. Borrelli F, Aviello G, Romano B, et al. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. J Mol Med (Berl). 2009;87(11):1111–1121. [PubMed]

30. Jamontt JM, Molleman A, Pertwee RG, Parsons ME. The effects of deltatetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. Br J Pharmacol. 2010;160(3):712–723. [PMC free article] [PubMed]

31. Cluny NL, Keenan CM, Duncan M, Fox A, Lutz B, Sharkey KA. Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (SAB378), a peripherally restricted cannabinoid CB1/CB2 receptor agonist, inhibits gastrointestinal motility but has no effect on experimental colitis in mice. J Pharmacol Exp Ther. 2010;334(3):973–980. [PubMed]

32. D'Argenio G, Valenti M, Scaglione G, Cosenza V, Sorrentini I, Di Marzo V. Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation. FASEB J. 2006;20(3):568–570. [PubMed]

33. Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM. Treatment of Crohn's disease with cannabis: an observational study. Isr Med Assoc J. 2011;13(8):455–458. [PubMed]

34. Lahat A, Lang A, Ben-Horin S. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. Digestion. 2012;85(1):1–8. [PubMed]

35. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 2013;11(10):1276–1280.e1. [PubMed]

36. Schicho R, Storr M. IBD: patients with IBD find symptom relief in the Cannabis field. Nat Rev Gastroenterol Hepatol. 2014;11(3):142–143. [PMC free article] [PubMed]

37. Herfarth HH, Long MD, Isaacs KL. If your physician cannot help, try cannabis: how trial design may lead to hazardous conclusions. Clin Gastroenterol Hepatol. 2014;12(5):897–898. [PubMed]

38. Lahiff C, Cheifetz AS. The holistic effects of cannabis in Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(5):898. [PubMed]

39. Vu MP, Melmed GY, Targan SR. Weeding out the facts: the reality about cannabis and Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(5):898–899. [PubMed]

40. Anthony JC, Warner L, Kessler R. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol. 1994;2:244–268.

41. Naftali T, Mechulam R, Lev LB, Konikoff FM. Cannabis for inflammatory bowel disease. Dig Dis. 2014;32(4):468–474. [PubMed]

42. Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004;53(11):1566–1570. [PMC free article] [PubMed]

43. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabi-noids: a systematic review. CMAJ. 2008;178(13):1669–1678. [PMC free article] [PubMed]

44. Zalesky A, Solowij N, Yücel M, et al. Effect of long-term cannabis use on axonal fibre connectivity. Brain. 2012;135:2245–2255. (pt 7) [PubMed]

45. Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. Exp Clin Psychopharmacol. 2012;20(5):420–429. [PubMed]

46. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012;109(40):e2657–e2664. [PMC free article] [PubMed]

47. Lee MHS, Hancox RJ. Effects of smoking cannabis on lung function. Expert Rev Respir Med. 2011;5(4):537–546. [PubMed]

48. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012;307(2):173–181. [PMC free article] [PubMed]

49. Bowles DW, O'Bryant CL, Camidge DR, Jimeno A. The intersection between cannabis and cancer in the United States. Crit Rev Oncol Hematol. 2012;83(1):1–10. [PubMed]

50. Sidney S. Cardiovascular consequences of marijuana use. J Clin Pharmacol. 2002;42(11) suppl:64S–70S. [PubMed]

51. Williams JC, Klein TW, Goldberger BA, Sleasman JW, Mackman N, Goode-now MM. A(9)-tetrahydrocannabinol (THC) enhances lipopolysaccharide-stim-ulated tissue factor in human monocytes and monocyte-derived microvesicles. J Inflamm (Lond). 2015:12–39. [PMC free article] [PubMed]

52. Cosnes J, Carbonnel F, Carrat F, Beaugerie L, Cattan S, Gendre J. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. Aliment Pharmacol Ther. 1999;13(11):1403–1411. [PubMed]

53. Gubatan J, Staller K, Barshop K, Kuo B. Cannabis abuse is increasing and associated with increased emergency department utilization in gastroenterology patients. Dig Dis Sci. 2016;61(7):1844–1852. [PubMed]

54. Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. Hepatology. 2005;42(1):63–71. [PubMed]

55. Teixeira-Clerc F, Julien B, Grenard P, et al. CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. Nat Med. 2006;12(6):671–676. [PubMed]

56. Brunet L, Moodie EE, Rollet K, et al. Canadian Co-infection Cohort Investigators. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: a longitudinal cohort analysis. Clin Infect Dis. 2013;57(5):663–670. [PMC free article] [PubMed]

57. Rajesh M, Mukhopadhyay P, Bátkai S, et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. J Am Coll Cardiol. 2010;56(25):2115–2125. [PMC free article] [PubMed]

58. Volz MS, Siegmund B, Häuser W. Efficacy, tolerability, and safety of cannabinoids in gastroenterology: a systematic review [in German] Schmerz. 2016;30(1):37–46. [PubMed]

Chronic urologic pain: Putting it all together

J. Curtis Nickel, MD, FRCSC

Department of University, Queen's University, Kingston, ON, Canada

Cite as: *Can Urol Assoc J* 2018;12(6Suppl3):S189-90. http://dx.doi.org/10.5489/cuaj.5334

We all struggle with how to approach, evaluate, and manage our patients with chronic urologic pain. I have been involved in research and clinical care for this patient population for over 25 years, but have learned many lessons from my urology friends who agreed to provide chapters in this supplement. It was an educational experience for me (and hopefully for the readers of this supplement as well) to discover how my colleagues understand, evaluate, and treat their patients with the various urologic pain syndromes. To put it all together, I have listed below some of the major lessons we can learn from this supplement.

Lesson 1: Mechanisms of chronic urologic pain

A practical understanding of the mechanisms operative in individual patients' pain experience may allow for optimal development of a personalized, mechanistic, directed treatment strategy.

Lesson 2: Evaluation of the female with urologic chronic pelvic pain syndrome

Assessment of the entire patient, including a complete history, focused physical examination, which must include a pelvic examination (including assessment of pelvic floor), a cystoscopy (under local anesthetic), as well as an understanding of the patient's quality of life, activities, and treatment goals will improve subsequent management strategies.

Lesson 3: Evaluation of the male with urologic chronic pelvic pain syndrome

A simple assessment with a focused history, physical examination (which includes pelvic floor evaluation as part of the digital rectal examination), symptom inventory, and screening for associated confusable pain conditions will result in a comprehensive determination of the patient's "clinical picture." Knowing the individual patient phenotype associated with the UCPPS clinical picture will allow for development of a personalized, phenotype-specific therapeutic plan.

Lesson 4: Medical management of chronic pain

Consider a multidisciplinary and multimodal approach in the management of complex chronic pain. Urologists managing chronic pain must know the options available and be ready to use them.

Lesson 5: Management of interstitial cystitis/bladder pain syndrome

It is our job as urologists to help patients set realistic expectations in order for them to learn to cope and to improve their quality of life. Successful management is to know all your treatment options and then to use them in a multimodal and individualized therapeutic strategy. Be ready to refer to appropriate consultants when other, non-urologic pain generators are present.

Lesson 6: Management of chronic prostatitis/chronic pelvic pain syndrome

The most successful management of male urinary chronic pelvic pain syndrome is not typically accomplished by a sequential monotherapeutic approach, but rather an individualized or personalized phenotype-directed multimodal approach. All the modalities of therapy outlined in the supplement must be considered as a possible therapeutic option for each individual patient.

Lesson 7: Management of chronic scrotal contents pain

The approach to best manage chronic scrotal contents pain includes first conservative therapy, then psychotherapy, physical therapy, medical neuromodulation, and nerve injections, followed by consideration of more invasive surgical options (vasovasotomy, epidymectomy, microsurgical denervation, and orchiectomy).

Lesson 8: Evaluation and management of chronic renal pain

For patients with either unexplained renal/flank pain or one of the enigmatic conditions for which we do not have evidence-based therapies, pharmacologic treatments, ancillary surgical procedures, and psychological support are required to reduce the impact of the pain on the patient's quality of life.

Lesson 9: Physiotherapy for urologic chronic pelvic pain

It is imperative for the urologist evaluating and managing patients with urologic chronic pelvic pain that they evaluate the pelvic floor for pain, spasm, and/or dysfunction. When diagnosed, the patient can be referred for pelvic floor physiotherapy. A physiotherapist with expertise in pelvic pain management will make a major difference in pain amelioration in these patients.

Lesson 10: Psychological correlates in urologic chronic pelvic pain

It is important for the urologist to understand the various psychological factors that can modulate the patient's pain experience — stress/anxiety, depression, pain contingent rest, spousal social support, and catastrophizing — as well as be employed in pain coping mechanisms in patients with chronic urologic pain. By recognizing the presence of these factors in individual patients, the urologist can address them and manage them as part of the overall pain management strategy.

Lesson 11: Nurses perspective in management of urologic chronic pelvic pain

A urology nurse dedicated and trained to deal and manage urologic chronic pain patients will allow for a more comprehensive assessment and ultimately improved management of the urology patient with UCPPS referred to a general urology clinic. The nurse can obtain an excellent history by having more time for active listening, can use the various symptom questionnaires, explore associated pain conditions, set up the urologic examination and cystoscopy by the urologist, and assist in developing personalized treatment plans that include patient education. This approach leads to less frustration for both the patient and the urologist, and undoubtedly better overall care and improved outcomes.

Lesson 12: Medical marijuana for urologic chronic pelvic pain

While marijuana or cannabis treatment may not lead to significant pain relief, it is a far superior approach to manage chronic pain compared to chronic opioid therapy. But it does seem to result in a wonderful placebo effect. It is further suggested that marijuana (or at least its placebo effect) appears to help many patients better cope with their chronic pain syndrome. Coping with chronic pain is the key to improved quality of life and improved mental and physical activity. But the urologist who prescribes marijuana must be educated in patient selection (including identifying patients at risk), marijuana components (TCH/CBD combinations), administration alternatives, doses, and clinical followup.

Lesson 13: Neuromodulation for urologic chronic pelvic pain

In many, if not most cases, chronic pelvic pain and associated urinary symptoms are neurologically mediated. By inhibitory stimulation of the pelvic floor and organs via the S3 nerve root, sacral neuromodulation provides an option for some patients with chronic pelvic pain syndrome.

Lesson 14: Nerve injection therapy for urologic chronic pelvic pain

Nerve blocks with short-acting local anesthetics of the spermatic cord nerve and pudendal nerve allows for better diagnosis of neuropathic-related orchiodynia and pelvic floor pain, respectively. Serial injections with long-acting local anesthetics provide the potential for improvement in long-term pain intensity, likely through a neurogenic down-regulation process.

The most important lesson

Managing an enigmatic, unexplained condition such as urologic chronic pain can be a confusing exercise in frustration. The most important question learned from this supplement is that when in doubt, who are you going to call? You call your friend and colleague, of course. In this unique supplement, our colleagues have indeed risen to the challenge and provided very practical tips and lessons on how to best manage this common and very important urologic patient population.

Correspondence: Dr. J. Curtis Nickel, Department of Urology, Queen's University, Kingston, ON, Canada; jcn@queensu.ca

SECTION I

[redacted]

[redacted]

1/16/19

Medical Marijuana Program
165 Capitol Avenue, Rm 145
Hartford, CT 06106-1630

To Whom it may concern

[redacted] is under my care for interstitial cystitis. Her treatment includes bladder instillation therapy, phenazopyridine, anticholinergics and analgesics. The treatments are effective; however, she does experience flare ups which at times are unbearable. The symptoms she experiences during her flare ups includes bladder/pelvic pain, urinary frequency and or urgency.

After reading the studies on medical cannabis for interstitial cystitis, I feel that [redacted] will benefit from medical marijuana. It will keep her symptoms under control and reduce the occurrence of flare ups.

Sincerely,

[redacted]

[redacted] APRN

[redacted]

SECTION J

Sexuality and Disability, Vol. 17, No. 1, 1999

When Pleasure Causes Pain: Living with Interstitial Cystitis

Naomi B. McCormick, Ph.D.[1]

Interstitial cystitis (IC) is a chronic inflammatory condition of the bladder wall associated with genital and bladder pain, urgency, and dyspareunia. Characterized by sterile urine culture, IC is poorly understood and resistant to treatment. This article contextualizes patients' experiences from the standpoint of age, ethnicity, gender, socioeconomic status, and the experience of concomitant disease. More than 90 percent of interstitial cystitis patients are women, an alarming number of whom have been misdiagnosed as having psychiatric disorders. Medical diagnosis and treatment are discussed from a feminist perspective. The sexual functioning of persons with IC is discussed in depth. Topics touched upon include menstrual cycle variations and pregnancy, sexual desire, pain during sexual activity, sexual side-effects of medications, sexual history, and sexual self-care.

KEY WORDS: interstitial cystitis; bladder pain; sexual dysfunction; dyspareunia; sexual self-care.

Interstitial cystitis (IC) is a chronic inflammatory condition of the bladder wall (1). My knowledge of this disease comes both from research and lived experience. I am a clinical psychologist, sexual scientist and an IC patient; I have talked to numerous patients about the disease in all three roles (2). The Interstitial Cystitis Association, founded in 1984, has been instrumental in educating the public and obtaining funding for research on this little-known disease (3,4).

Although IC was first recognized clinically in 1887, it remains poorly understood and resistant to treatment (5). A painful bladder syndrome that affects an estimated 450,000 Americans, more than 90% of all diagnosed interstitial cystitis patients are women (6,7,8).

[1]Address correspondence to Naomi B. McCormick, Ph.D., Clinical Health Psychologist, Allen Memorial Hospital, 1825 Logan Avenue, Waterloo, IA 50703-1999; e-mail: NMcCormick@CFU-Cybernet.net.

0146-1044/99/0300-0007$16.00/0

Most patients are middle-aged adults but interstitial cystitis can occur at any age (9). Diagnosed IC sufferers are almost always Caucasian women, but this may reflect access to medical care more than demographic differences in susceptibility (1,9). Minority women do suffer from interstitial cystitis, but wait longer than white women to receive an accurate diagnosis (10,9). Socioeconomic status is inversely associated with the severity of reported symptoms. Severe IC symptoms are associated with having little education, being unemployed or underemployed, changing jobs frequently, and having a low household income (7).

Interstitial cystitis patients often suffer from other diseases. A national database study revealed that IC patients were significantly more likely than the general population to be treated for allergies, irritable bowel syndrome, sensitive skin, vulvodynia, and fibromyalgia (11). Vulvodynia is characterized by painful red patches in the vaginal vestibule; patients with active symptoms find genital touch excruciating. Vulvodynia, in combination with IC, has an especially deleterious effect on sexual desire and pleasure.

Characteristic interstitial cystitis symptoms include intense pain in the genital and bladder regions, an unrelenting urge to void, bladder spasms, and dyspareunia or painful sexual intercourse (12,13,1).

> IC patients have described the pain associated with their disease as feeling "like a hot poker is being held against the bladder wall," like "acid on an open wound," or "like razor blades in the bladder".... IC pain can be unremitting.... Urinary frequency of 10 to 50 times—sometimes even more—in 24 hours is another hallmark symptom of IC. Many patients have the urgent need to urinate every 5 to 15 minutes and may wake to urinate numerous times during the night. Some . . . sleep on the bathroom floor to be near the toilet (14, pp. 10–11)

Lower back pain and pain of the urethra, vulva, or anus are also reported (13). Some patients live lives of intractable pain, making travel impossible and leaving many patients homebound (15). For many individuals who have active symptoms, pain is relieved only briefly when voiding. Since pain and urgency contribute to sleep deprivation, many interstitial cystitis patients also suffer from extreme fatigue (12). On a bad night, for example, I visit the toilet every 20 minutes and end up with only two or three hours of uninterrupted sleep.

Very few people have heard of interstitial cystitis (12). Until recently, many physicians (including a surprising number of urologists) knew little about the disease or how to diagnose and treat patients. Although there is a growing amount of research, the cause of this disease remains mysterious (16,17,6). To date, the best treatments for IC yield temporary and sometimes disappointing results. It often takes years for a patient to be diagnosed correctly and longer still to find a treatment or combination of treatments which provides sufficient relief from symptoms (12). The great challenge of this disease is learning to live with uncertainty, frustration, urgency, and chronic pain.

DIAGNOSIS AND TREATMENT

To diagnose interstitial cystitis, the urologist distends the patient's bladder under anesthesia and looks for glomerulations (pin-point hemorrhages) or less often, a classic Hunner's ulcer (9,1,6). The typical IC patient has less than 350 cc maximal bladder capacity while awake and experiences involuntary bladder contractions. Other diseases (such as genital herpes, vaginitis, tuberculosis, prostate infection and cancer) must be ruled out.

There is no consensus on the etiology of interstitial cystitis which may be multifactoral (17). The urine culture of an IC patient is usually sterile. Researchers have attributed the syndrome to difficult-to-culture infections from viruses or fastidious bacteria, damage to the bladder mucosa or bladder glycosaminoglycan (GAG) protective layer, neurally mediated inflammation, autoimmune disease, vascular or lymphatic obstruction, toxic urinary agents, and other causes (18,6,9,17).

A wide variety of medical treatments have been used to manage IC (1,13). Surgical removal of the bladder is no longer recommended although patients with intractable pain sometimes seek this option. Common and more conservative treatments include bladder instillation of dimethyl sulfoxide (DMSO), which has anti-inflammatory properties, and the attempt to create an artificial protective layer in the bladder with heparin, sodium pentosan-polysulfite (Elmiron), and sodium hyaluronate (Cystistat). IC patients are also prescribed antidepressants, antispasmodic drugs, antihistamines and other drugs, especially pain-control agents. Some patients undergo periodic bladder hyperdistentation in an attempt to expand bladder capacity and relieve symptoms. Others vary diet and lifestyle, avoiding caffeine and spicy foods and undertaking regular exercise to enhance their overall sense of well-being. Transcutaneous electrical stimulation (TENS), acupuncture, and other pain-management techniques have been employed by some patients (13). Patients typically try many treatments and combinations of treatments before obtaining relief (which is usually temporary). The most popular self-care strategies for acute attacks of interstitial cystitis are praying and recalling past relief (19).

Under-Diagnosis and Misdiagnosis

Interstitial cystitis has until recently been under-diagnosed and misdiagnosed. Patients, especially female patients, who present complaints that do not appear to have a readily known physiological basis tend to be labeled as "somaticizers, hypochondriacs, or overutilizers" (20, p. 191). Until recently, IC patients stood a good chance of being misdiagnosed as having a somaticization disorder (21). As Denise Webster explains, medical conditions that are difficult

to diagnose, respond poorly to treatment, and afflict women more than men are often suspected by physicians to be symptomatic of psychiatric disturbance. For example, I was referred to a psychologist even after I was diagnosed with interstitial cystitis to assess why my pain had not been alleviated by conventional medical treatment. A more useful referral would have been to a pain management specialist.

Interstitial Cystitis Association activists point out that IC pain can be excruciating and unremitting and "should be treated as aggressively as the acute pain of injuries, burns, [and] cancers" (14, p. 11). Unfortunately, this is rarely the case. Forty-three percent of the women with IC who participated in Webster's (21) research had been previously misdiagnosed as having a psychiatric disorder. Too many health care practitioners who should know better erroneously attribute the psychological distress experienced by painful bladder syndrome patients to their presumed mental illness (13).

SEXUAL FUNCTIONING

Menstrual Cycle and Pregnancy

Hormone fluctuations may play a role in the syndrome. Many women with IC report that their symptoms are worse from midcycle until menstruation but they experience remission during pregnancy (22,18,19). Because most patients have dyspareunia, getting pregnant can be painful (14). Sexual activity is particularly painful for younger, premenopausal women (23). The unpredictability of interstitial cystitis makes it difficult for patients to anticipate how it will affect their sexual relationship and ability to function as parents (24,14).

Sexual Desire and Pain

Frequently, interstitial cystitis has a devastating impact on sexuality (25,26,27,28,8,13,15,22,23). Most patients complain of decreased interest in sexual interactions. And, depending upon the study cited and how questions are phrased, approximately 50 to 90 percent of heterosexual women with IC report that sexual intercourse is now sometimes or always painful (13). Webster notes the methodological problem inherent in asking IC patients whether or not they experience painful intercourse.

> Part of the difficulty in obtaining accurate information about rates of dyspareunia lies in patients' interpretation of the term *painful intercourse.* In my survey of 138 women with IC, I found many women indicated that they did not have pain with intercourse—but

> several wrote in the margin that this was because they no longer had intercourse—because of the likelihood of pain! In other cases women wrote that they didn't have pain *during* intercourse but would find they had increased pain the next day and several days thereafter (13, p. 199).

There is no systematic research on the sexual problems faced by men with IC, but physicians suggest that these men also experience painful intercourse (29). Adding to the sexual concerns of men with IC, a number have undergone prostrate surgery as a result of prior misdiagnosis. Unfortunately, this type of surgery increases their risk for erection difficulties (30,2).

To date, there is no systematic research on the sexual experiences of bisexual and homosexual persons with interstitial cystitis. I have yet to read a single case study describing the sexual adjustment of a lesbian or gay man with IC. This gap in the literature is most unfortunate. Unlike heterosexuals, gay, lesbian and bisexual persons are unlikely to have intercourse, the most problematic sexual activity for IC patients. Also, same-sex couples may engage in a greater variety of sensual and sexual activities with partners than their heterosexual counterparts (31). Their strategies for remaining sexual despite interstitial cystitis may be instructive and beneficial for patients of all sexual orientations.

One third of women with IC complain that having their genitals touched and most of all, experiencing orgasms, exacerbates their pain (26,8,13). Because they fear additional pain and often live with constant, excruciating pain, many IC patients reduce the frequency of their sexual activities dramatically, especially that of sexual intercourse (23,26). Couples often grieve this change in their sexuality. Decreased sexual contact and enjoyment of sexual interactions can be very depressing to those who previously took great pleasure and pride in sexual expression.

It is not unusual for partners to report that they have developed sexual dysfunctions out of sympathy for their loved one who suffers from IC. Specifically, arousal or erection difficulties may be precipitated by anxiety about harming a partner during sexual activity; these in turn interfere with sexual enjoyment during the all-too-few times that IC patients desire or initiate lovemaking (32,26).

Interstitial cystitis can destroy the romantic ambiance (33,8,13,26,32). Frequent trips to the toilet during sexual activity can interfere with a couple's sexual mood. The sensation of unrelenting genital pain may cloud patients' awareness of sexual excitement or alternatively, may mimic vasocongestion, making the patient wonder whether her IC is acting up or she is experiencing insatiable sexual desire.

Many interstitial cystitis patients complain of low sexual desire. Equally problematic, IC patients occasionally report having sex with partners regularly, even though it is painful, because of guilt, fear of rejection, or a sense of duty.

The sexual problems which are caused by interstitial cystitis are exacerbated by guilt and women's sense of duty. Traditional sex-role socialization teaches heterosexual women to be more concerned with male pleasure than their own pleasure (31). For women with IC, traditional sexual scripts can have disastrous consequences.

Sexual Side-Effects of Medications

A number of medications used by patients to control pain or reduce urgency may interfere with lubrication, arousal, and orgasm (34,35,36,37,38). Antidepressants, for example, are widely used by IC patients to reduce urgency as well as sensations of suprapubic pain. Unfortunately, these very drugs, especially at higher doses, can inhibit lubrication, make genital contact uncomfortable, and even delay or prevent orgasm and ejaculation. An increasing number of IC patients, myself included, use antidepressants that block serotonin reuptake to manage symptoms. Although these drugs don't have the drying effects of amitriptyline or imipramine (medications which stimulate the activity of both norepinephrine and serotonin), fluoxetine and related serotonin-enhancing drugs are much more likely to contribute to sexual dysfunction (36). Antidepressants have been linked to delayed orgasm, inability to climax, and erectile difficulties. Men are more likely than women to complain to their physicians about these sexual side-effects, but that does not mean that women aren't equally troubled (39). Recently, skilled psychiatrists have developed effective medical strategies for reducing the likelihood of antidepressant-induced sexual dysfunctions. Research suggests that drugs like bupropion may alleviate sexual difficulties experienced by some patients who otherwise benefit from the new antidepressants.

No discussion of medication is complete without consideration of dimethyl sulfoxide or DMSO (40,1,13). DMSO is a popular, time-tested treatment for providing IC patients with symptomatic relief. Unfortunately, the drug has a nasty side-effect: powerful and long-lasting garlic-like breath odor and taste in the mouth. The smelly side-effect lasts between 24 and 48 hours. As a result, most patients feel self-conscious and try to avoid social interactions for several hours. Needless to say, a powerful garlic odor does not enhance sexual attractiveness. My husband and I still joke about the day I attempted to kiss him when he was driving me home from a DMSO injection. It was below zero and he had rolled down all the car windows. Although he is unusually supportive, he was absolutely repulsed by my kiss. Apparently I smelled and tasted like the putrid garbage one would find behind a pizza parlor. I definitely would not recommend DMSO as an aphrodisiac!

Previous Sexual History

Some mental health professionals have associated IC patients' symptoms of genital pain and pain during intercourse with a possible history of sexual abuse (41). I agree that sexual abuse and assault are all too common female experiences (31). However, this is no excuse to again blame women for their urological symptoms. Many women who have experienced sexual abuse or coercion never develop interstitial cystitis. Even if a patient recalls having been sexually abused, this is not evidence that her suprapubic pain and discomfort during intercourse are caused by psychopathology, not bladder disease (41).

Adjusting to Sexual Difficulties

Although most IC patients report that their symptoms interfere with sexual responsiveness and enjoyment, a few indicate that interstitial cystitis has had no effect on their sexuality or has enhanced their sexual creativity and energy (42,2,32,33). Some remarkable IC patients I have talked with, for example, have retained or even enhanced sexual pleasure by initiating erotic activity and choreography to reassure partners that they truly desired sex, catheterizing themselves to anesthetize their bladders prior to sexual intercourse, and keeping a plastic-lined, garbage can at bedside for voiding so they don't have to interrupt lovemaking with frequent visits to the toilet (30).

Obviously, it is difficult to enjoy sex with excruciating suprapubic pain. One of the most popular sexual self-care strategies is to avoid sexual activity, especially intercourse, when IC symptoms are troubling (13,23). IC patients also report emptying their bladders before and after sexual activity, avoiding prolonged intercourse, experimenting with sexual positions and activities that minimize pressure on the urethra, minimizing post-coital irritation by cleansing sexual secretions and spermicides, and taking pain-controlling or antispasmodic medications prior to sexual activity (23,26,28). Some IC patients I talked with said that oral sex was more pleasurable and less likely to bring about discomfort than intercourse (30).

Remaining sexual as an IC patient requires flexibility and ingenuity. My husband and I, for example, have learned to schedule our sexual interactions in the early morning, when my symptoms are least problematic. I also prefer sex in the morning because it gives me a whole day to recover from any lingering spasms. Other women are more sexually ingenious. Denise Webster has talked to women who freeze water in balloons, inserting these inside their vaginas to dull pain from intercourse.

In order to make a satisfactory sexual adjustment to IC, patients may find it helpful to give up our culture's incredible obsession with intercourse and

orgasms. Interstitial cystitis patients, like others who live with disability, have much to teach the rest of the population about sex. Sex is more or should be much more than Tab A into Slot B accompanied by orgasms (31,42). Sex ideally includes all aspects of intimacy, physical and emotional.

IC patients and their partners adjust best if they reframe sexuality to include any and all forms of whole body sensual expression and emotional and intellectual sharing. Traditional sexual scripts need to be replaced by doing things like holding a partner who masturbates to orgasm or sharing a sensual massage (26). Regardless of how often patients feel up to sex or how varied (or not) their sexual activities have become, they need to remind themselves that they are lovable, sexual persons who don't have to engage in frequent, genital gymnastics in order to prove their adequacy (2). Unflinching self acceptance and a solid, open relationship with a sensitive partner are prerequisites to satisfactory sexual adjustment.

Relationship Issues

Chronically ill persons who have supportive partners and families cope better with pain and other symptoms than their less fortunate counterparts (43). IC generally is not associated with marital or family disruption (22). In fact, IC patients turn to their partner or spouse more than anyone else when they seek emotional support for their illness (44,19). Nonetheless, I do not want to paint an unrealistically positive picture. I have talked to nearly fifty partners of IC patients about their experiences in workshops (45). A number of these individuals complain of a worsened quality of life. Specifically, healthy partners say that their partner's painful bladder disease contributed to disturbed sleep, increased household and childcare responsibilities, financial hardships, and isolation. Their biggest complaint is that their partner's suffering makes them suffer too; they are upset about their inability to stop their loved one's pain.

Despite the disease's negative consequences, some couples have told me that the challenge of IC has actually improved their relationship (26,45). These individuals point out improved communication and trust, closer team-work, enhanced self-esteem, and renewed gratitude for "the little things" that make their relationship so special. Some couples report enhanced intimacy and the eroticization of nongenital sex in response to one partner's interstitial cystitis. Sometimes, interstitial cystitis can enhance partners' sense of purpose. Several couples I have met at meetings of the Interstitial Cystitis Association have adjusted to IC by focusing on their relationship more than the disease.

Sexual Self-Care

The primary symptoms of interstitial cystitis are low pelvic pain and urgency. Few diseases present a greater sexual challenge. Many IC patients worry about maintaining their sexual relationships despite having a disease that can turn pleasure (intercourse and even orgasm) into pain. Denise Webster's research is essential reading for women with interstitial cystitis. Webster has archived a rich variety of sexual self-care strategies, including the following (13, see p. 201):

- Urinating before and immediately after sexual activity.
- Avoiding intercourse when symptoms are most active; avoiding prolonged sexual intercourse.
- Experimenting with sexual positions that put less pressure on the urethra.
- Employing vaginal lubricants to reduce sexual discomfort.
- Taking antispasmodic medication before sexual activity.
- Avoiding diaphragms and condoms if these are irritants.
- Increasing sexual honesty; telling a partner exactly what is pleasurable and what is painful.
- Becoming more sensual; making sexual interactions less genital and more whole-body, whole-mind experiences.

The Major Challenge

The major challenge of remaining sexual despite IC is cognitive. How can patients continue to see ourselves as sexual and attractive when we spend so much of our lives visiting the toilet or thinking about visiting the toilet? How can we continue to be sexual when activities that used to be pleasurable may now cause pain? My own spiritual journey, like that of so many others who live with disability, has been to reframe illness into something that is normal and even inspirational (46,2). I have reframed the disease, including my sexual symptoms, as being a part of my life but not who I am. I use humor to reduce the power of the disease and to reshape my sexuality, I laugh at the irony of a sex researcher living with a disease that causes "crotch pain" as a friend with IC and I call it. She and I purchased a pair of vulva-shaped earrings; darkly pink, they remind us of the unexpected similarity between sensations of engorgement and genital pain.

I delight in the triumphant humor of other interstitial cystitis patients. I attack the shame of living with chronic illness by telling others of my invisible

disability (as if they wouldn't guess it from watching my frequent trips to public toilets). Coping with IC, remaining sexual despite IC, requires me, requires my sister and brother patients, to come out of our collective water closets (47). Once we can be sexually honest with ourselves and our partners, the rest is easier.

For women (and almost all patients with IC are women), the challenge is also breaking out of traditional sex roles. We cannot be sexually passive anymore; we must tell our partners when we want sex, when we don't want it, and how we want it. We must see ourselves as sexual actors who have sexual rights, not as sexual objects whose major role is to please others (31). To experience sexual pleasure, women with IC must assume sexual responsibility, embracing partners who are not threatened by honesty and erotic creativity. My life has been enriched by the many couples I have met at meetings of the Interstitial Cystitis Association who do just that. IC, they tell me, has motivated them to enhance their communication and mutual trust (2). Interstitial cystitis, they explain, has led to increased self-acceptance. IC, they note, has stimulated them to focus more on their relationships and less on their health problems, enhancing their pleasure and managing their pain to the best of their abilities.

REFERENCES

1. Toozs-Hobson P, Gleeson C, Cardozo L: Interstitial cystitis—still an enigma after 80 years. *British Journal of Obstetrics and Gynaecology* 103:621–624, 1996
2. McCormick NB. Psychological aspects of interstitial cystitis. *In* Interstitial Cystitis, GR Sant (ed). Philadelphia: Lippincott-Raven, 1997, 193–203
3. Interstitial Cystitis Association, 51 Monroe Street, Suite 1402, Rockville, MD 20850; http://www.ichelp.com
4. Wein AJ, Hanno PM: Introduction: Interstitial cystitis: An update of current information. *In*: Interstitial Cystitis: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A): 1, supplement to May 1997
5. Hofmeister MA, Fang H, Ratliff TL, Mahoney T, Becich MJ: Mast cells and nerve fibers in interstitial cystitis (IC: An algorithm for histologic diagnosis via quantitative image analysis and morphometry (QIAM). *In*: Interstitial Cystitits: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A): 41–47, supplement to May 1997
6. Mobley DF, Baum N: Interstitial cystitis: When urgency and frequency mean more than routine inflammation. Postgraduate Medicine 99(5):201–208, 1996
7. Simon LJ, Landis R, Erickson DR, Nyberg LM, ICDB Study Group: The Interstitial Cystitis Data Base Study: Concepts and preliminary baseline descriptive statistics. *In*: Interstitial Cystitits: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A): 64–75, supplement to May 1997
8. Webster DC: Sex and interstitial cystitis: Explaining the pain and planning self-care. Urologic Nursing 13(1):4–11, 1993
9. Jones CA, Nyberg LM Jr: Epidemiology of interstitial cystitis. *In*: Interstitial Cystitits: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A): 2–9, supplement to May 1997
10. Sant G: interstitial cystitis in minority women. Journal of the Association for Academic Minority Physicians 4(3):89–92, 1993

11. Alagiri M, Chottiner S, Ratner V, Slade D, Hanno PM: Interstitial cystitis: Unexplained associations with other chronic disease and pain syndromes. *In*: Interstitial Cystitis: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A):52–57, supplement to May 1997
12. Rabin C: Interstitial cystitis: An underrecognized women's health condition. The Health Psychologist 19(2):6, 20–21, Spring 1997
13. Webster DC: Sex, lies, and stereotypes: Women and interstitial cystitis. *In*: Bodies Besieged: The Impact of Chronic and Serious Physical Illness on Sexuality, Passion, and Desire, NB McCormick (special issue ed). The Journal of Sex Research 33(3):197–203, 1996
14. Slade D, Ratner V, Chalker R: A collaborative approach to managing interstitial cystitis. *In*: Interstitial Cystitis: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A): 10–13, supplement to May 1997
15. Ratner V, Slade D, Whitmore KE: Interstitial cystitis: A bladder disease finds legitimacy. Journal of Women's Health 1(1):63–68, 1992
16. Elbadawi A: Interstitial cystitis: A critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. *In*: Interstitial Cystitis: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A): 14–40, supplement to May 1997
17. Ratliff TL, Klutke CG, McDougall EM: The etiology of interstitial cystitis. Urological Clinics of North America 21:21–30, 1994
18. Letourneau R, Pang X, Sant GR, Theoharides TC: Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. British Journal of Urology 77:41–54, 1996
19. Webster DC, Brennan T: Self-care strategies used for acute attack states of interstitial cystitis. Urologic Nursing 15(3):86–93, 1995
20. Draucker CB: Coping with a difficult-to-diagnose illness: The example of interstitial cystitis. Health Care for Women International 12:191–198, 1991
21. Webster D: Interstitial cystitis: Women at risk for psychiatric misdiagnosis. AWHONN's Clinical Issues in Perinatal and Women's Health Nursing 4:(2)236–243, 1993
22. Chalker R, Whitmore K: Overcoming Bladder Disorders. New York: Harper and Row, 1990
23. Webster DC, Brennan T: Use and effectiveness of sexual self-care strategies for interstitial cystitis. Urologic Nursing 15(1):14–22, 1995
24. Webster DC, Brennan T: Use and effectiveness of psychological self-care strategies for interstitial cystitis. Health Care for Women International 16:463–475, 1995
25. Keltikangas-Jarvinen L, Auvinen L, Lehtonen T: Psychological factors related to interstitial cystitis. European Urology (ENM) 15:69–72, 1988
26. McCormick NB: Is there sex after IC? ICA Update 5(3):4–5, Fall 1990
27. Slade DKA: Interstitial cystitis: A challenge to urology. Urological Nursing 9(3):5–7, 1989
28. Webster D: Survey on sexual problems and IC. ICA Update 8(4):4, Fall 1993
29. Evans, R: Men with IC. Presented at the 7th national meeting of the Interstitial Cystitis Association, Orlando FLA, October, 1993
30. McCormick NB: Sex despite interstitial cystitis. Presented at the 8th national meeting of the Interstitial Cystitis Association. San Diego CA, October 1995
31. McCormick NB: Sexual Salvation: Affirming Women's Sexual Rights and Pleasures. Westport, CT: Prager, 1994
32. McCormick NB, Vinson RK: Sexual difficulties experienced by women with interstitial cystitis. Women & Therapy: 7(2–3):109–119, 1988
33. McCormick NB, Vinson RK: Interstitial cystitis: How women cope. Urological Nursing 9(4):11, 14–17, 1989
34. Angier N: Drug works, but questions remain. The New York Times 143(49,544):B8, December 13, 1993
35. Linn A: Drugs that can ruin your sex life. Ladies Home Journal 92,98,100–101, September 1994
36. McCormick NB: Undesirable sexual side-effects of medications. ICA Update: 10(2):5–6, Summer 1995
37. Riley AJ, Peet M, Wilson C. (eds): Sexual pharmacology. Oxford, UK, Clarendon Press, 1993

38. Schover LR, Jensen SB: Sexuality and chronic illness: A comprehensive approach. New York: NY: Guilford, 1988
39. Ashton AK: Management of sexual dysfunction caused by serotonin re-uptake inhibiting antidepressants. Presented at the annual meeting of the Society for Sex Therapy and Research, Chicago, IL, March 1997
40. Parkin J, Shea C, Sant GR: Intravesical Dimethyl Sulfoxide (DMSO) for interstitial cystitis—A practical approach. *In*: Interstitial Cystitis: An Update of Current Information, AJ Wein, PM Hanno (guest eds.) Urology 49(5A):105–107, supplement to May 1997
41. Webster D: Reframing women's health: Tension and paradox in framing interstitial cystitis. Journal of Women's Health: 2(1):81–84, 1993
42. Webster D: Sexuality and IC. Presented at the 7th national meeting of the Interstitial Cystitis Association, Orlando FLA, October, 1993
43. Roberto KA: The study of chronic pain in later life: Where are the women? Journal of Women and Aging 6(4), 1–7, 1994
44. Webster D: Comparing patients' and nurses' views of interstitial cystitis: A pilot study. Urologic Nursing 10(3):10–15, 1990
45. McCormick NB: When your spouse has interstitial cystitis. Presented at the 5th annual meeting of the Interstitial Cystitis Association, New Orleans LA, May 1990
46. Robinson CA: Managing life with a chronic condition: The story of normalization. Qualitative Health Research 3(1), 6–28, 1993
47. McCormick NB: Coming out of our water closet: Attacking shame associated with interstitial cystitis. Presented at the 10th anniversary luncheon and benefit gala of the Interstitial Cystitis Association. New York NY, September 15, 1994

SECTION 5

JOURNAL OF WOMEN'S HEALTH
Volume 18, Number 9, 2009

DOI: 10.1089/jwh.2008.1270

Original Article

Severity of Interstitial Cystitis Symptoms and Quality of Life in Female Patients

Samar R. El Khoudary, Ph.D., M.P.H.,[1] Evelyn O. Talbott, Dr.P.H., M.P.H.,[1]
Joyce T. Bromberger, Ph.D.,[1] Chung-Chou Ho Chang, Ph.D.,[2]
Thomas J. Songer, Ph.D., M.P.H., M.Sc.,[1] and Edward L. Davis, M.D.[3]

Abstract

Objective: Interstitial cystitis (IC) is a visceral pain syndrome with a profound impact on quality of life (QOL). The main aims of the current study are as follows: (1) to determine possible factors that may increase the severity of symptoms and decrease QOL in women diagnosed with IC; (2) to study how symptom severity affects QOL adjusting for these factors; and (3) to investigate which symptom is most likely to impair IC patients' physical and mental QOL.

Methods: Forty-one women (age, 20–71 years) with moderate/severe IC enrolled in a clinical trial of intravesical pentosan polysulfate sodium in California (USA) were included in this cross-sectional analysis. Demographic and clinical characteristics were evaluated at baseline using the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI), pain assessment, urgency scale, voiding log for 24 h, and the Short Form-36 (SF-36).

Results: Being currently unmarried was associated with more severe symptoms. Being unemployed, currently unmarried, obese, never pregnant, and ever use of oral contraceptive were associated with a decrement in at least one QOL domain. Symptom severity was an independent predictor of worse QOL on three domains: bodily pain, general health, and mental health. Pain and nocturia were the only symptoms found to be associated with decline in overall physical quality of life. None of the symptoms had significant impact on the mental component summary of QOL.

Conclusions: Symptom severity and being currently unmarried were found to be associated with impairment in QOL in IC patients. Managing pain and nocturia may improve the patients' overall physical QOL.

Introduction

Interstitial cystitis (IC) is a devastating urinary bladder condition characterized by pelvic pain, urinary frequency, urgency, and nocturia.[1] Recently, researchers have started to use the term "painful bladder syndrome" (PBS) to describe cases with painful urinary symptoms that may not meet the strictest definition of IC. The term "IC" is used alone when describing cases that meet all of the IC criteria established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).[2]

The actual prevalence rate of IC is unknown, and estimates range widely from 67 per 100,000[3] to 575 per 100,000[4] based on the diagnostic criteria and methods used in estimating the rate. IC is mainly diagnosed among white females, with a median age at diagnosis of 42–46 years old.[3] Although IC has been known since 1836,[5] its etiology and pathogenesis are still unclear. Therefore, it is not surprising that IC patients suffer 5–7 years on average and often visit as many as eight physicians before the correct diagnosis is made.[6] The debilitating symptoms of IC leave many patients unable to cope with basic daily function. In severe cases, patients often need to void more than 60 times a day and experience severe pelvic pain and dysparunia,[7] which can isolate them from social life and result in severe depression.

Previous epidemiological studies of IC have measured Quality Of Life (QOL) in either IC patients only,[8,9] or IC patients and a control group.[6,10] Comparison across these studies is limited because each used different measurement instruments. In addition, very few studies have assessed the impact of IC symptoms and their severity on QOL.[8,11] None of these studies considered covariates that may confound the

Departments of [1]Epidemiology and [2]Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania.
[3]Citrus Valley Medical Research, Inc., Glendora, California.

association between symptom severity and QOL. Moreover, none of these studies used a validated instrument to measure the severity of IC symptoms.

To the best of our knowledge, this is the first evaluation of the association between severity of IC symptoms and QOL taking into consideration a wide variety of possible covariates that may modify the direct association. The main objectives of the current study were as follows: (1) to determine to what extent socio-demographic, lifestyle, reproductive, and clinical factors are associated with symptom severity and impairment in different domains of QOL among women diagnosed with IC; (2) to assess if the severity of IC symptoms is associated with impairment in all QOL domains after adjusting for the important covariates; and (3) to investigate which symptom is most likely to impair IC patients QOL summary components (physical and mental).

Methods

Subjects and study design

This is a cross-sectional analysis of 41 subjects enrolled in an 18-week randomized double-blind placebo controlled clinical trial to assess the efficacy and safety of a combination of intravesical and oral Pentosan Polysulfate Sodium (PPS) compared to placebo as a new therapeutic option for IC.[12] In brief, females ≥18 years old who recently met the NIDDK criteria for IC and were previously untreated with PPS were recruited from IC patients of Citrus Valley Medical Research, Inc. (Glendora, CA). Women were also required to have negative urine culture, a score of at least 4 on a nine-point pain scale and 5 on the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) at baseline. All subjects signed informed consent, and the study design was approved by the Institutional Review Board (IRB) of Foothill Presbyterian Hospital (Glendora, CA) and the IRB of the University of Pittsburgh (Pittsburgh, PA).

Study measures

Socio-demographic, lifestyle (Body Mass Index [BMI] and smoking status), reproductive (ever pregnant, number of pregnancies, using oral contraceptive (OC), and menopausal status) and clinical factors (presence of Hunner's ulcer, severity of glomerulations and co-morbid conditions) were evaluated at baseline. Symptom severity was measured using ICSI, a well-known, validated, self-administered instrument.[13]

ICSI includes four items that measure the frequency of IC main symptoms and provide a symptom severity cumulative score (range, 0–20; 0 = no symptoms, and 20 = severe symptoms). The severity of each symptom was also assessed separately for a 24-h period using a voiding log to measure both urinary frequency and nocturia; a pain assessment scale (range, 1–9; 1 = no pain, and 9 = severe pain) to assess pain at the time of each void and an urgency scale (range, 1–5; 1 = no urgency, and 5 = severe urgency) to measure level of urgency at the time of each void. QOL was assessed using Short Form-36 (SF-36),[14] a widely used, validated instrument that assesses eight different domains of QOL: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The eight domains of the SF-36 can be grouped into two summary scales: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS assesses physical health based on physical functioning, role limitations due to physical problems, bodily pain, and general health scales. The MCS assesses mental health based on the mental health, role limitations due to emotional problems, vitality, and social functioning scales. Each of the eight domains, as well as the two summary component scales (range, 0–100), is presented in the norm-based score format.[15]

Table 1. Sociodemographic and Clinical Characteristics of the Study Population

Characteristics	N	*Median (25th percentile, 75th percentile) or %*
Age	41	37.8 (28.1, 44.9)
Ethnicity	41	
Caucasian	29	70.7
Not caucasian	12	29.3
Marital status	41	
Married	23	56.1
Not married	18	43.9
Education	41	
Elementary-secondary	13	31.7
Post-secondary	28	68.3
Employment	41	
Employed	32	78.0
Not employed	9	22.0
Menopausal status	41	
Postmenopausal	15	36.6
Not postmenopausal	26	63.4
Ever used oral contraceptive (OC)	41	
Yes	36	87.8
No	5	12.2
BMI[a] (Kg/m^2)	41	24.4 (21.9, 27.5)
Number of co-morbid condition[b]	41	3 (2, 5)
Severity of IC symptoms[c]	41	
Mild (0–6)	1	2.4
Moderate (7–13)	19	46.3
Severe (14–20)	21	51.2
Pain score (1–9)[d]	41	4 (4, 5)
Urgency score (1–5)[d]	41	3 (2.6, 3.5)
Urinary frequency	41	12 (9.5, 17)
Nocturia	41	2 (1, 4)

[a]Body Mass Index (BMI) was based on self-reported weight and height.
[b]Concomitant conditions, e.g., endometriosis, irritable bowel syndrome, stress, depression, fibromyalgia, hypertension, diabetes.
[c]Severity of interstitial cystitis (IC) symptoms was based on the O'Leary-Sant Interstitial Cystitis Symptom Index score, range of 0–20.
[d]Pain score: 1 = no pain; 9 = severe pain. Urgency score: 1 = no urgency; 5 = severe urgency.

Statistical analysis

The inferences of the parametric technique are based on the large sample properties. With a sample size of 41, the properties may not be applied. Therefore, we used non-parametric approach to assess the study aims.[16] Continuous variables were presented as median, and 25th and 75th percentiles, while

categorical variables were presented as percentages. Spearman correlations, Mann-Whitney *U*-tests, and Kruskal-Wallis tests were used to assess the univariate associations. Multiple median regressions were used to investigate the impact of symptom severity on QOL as well as to determine factors that impair the severity of symptoms and the QOL. All the covariates with a p-value of <0.1 in the univariate analysis were included during model building. Both age and co-morbidity were forced in all models because of their well-known significant impact on study outcomes (symptom severity and QOL).[10,17] All statistical tests were two sided and used a significance level of 5%. All analyses were conducted using STATA version 10.0 (StataCorp LP., College Station, TX).

Results

The study population consisted of 41 IC female patients with a median age of 38 years (range, 20–71 years). The socio-demographic and clinical characteristics of the study population are summarized in Table 1.

QOL of the study population

Figure 1 shows QOL scores of the eight domains and the two summary components of SF-36 in the current study population compared to those of a normative sample of U.S. females (age range, 18–65+ years).[15] Importantly, all the scores of the different domains and the summary components were substantially below the 50 score value, which indicates that the QOL of IC patients is markedly lower than that for women in the United States in general.

Socio-demographic, reproductive, and clinical factors and symptom severity

Univariate analyses were carried out to determine if socio-demographic factors, reproductive, clinical and lifestyle factors were associated with an increase in the severity of IC symptoms. Results showed that only being unmarried (median ICSI score: 16 for unmarried and 11 for married, $p = 0.02$) and postmenopausal (median ICSI score: 16 for postmenopausal and 11.5 for not postmenopausal, $p = 0.02$) were each significantly associated with increased severity of IC symptoms (Table 2).

In multiple median regression and before adjusting for age and co-morbidity in the final model, both marital status and menopausal status had independent, significant associations with the severity of IC symptoms ($\beta = -4$, $p = 0.03$; $\beta = 4$, $p = 0.04$, respectively). After adjusting for age and co-morbidity, only marital status remained significant in the model. The median ICSI score for married subjects was approximately four points less than the median score for currently unmarried subjects, $p = 0.03$ (data not shown in the tables).

Socio-demographic, reproductive, and clinical factors and QOL domains

In the univariate analyses (data not shown), multiple associations were found between the socio-demographic and reproductive variables and the individual QOL domains. Being unemployed was associated with lower physical functioning. Being unmarried and OC use were associated with lower role-physical. Being unmarried was associated with higher bodily pain. Being unmarried and having larger BMI were associated with worse general health and vitality. Unmarried individuals reported significantly lower social functioning; while women who were never pregnant reported worse mental health. Table 3 shows the results of the multiple median regressions for each of the eight domains adjusting for age and co-morbidities. Interestingly, independent of all other factors, being married was found to be significantly associated with better physical functioning, role-physical, vitality, and social functioning.

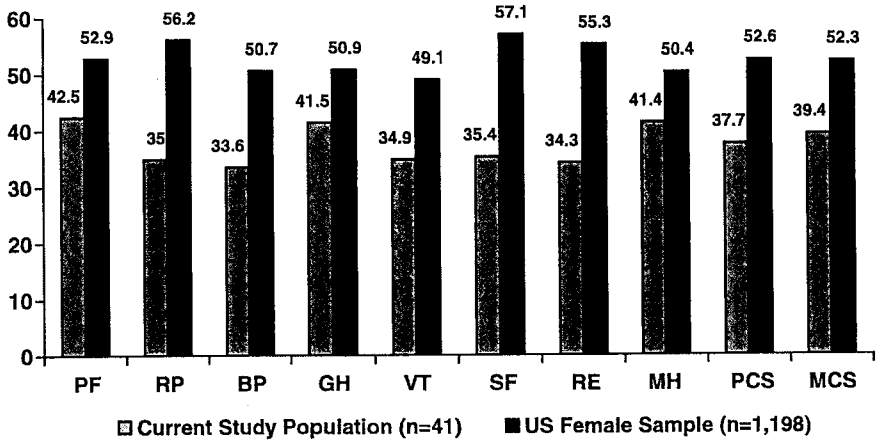


FIG. 1. Quality of life scores of the study population and a normative sample of U.S. females (age range, 18–65+ years), General Social Survey, 1998.[15] PF, physical function; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social function; RE, role- emotional; MH, mental health; PCS, physical component summary that assesses physical health based on physical functioning, role limitations due to physical problems and bodily pain scales; MCS, mental component summary that assesses mental health based on the mental health, role limitations due to emotional problems and social functioning scales. Each of the eight domains, as well as the two summary component scales (range, 0–100), is presented in the norm-based score format. Therefore, any score above or below 50 is above or below the average of the general U.S. population (General Social Survey, 1998) and each one difference in the score is one-tenth of a standard deviation.[15]

TABLE 2. UNIVARIATE ANALYSES FOR INTERSTITIAL CYSTITIS SYMPTOMS SEVERITY (ICSI SCORES) BY STUDY COVARIATES

Study covariates	N	*(ICSI Scores, median (25^{th} percentile, 75^{th} percentile)*	p *value*[a]
Demographical factors			
Ethnicity	41		0.1
Caucasian	29	15 (10.5, 16.5)	
Not Caucasian[b]	12	11 (8.5, 14.8)	
Marital status	41		0.02
Married	23	11 (8, 15)	
Currently not married[c]	18	16 (12.8, 17)	
Educational levels	41		0.9
Elementary and secondary	13	13 (10.5, 17)	
Post-Secondary	28	14 (10, 16)	
Employment status	41		0.8
Employed	32	13.5 (10, 16)	
Not employed	9	14 (10.5, 16.5)	
Reproductive and lifestyle factors			
Ever pregnant	41		0.7
Yes	31	13 (10, 16)	
No	10	15 (10, 16.3)	
Number of pregnancies	31		0.6
1–2	17	14 (10, 17)	
3+	14	12 (8.8, 16)	
Menopausal status	41		0.02
Postmenopausal	15	16 (13, 17)	
Not postmenopausal	26	11.5 (9.5, 16)	
Ever used oral contraceptive (OC)	41		0.9
Yes	36	13.5 (10, 16.7)	
No	5	14 (10.5, 16)	
Ever smoked	41		0.8
Yes	24	14 (10, 16)	
No	17	13 (10.5, 16.5)	
Clinical factors			
Severity of glomerulations[d]	41		0.4
Mild	4	15.5 (9, 18.3)	
Moderate	6	15.5 (12.3, 17.3)	
Severe	31	13 (10, 16)	
Presence of Hunner's ulcer	41		0.8
Yes	6	14 (8.3, 16.5)	
No	35	14 (10, 16)	

[a]*p* value: Mann-Whitney *U*-test or Kruskal-Wallis test. Age, Body Mass Index (BMI), and number of co-morbid conditions were assessed using spearman correlations. None was found to be significantly associated with ICSI (data not shown).

[b]Not Caucasian = Black, Hispanic, Asian, and other.

[c]Currently not married = widowed, divorced, never married, and other.

[d]All study participants had glomerulations. Severity of glomerulations was based on the following clinical definitions: **Glomerulations:** Refers to bladder hemorrhages. The presence of glomerulations, also known as petechial hemorrhages, in the bladder suggests that the bladder wall has been damaged, irritated, and/or inflamed. The NIDDK Diagnostic Criteria for IC, developed in 1987, required the presence of glomerulations or Hunner's ulcers to make a firm diagnosis of IC to determine patient eligibility for clinical trials. **Mild glomerulations:** Few submucosal glomerulations (i.e., 0–5 lesions per cystoscopic view), associated with submucosal vascular injection. Vascular injection, meaning that the mucosa turns red, but there are none to only a few glomerulations. **Moderate glomerulations:** On hydrodistension, the bladder membrane turns red with vascular injection, and there are more than 10 but less than 15 glomerulations per cystoscopic view. **Severe glomerulations:** On hydrodistension, the bladder membrane turns red with vascular injection, and there are submucosal glomerulations too numerous to count in nearly all of the bladder cystoscopic views. This can be with or without Hunner's ulcers/lesion, which is defined as a circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area.

Symptom severity and QOL domains and summary components

The univariate analyses showed that symptom severity was significantly related to less physical functioning, role-physical and social functioning and more bodily pain (Table 4). After adjusting for study covariates, severity of symptoms was found to be independently associated with worse bodily pain, general health, and mental health in IC patients (Table 5).

Table 6 shows the multivariate results for specific IC symptoms and PCS. Only pain and nocturia were found to

TABLE 3. MULTIVARIATE MEDIAN REGRESSIONS FOR EACH DOMAIN OF THE SHORT FORM = 36 HEALTH SURVEY (SF-36) AND THE FACTORS THAT WERE FOUND TO BE ASSOCIATED WITH EACH DOMAIN IN THE UNIVARIATE ASSESSMENTS AFTER ADJUSTING FOR BOTH AGE AND COMORBIDITY

	SF-36 domains[a]															
	PF		*RP*		*BP*		*GH*		*VT*		*SF*		*RE*		*MH*	
Covariates	*β*	p *value*	*β*	p *value*	*β*	p *value*	*β*	p *value*	*β*	p *value*	*β*	p *value*	*β*	p *value*	*β*	p *value*
Employed[b]	15.9	<0.001	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Married[b]	12.7	<0.001	8.49	0.006	7.34	0.06	9.14	0.08	8.1	0.006	13.09	0.01	–	–	–	–
BMI	–	–	–	–	–	–	−1.05	0.007	−0.37	0.05	–	–	–	–	–	–
Never use OC[b]	–	–	12.7	0.007	–	–	–	–	–	–	–	–	–	–	–	–
Never pregnant[b]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−9.52	0.003

[a]Norm-based scores, all scores above or below the 50 are above or below the average, respectively, in the 1998 general US population.[15]
[b]Reference category: not employed; currently not married; ever use OC; ever pregnant.
PF, physical function; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social function; RE, role-emotional; MH, mental health; BMI, Body Mass Index; OC, oral contraceptive.

be significantly inversely associated with the PCS after adjusting for age, co-morbidity, and marital status. Because we found significant correlations between IC symptoms (pain and urgency $\rho = 0.4$, $p = 0.01$; urinary frequency and nocturia $\rho = 0.4$, $p = 0.004$), we were not able to include all four symptoms in one model. Importantly, none of IC symptoms were significantly found to be associated with the mental component of the SF-36 (not shown in tables).

Discussion

The results from the current study highlight the profound impact of symptom severity on IC patients' QOL. Our analysis showed that symptom severity significantly impairs two of the physical components and one of the mental components of QOL. Moreover, being unmarried was significantly related to both the severity of symptoms and multiple QOL domains. We also found that pain at the time of voiding and nocturia were the only symptoms that were associated independently with worse overall physical quality of life.

IC remains an idiopathic illness with substantial morbidity in those affected. Previous researchers have studied risk factors for IC, but few have focused on factors that increase symptom severity.[8,18,19] We investigated the effect of sociodemographic, reproductive, lifestyle, and clinical factors on the severity of symptoms among a clinical sample of females with IC. In contrast to other researchers,[8] we found a significant association between marital status and IC symptom severity. A partner or spouse may provide an additional source of social support not available to women without a partner. Social support may be a resource that helps women accommodate to the devastating symptoms of IC. Whether the IC patients who are married experience fewer symptoms or whether increased symptoms are related to not being currently married is a difficult relationship to study in a cross-sectional study, and a prospective study is necessary to confirm this observation.

We observed that postmenopausal women reported higher symptom severity scores. This association, though, was not significant after adjusting for age, co-morbidity, and marital status. Clemens et al. reported that postmenopausal status was associated with worse symptoms and that this association remained significant after adjusting for educational level, depression, frequency, and urgency.[19] After menopause, an

TABLE 4. UNIVARIATE ANALYSES FOR THE EFFECT OF SYMPTOM SEVERITY (ICSI SCORE) ON THE EIGHT DOMAINS OF SHORT FORM = 36 HEALTH SURVEY (SF-36)

	Severity of interstitial cystitis symptoms (ICSI Score)[b]	
SF-36 domains[a]	*Spearman correlation coefficients, ρ*	p *value*
Physical functioning	−0.4	0.007
Role-physical	−0.4	0.005
Bodily pain	−0.5	0.001
General health	−0.3	0.06
Vitality	−0.3	0.1
Social functioning	−0.5	0.001
Role-emotional	−0.1	0.6
Mental health	−0.1	0.5

[a]Norm-based scores: all scores above or below the 50 are above or below the average, respectively, in the 1998 general U.S. population. Each one difference in score is one tenth of a standard deviation.
[b]Interstitial Cystitis Symptom Index (ICSI): 0, no symptoms; 20, severe symptoms.

TABLE 5. MULTIPLE MEDIAN REGRESSION FOR SYMPTOM SEVERITY (ICSI SCORE) AND QOL DOMAINS (SF-36) ADJUSTING FOR STUDY COVARIATES[a], ($N=41$)

	Severity of interstitial cystitis symptoms ICSI score[b]	
SF-36 domains	*β coefficients*	p *value*
Physical functioning	−0.22	0.4
Role-physical	−0.57	0.08
Bodily pain	−0.83	0.04
General health	−1.62	0.001
Vitality	0.18	0.6
Social functioning	−1.27	0.3
Role-emotional	−0.48	0.4
Mental health	−0.56	0.01

[a]Age, co-morbidity, and marital status for the bodily pain model; age, co-morbidity, marital status, and Body Mass Index (BMI) for the general health and age, co-morbidity, and never pregnant for the mental health model.
[b]Interstitial Cystitis Symptom Index (ICSI): 0, no symptoms; 20, severe symptoms.
SF-36, Short Form-36 Health Survey.

alteration in the vaginal flora occurs, with decreased lactobacilli leading to increased colonization by pathogenic fecal flora.[20] This increases the incidence of urinary tract infections (UTI). Furthermore, estrogen deficiency after menopause results in generalized urogenital atrophy. Therefore, postmenopausal women are also at increased risk of dyspareunia, vaginal irritation, pruritus, pain, and symptoms of urgency, frequency, dysuria, and urinary incontinence.[20] While it seems probable that the postmenopausal decline in estrogen levels has a major impact on the lower urinary tract, it is possible that the increase in urinary symptoms at this time is simply due to the aging process, which may explain the attenuation of the significant effect that we found before adjusting for age. Previous studies in women have reported an increased incidence of urinary symptoms starting as early as 10 years before the menopause.[21]

TABLE 6. MULTIPLE MEDIAN REGRESSIONS FOR THE PCS AND EACH SYMPTOM OF INTERSTITIAL CYSTITIS (IC), $N=41$

	PCS[b]	
Symptom of IC[a]	*β*	p *value*
Model 1		
Pain[c]	−2.79	0.04
Model 2		
Urinary frequency	−0.49	0.09
Model 3		
Nocturia	−1.80	0.01
Model 4		
Urgency[d]	−5.45	0.1

[a]All models were adjusted for age, co-morbidity, and marital status.
[b]Physical Component Summary (PCS): a norm-based score. A score above or below the 50 is above or below the average, respectively, in the 1998 general U.S. population.[15]
[c]Pain at the time of voiding (1–9). A score of 1 = no pain; a score of 9 = severe pain.
[d]Urgency scale (1–5). A score of 1 = no urgency; a score of 5 = severe urgency.

Our results are consistent with those from previous research showing that patients with IC reported significantly poorer QOL than controls across all SF-36 domains ($p<0.01$).[11] Although we did not have a control group, the negative impact on QOL was also demonstrated in our sample of IC patients when compared to a normative sample of U.S. females.[15] Ware et al. suggested that a five-point difference on SF-36 subscales is indicative of a clinically meaningful decrease in QOL.[14] We found subscale differences between 16 and 46.5 points (using the original score). Clearly, the degree of impairment experienced by patients with IC is substantial.

Limited studies have addressed how socio-demographic, reproductive, lifestyle, and clinical history factors affect QOL in IC patients. Although cross-sectional, our study is the first to assess the impact of each of these factors on all domains of SF-36. As expected, we found a significant association between employment status and physical functioning in analyses adjusting for age and co-morbidity. This may be due to the "healthy worker effect" reported in research on other diseases.[17] That is, healthier and better functioning individuals are employed.

As social support is an important predictor of QOL,[22] marital status might be expected to be significantly associated with lower scores of various domains of QOL. This was supported in our analyses. We consistently observed significant associations between being unmarried and worse role-physical, bodily pain, general health, vitality, and social functioning in the univariate analyses. Importantly, even after adjusting for age, co-morbidity, and certain study covariates, marital status was an independent predictor for physical functioning, role-physical, vitality, and social functioning, which suggests a possible substantial impact of marital status on the QOL of IC patients.

Data on the role of symptom severity in IC patients' QOL is limited and inconsistent. For example, Simon et al. showed that patients with severe symptoms report significantly greater limitations in basic daily functions,[8] and Rothrock et al. reported these greater limitations in physical, social functioning, and mental health.[11] More recently, Nickel et al. reported significant effects of IC pain on the physical

component but not on the mental component of SF-36 after adjusting for employment status and sexual functioning.[23] Consistent with Nickel et al. findings, our study reported a significant effect of symptom severity on the physical components more than the mental components of QOL.

We investigated which IC symptoms were associated with impairment in PCS and/or MCS, and found that after adjusting for age, co-morbidity, and marital status, pain at the time of voiding and nocturia were significantly associated with impairment in PCS. No specific symptoms were associated with MCS. This was consistent with Nickel et al., who found a significant effect of pain on PCS but not on MCS in a similar study population.[23]

The current study had several strengths and limitations. The main strengths were being the first to (1) comprehensively assess the extent to which a wide variety of factors affect both the severity of IC symptoms and the QOL and (2) to examine the association between symptom severity and QOL after adjusting for important covariates and using well-known validated instruments. On the other hand, the major limitations were (1) the cross-sectional design that limits our ability to determine the direction of causality between symptom severity and QOL; (2) the small sample size; (3) the strict application of the NIDDK criteria, which resulted in the exclusion of mild cases and having a sample of moderate to severe cases; and (4) including only female patients who were mainly white. Therefore, the results may not be generalized to mild cases, men with IC, and those of different racial or ethnic groups, although one can argue that mild cases would not necessarily be bad enough to seek care or to show improvement results.

Future studies should confirm what we have reported among mild and moderate cases of other racial and ethnic groups. Researchers should extensively investigate the role of marital status on both symptom severity and quality of life of IC patients. It will be of great interest to confirm the reported protective effect of being married prospectively, and to investigate the possibility that having severe symptoms can also be a reason for not being married or for getting divorced. Future studies should also assess the possible confounding effect of impairment in sexual functioning[23] on the reported associations between marital status, symptom severity, and QOL in IC patients.

Conclusions

The findings from the current analyses may have significant implications for both IC research and well-being of IC patients. Symptom severity and being currently unmarried were important factors found to be associated with impairment in QOL in IC patients. Managing pain and nocturia, in particular, may improve the patients' overall physical quality of life.

Acknowledgments

We thank Josephine Davis and Lisa Regan for their great cooperation and assistance. The clinical trial was supported by Ortho-McNeil Janssen Scientific Affairs, LLC (Raritan, NJ).

Disclosure Statement

No competing financial interests exist.

References

1. Nordling J. Interstitial cystitis: how should we diagnose it and treat it in 2004? Curr Opin Urol 2004;14:323–327.
2. NIDDK National Kidney and Urology Diseases Information Clearinghouse. Interstitial cystitis/Painful Bladder Syndrome. Available at: http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis/. Accessed January 21, 2006.
3. Curhan GC, Speizer FE, Hunter DJ, et al. Epidemiology of interstitial cystitis: a population based study. J Urol 1999; 161:549–552.
4. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. J Urol 2005;174:2231–2234.
5. Christmas TJ. Historical aspects of interstitial cystitis. In: Sant GR, ed. Interstitial Cystitis. New York: Lippincott-Raven, 1997.
6. Held PJ, Hanno PM, Wein AJ, et al. Epidemiology of interstitial cystitis 2. In: Hanno PM, Staskin DR, Krane RJ, et al., eds. Interstitial Cystitis. New York: Springer-Verlag, 1990; 29–48.
7. National Kidney and Urologic Disease Information Clearinghouse. Interstitial Cystitis. NIH Publication No. 99–3220. Bethesda, MD: NIH, 1999.
8. Simon LJ, Landis JR, Erickson DR, et al. The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. Urology 1997;49:64–75.
9. Koziol JA. Epidemiology of interstitial cystitis. Urol Clin North Am 1994;21:7–20.
10. Michael YL, Kawachi I, Stampfer MJ, et al. Quality of life among women with interstitial cystitis. J Urol 2000;164:423–427.
11. Rothrock NE, Lutgendorf SK, Hoffman A, et al. Depressive symptoms and quality of life in patients with interstitial cystitis. J Urol 2002;167:1763–1767.
12. Davis EL, El Khoudary SR, Talbott EO, et al. Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial. J Urol 2008;179:177–185.
13. O'Leary MP, Sant GR, Fowler FJJR, et al. The interstitial cystitis symptom index and problem index. Urology 1997;49: 58–63.
14. Ware JE, Snow KK, Kosinski M, et al. SF-36 Health Survey: Manual and Interpretation Guide, 1st ed. Boston: The Health Institute, New England Medical Center, 1992.
15. Ware JE, Kosinski M. SF-36 Physical and Mental Health Summary Scales: A Manual for Users of Version 1, 2nd ed. Lincoln, RI: QualityMetric Inc., 2001.
16. Rosner B. Non-parametric methods. In: Rosner B, ed. Fundamentals of Biostatistics. New York: Duxbury Thomson Learning, 2000; 331.
17. Papadopoulos AA, Kontodimopoulos N, Frydas A, et al. Predictors of health-related quality of life in type II diabetic patients in Greece. BMC Public Health 2007;7:186.
18. Temml C, Wehrberger C, Riedl C, et al. Prevalence and correlates for interstitial cystitis symptoms in women participating in health screening project. Eur Urol 2007;51:803–809.
19. Clemens JQ, Brown SO, Kozloff L, et al. Predictors of symptom severity in patients with chronic prostatitis and interstitial cystitis. J Urol 2006;175:963–967.
20. Bachmann GA. Vulvovaginal complaints. In: Lobo RA, ed. Treatment of Postmenopausal Women: Basic and Clinical Aspects. New York: Raven Press, 1994; 137–142.

21. Hextall A, Cardozol L. Managing postmenopausal cystitis. Hosp Pract (Minneap) 1997;32:191–198.
22. Bosworth HB, Siegler IC, Olsen MK, et al. Social support and quality of life in patients with coronary artery disease. Qual Life Res 2000;9:829–839.
23. Nickel JC, Tripp D, Teal V, et al. Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. J Urol 2007;177:1832–1836.

Address correspondence to:
Samar R. El Khoudary, Ph.D., M.P.H.
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, PA 15261

E-mail: elkhoudarys@edc.pitt.edu