

# Treatment effectiveness in interstitial cystitis/bladder pain syndrome: Do patient perceptions align with efficacy-based guidelines?

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## Abstract

**Introduction:** We sought to determine if patients' perceptions of success or failure of interstitial cystitis/bladder pain syndrome (IC/BPS) therapies proposed in treatment guidelines align with the evidence from available clinical trial treatment data.

**Methods:** A total of 1628 adult females with a self-reported diagnosis of IC completed a web-based survey in which patients described their perceived outcomes with the therapies they were exposed to. Previously published literature, used in part to develop IC/BPS guidelines, provided the clinical trial data outcomes. Patient-reported outcomes were compared to available clinical trial outcomes and published treatment guidelines.

**Results:** Based on patient perceived outcomes (benefit:risk ratio), the most effective treatments were opioids, phenazopyridine, and alkalinizing agents, with amitriptyline and antihistamines reported as moderately effective. The only surgical procedure with any effectiveness was electrocautery of Hunner's lesions. In order of efficacy reported in the literature, the therapies for IC/BPS with predicted superior outcomes should be: cyclosporine A, amitriptyline, hyperbaric oxygen, pentosan polysulfate plus subcutaneous heparin, botulinum toxin A plus hydrodistension, and L-arginine. While some of the guideline recommendations aligned with patient-reported effectiveness data, there was a general disconnect between guidelines and effectiveness reported in clinical practice.

**Conclusions:** There is a disconnect between real-world patient perceived effectiveness of IC/BPS treatments compared to the efficacy reported from clinical trial data and subsequent guidelines developed from this efficacy data. Optimal therapy must include the best evidence from clinical research, but should also include real-life clinical practice implementation and effectiveness.

## Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a urological pain condition associated with urinary storage symptoms that, once diagnosed, is managed with a variety of

therapeutic strategies. Treatment has generally been empirical, but mostly based on theoretical and evidence-based considerations. The development of treatment guidelines, a strategy to improve outcomes by developing a standardized treatment approach, is shaped by clinical trial efficacy data.<sup>1-5</sup> In real-world practice, urologists are encouraged to employ efficacy data and guidelines to prescribe effective therapies and treatments for patients suffering from IC/BPS. There is, however, limited information on the effectiveness of IC/BPS treatments and patients' perceptions of these treatments in real-life clinical practice.

The purpose of this study was to determine if treatments IC/BPS patients perceived to be effective in a web-based questionnaire aligned with clinical trial efficacy data and associated published guidelines in IC/BPS.

## Methods

Clinical efficacy considerations were abstracted from a recent comprehensive review/meta-analysis performed by one of the authors (JCN) and colleagues<sup>4</sup> and guideline updates for the treatment of IC/BPS from the European Association of Urology (EAU), American Urological Association (AUA), Royal College of Obstetricians and Gynecologists/British Society of Urogynecologists (RCOG/BSUG), and Canadian Urological Association (CUA).<sup>1-4</sup> Clinical effectiveness was estimated from a patient-centred, web-based questionnaire. An initial analysis has been published and describes the diagnostic and therapeutic experience of the first 750 patients completing the survey.<sup>6</sup> The questionnaire was promoted by IC/BPS support groups and queried the impact of therapies (beneficial and deleterious effects) using a total of 202 unvalidated questions. Standard and common IC/BPS therapies, such as oral medications, intravesical therapies, and surgery, were addressed and patients were asked whether symptoms were improved, deteriorated, or were unchanged. The questionnaire was designed and implemented by two of the authors (EK, KZ) and the collected data independently analyzed by the Queen's University group (AL, VT, JCN). Effectiveness was estimated based on

benefit:risk ratio (risk being defined as worsening of symptoms) reported by patients (benefit:risk ratio not effective = 1:1 or <1; mildly effective = >1:1 but <5:1; moderately effective = >5:1 but <10:1; markedly effective = >10:1). Informed consent was obtained online. Data was collected from 2004–2010. Descriptive statistics were calculated to compare the efficacy, guideline recommendations, and real-life effectiveness of the various treatments.

## Results

One thousand six hundred and twenty-eight women with a self-reported diagnosis of IC/BPS responded to the survey. Women reported from 48 different countries with a mean age of 39.6 years (standard deviation [SD]  $\pm$  12.8 years); 95.9% were Caucasian, 1.4% were African American, and 0.6% were Asian/Pacific Islander.

Therapies achieving an improvement rate of over 50% included opioids (405/621; 65.2%), phenazopyridine (390/638; 61.1%), intravesical heparin (50/89; 56.2%), alkalinizing agents (365/660; 55.3%), and pentosan polysulfate (359/698; 51.4%); however, in order of effectiveness (based on benefit:risk ratio), marked effectiveness was only achieved with opioids (27:1), alkalinizing agents (22.8:1), and phenazopyridine (13.9:1). Moderate effectiveness was reported for amitriptyline (9.2:1) and antihistamines (6.5:1). Cimetidine, intravesical heparin, and intravesical hyaluronic acid were associated with mild effectiveness, while electrocautery, pentosan polysulfate, intravesical lidocaine, and dimethylsulfoxide (DMSO) showed mild but equivocal effectiveness. Hydrodistension and antibiotics were not effective (although antibiotics were associated with a 49.4% improvement rate, they also had worsening of symptoms, reported by 47.1% of patients). Gabapentinoids, major surgery, and urethral dilation were not effective. Table 1 describes the number of patients exposed to each treatment, the improvement and worsening of symptoms reported, and the subsequent benefit:risk ratio for each reported treatment modality.

Table 2 summarizes the interventions proven to be efficacious based on clinical trial data (the data was based on pain, frequency, urgency, and Interstitial Cystitis Symptom Index [ICSI] symptoms). Table 2 also summarizes the recommendations (and grade of recommendation) for the EAU, AUA, RCOG/BSUG, and CUA guidelines compared to patient-perceived effectiveness based on the benefit:risk ratio determined for each intervention.<sup>1-4</sup>

## Discussion

The most recent and accepted definition of IC/BPS from the 2014 AUA guidelines states it is “an unpleasant sensation (pain, pressure, discomfort), perceived to be related to the urinary bladder, associated with lower urinary tract

**Table 1. Patient-reported treatment effectiveness**

Treatment	Improved	Worse	Benefit:risk ratio
Opioids	65.5% (405/621)	2.4% (15/621)	27:1
Alkalinizing agents	55.3% (365/660)	2.4% (16/660)	22.8:1
Phenazopyridine	61.1% (390/638)	4.4% (28/638)	13.9:1
Amitriptyline	45.5% (231/512)	4.9% (25/512)	9.2:1
Antihistamines	35.1% (203/579)	5.4% (31/579)	6.5:1
Cimetidine	27.6% (54/196)	8.7% (17/196)	3.2:1
Intravesical heparin	56.2% (50/89)	19.1% (17/89)	2.9:1
Intravesical hyaluronic acid	31.9% (22/69)	14.5% (10/69)	2.2:1
Electrocautery	26.4% (31/121)	16.5% (20/121)	1.6:1
Pentosan polysulfate	51.4% (359/698)	34.5% (241/698)	1.5:1
Intravesical lidocaine	33.3% (6/18)	27.8% (5/18)	1.2:1
Antibiotics	49.4% (674/1364)	47.1% (642/1364)-N	1:1
Intravesical DMSO	36.9% (148/401)	32.7% (131/401)	1.1:1
Hydrodistension	27.9% (218/780)	27.6% (215/780)	1:1
Gabapentinoids	26.1% (58/222)	4.6% (99/222)	0.6:1
Major surgery	14.3% (28/196)	41.3% (81/196)	0.3:1
Urethral dilation	22.5% (115/512)	22.3% (114/512)	0.1:1
BoNT/A intravesical injection	N not sufficient	N not sufficient	N not sufficient

BoNT/A: botulinum toxin A; DMSO: dimethylsulfoxide.

symptoms of more than six weeks' duration, in the absence of infection or other identifiable cause".<sup>2,4</sup> IC/BPS is a disease complex that is diagnosed after the exclusion of an infectious or neoplastic process.<sup>2,4</sup> In reality, it appears to take a significant amount of time for patients to obtain a diagnosis.<sup>4</sup> Theoretically, once the diagnosis has been made, a strategy to flow patients through a treatment algorithm, such as those based on the EAU, AUA, RCOG/BSUG, or CUA guidelines, should be the optimal way to manage this condition.<sup>1-4</sup> This can only be predicted if the evidence-based efficacy data mirrors the actual effectiveness seen in the real world. Clinical trial data would predict that the most beneficial therapies would include cyclosporine A, amitriptyline, hyperbaric oxygen, pentosan polysulfate plus subcutaneous heparin, botulinum toxin A plus hydrodistension, and L-arginine, in no particular order.<sup>4</sup> Guideline recommendations from the EAU, AUA, RCOG/BSUG, and CUA follow as best they can with the clinical evidence modified by expert opinion.<sup>1-4</sup> Our survey of patients' perceptions of what treatments they actually receive and how much benefit (or harm) they experience does not always align well with either the clinical trial efficacy data or the guideline recommendations.

**Table 2. IC/BPS treatment: Efficacy, guidelines, and effectiveness**

IC/BPS treatment recommendations	Efficacy* (effect)	EAU grade of recommendation	AUA recommendation – grade and use	RCOG/BSUG grade of recommendation	CUA grade of recommendation	Effectiveness**
Opioids	ID	NR	Should be initiated with a multimodal therapy regimen	NR	NR	Markedly effective
Alkalinizing agents	ID	NR	NR	NR	NR	Markedly effective
Phenazopyridine	ID	NR	NR	NR	NR	Markedly effective
Analgesics	ID	C	1 <sup>st</sup> line	Recommended***	NR	ID
Amitriptyline	Small-great (ICSI, pain, urgency, and frequency)****	A	2 <sup>nd</sup> line; B	B	Optional; B	Moderately effective
Cimetidine	Small (urgency + frequency)	NR	2 <sup>nd</sup> line; B	B	Optional; B	Mildly effective
Hydroxyzine (±PPS)	Small (ICSI + pain + urgency + frequency)	A	2 <sup>nd</sup> line; C	Not recommended; B	Optional; C (with allergic phenotype)	ID
Intravesical heparin	ID	NR	2 <sup>nd</sup> line; C	D	Recommended; C	Mildly effective
Intravesical hyaluronic acid	ID	B	NR	B	Optional; C	Mildly effective
Electrocautery	ID	Recommended (for Hunner's lesion)	3 <sup>rd</sup> line; C	Recommended***	Recommended; B (for Hunner's lesion)	Mildly effective
Pentosan polysulfate	Small (pain)*****	A	2 <sup>nd</sup> line; B	Not recommended; A	Optional; D	Mildly effective
Intravesical lidocaine (+ sodium bicarbonate)	Medium (urgency); Small (ICSI + pain + frequency)	NR	2 <sup>nd</sup> line; B	B	Recommended; B	Mildly effective
Antibiotics	Small (frequency)	NR	NR	Not recommended***	NR	Not effective
Intravesical DMSO	ID	A	2 <sup>nd</sup> line; C	C	Recommended; B	Not effective
Hydrodistension	Small (ICSI)	C	3 <sup>rd</sup> line; C	D	Optional; C	Not effective
Gabapentanoids	ID	NR	NR	NR	Optional; C (for neuropathic pain)	Not effective
Major surgery	Inconclusive	NR	6 <sup>th</sup> line; C	D	Optional; C (severe refractory/last resort)	Not effective
Urethral dilation	ID	NR	NR	NR	NR	Not effective
Intravesical BoNT/A (+ hydrodistension)	Great (pain); Medium (ICSI); Small (frequency)	NR	4 <sup>th</sup> line; C	B	Optional; C	ID
Cyclosporine A	Great (ICSI + pain + frequency)	A	5 <sup>th</sup> line; C	D	Optional; C (last resort with inflammation)	ID
Intravesical chondroitin sulfate	Small (ICSI + pain + frequency)	B	NR	D	Optional; D	ID
Hyperbaric oxygen	Great (ICSI + pain); Medium (frequency); Small (urgency)	NR	NR	NR	Optional; refractory to other options	ID
Intravesical BCG	Medium (ICSI + pain); Small (ICSI + pain + urgency + frequency)	NR	NR	Not recommended***	Not recommended; B	ID

\*Based on size of impact on specific symptoms. \*\*Benefit:risk ratio=not effective (1:1 or <1); mildly effective(>1:1 but <5:1); moderately effective (>5:1 but <10:1); markedly effective (>10:1). \*\*\*Best practice recommendation based on the clinical experience of the guidelines development group. \*\*\*\*Efficacy dose dependent. \*\*\*\*\*Great (pain + frequency) when combined with subcutaneous heparin. BCG: Bacillus Calmette–Guérin; BoNT/A: botulinum toxin A; DMSO: dimethylsulfoxide; ICSI: Interstitial Cystitis Symptoms Index; ID: insufficient data; NR: no recommendation.

In this study, the terms efficacy and effectiveness are separate entities. Efficacy is defined as the power to produce a desired result and effectiveness is the degree to which a treatment is successful in producing a desired result.<sup>7</sup> This study clearly shows there is a disconnect between real-world, patient-perceived effectiveness of IC/BPS treatments compared to the efficacy clinical trial data. Patients perceived the following treatments to be effective: opioids, alkalinizing agents, phenazopyridine, amitriptyline, and antihistamines. Intravesical heparin and pentosan polysulfate were associated with reports of high improvement rates, but also of worsening of symptoms, making them only moderately effective. Antibiotics were associated with almost half of the patients reporting improvement, but also half reporting worsening of symptoms and, therefore, based on our benefit:risk ratio, would be considered not effective. Based on benefit and risk, the other treatments examined showed either equivocal results or no effectiveness.

The only therapies that seem to align between this reported effectiveness and published efficacy include amitriptyline (with the strongest alignment), pentosan polysulfate, hydroxyzine, and/or combinations. Most of the treatments noted to have the best efficacy from the review of published literature were associated with either equivocal patient-perceived effectiveness or these therapies worsened patients' symptoms. When comparing the patient-perceived effectiveness to the most recent EAU, AUA, RCOG/BSUG, and CUA guidelines, hydroxyzine, amitriptyline, and pentosan polysulfate were included as Grade A recommendations by the EAU and Grade B and C recommendations by the AUA and CUA, respectively.<sup>1,2,4</sup> The RCOG/BSUG endorsed amitriptyline with a Grade B recommendation; however, did not advise hydroxyzine or pentosan polysulfate treatments, with Grade B and A recommendations, against both treatments, respectively.<sup>3</sup> The intravesical therapies that patients perceived to have equivocal results, including intravesical DMSO, lidocaine and bladder hydrodistension, were listed as Grade A and B recommendations in the EAU, but Grade C and D recommendations in the AUA and CUA guidelines<sup>1,2,4</sup> and ranged from B, C, and D recommendations in the RCOG/BSUG guidelines.<sup>3</sup> This highlights not only the differences between guidelines based on the same available efficacy data, but also some disconnect between patient-perceived effectiveness and the recommendations that major urological associations promote. The most glaring example of this disconnect is with opioid therapy. It is certainly interesting that opioids are not only one of the most prescribed medications for IC/BPS, but also perceived to be one of the most effective according to patients exposed to this treatment. Opioids are not recommended in the EAU guidelines, while the AUA guidelines "suggest" that opioid therapy can be considered for "multimodal pain therapy" and list six essential principles that should be followed if/

when a narcotic is prescribed to a patient for pain management.<sup>1,2</sup> The RCOG/BSUG suggests opioids should be used with caution in patients with long-term chronic pain and early referral to a pain clinic for patients with refractory symptoms, while the CUA guidelines do not discuss opioid treatment.<sup>3,4</sup> Opioid therapy in IC/BPS, which has been very poorly studied, needs to be rigorously evaluated to determine its role for pain management.

Why is there such a disconnect between efficacy (and guideline recommendations based on efficacy) and effectiveness? Most of the therapies evaluated in large, randomized, placebo-controlled trials are performed on promising approaches that industry hopes to commercialize. These studies have very rigid inclusion and exclusion criteria that typically enrol only a very small percentage of patients who are screened. The efficacy data may be appropriate in the population studied, but may not reflect the actual patient population in clinical practice. Those treatments that are deemed successful are sometimes financially out of reach for the average patient. Similarly, some treatments recommended in the guidelines (e.g., neuromodulation) are not in general use or available in the real world. The therapies most often used by clinicians are usually generic and funding for evaluating such treatments is almost non-existent. Some of the best approaches include conservative management, such as diet manipulation,<sup>8</sup> exercise,<sup>9</sup> improving coping skills, and even cognitive behavioural therapy;<sup>9</sup> all treatments never rigorously evaluated. One recent exception is pelvic floor physiotherapy in which the benefits suggested by early, small, uncontrolled studies have now been confirmed by NIH randomized, controlled trials.<sup>10,11</sup> Physiotherapy is now being prescribed more frequently for IC/BPS patients with pelvic floor dysfunctional pain and we would like to believe that a contemporary survey would show a correlation between patients' perceived effectiveness and clinical trial efficacy.<sup>10,11</sup>

We cannot abandon our evidence-based approach to developing treatment algorithms and guidelines. We certainly cannot develop these strategies based on uncontrolled data collection of patients' perceptions; however, to be truly effective, there must be some alignment between what we determine in our limited clinical trials and what the patients are actually telling us. We must incorporate patient input of what they value in terms of treatments and outcomes in future treatment algorithm development. To accomplish this, we must try and collect real-life clinical data in this difficult condition using validated real-life clinical practice methodology, including prospective, observational, and/or registry trials.

The limitations to this study are fairly obvious. We are comparing apples (efficacy) and oranges (effectiveness) with the guidelines attempting to provide a balance between the two (expert opinion). The web-based questionnaire included questions that were never validated and was based on



patient self-identified diagnosis, with all the sampling bias that this carries with it (including selection bias and lack of control patients). We were unable to provide clinical confirmation regarding diagnosis, clinical phenotyping (e.g., Hunner's lesion), treatment actually prescribed, or therapeutic response, but rather relied on self-diagnosis and patients' perception of response. Some of the results are difficult to interpret, as few patients received some treatments listed (for example, botulinum toxin A and cyclosporine A), resulting in a small sample size. The questionnaire is dated and may influence this disconnect between patient perceptions and the more recent guidelines, but would not overly influence the comparison to efficacy since most data presented was available at the time of the questionnaire. We also have no information as to how the various treatments were applied in clinical practice (e.g., duration or order of treatment modalities in individual patients); however, real-life clinical practice in this enigmatic condition is messy and does not follow the niceties of recommended algorithms. We believe that this questionnaire, with its acknowledged limitations, reflects the IC/BPS patients' real-life experience with the treatments we, as clinicians, regularly administer.

## Conclusion

There is a disconnect between IC/BPS treatment guidelines based on clinical trial data efficacy and effectiveness in real-world clinical practice. Optimal therapy must include the best evidence from clinical trial research, but should also include patient experience from real-life practice.

**Competing interests:** Dr. Nickel has been a consultant for Astellas, Auxillium, Eli Lilly, Farr Labs, Ferring, GSK, Pfizer, Taris Biomedical, Tribute, and Trillium Therapeutics; a lecturer for Astellas and Eli

Lilly; and has participated in clinical trials supported by Eli Lilly, GSK, J&J, Pfizer, and Taris Biomedical. The remaining authors report no competing personal or financial interests.

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