**PHARMACOLOGICAL TREATMENTS OF INTERSTITIAL CYSTITIS: A REVIEW OF THE LITERATURE**

by

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**ABSTRACT**

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It is reported that three to eight million women suffer from interstitial cystitis/bladder pain syndrome in the United States. Two front-line pharmacological methods of treatment include: Pentosan Polysulfate and Dimethyl Sulfoxide. Secondary to these treatments, patients can receive injections of Onabotulinum Toxin A, although not FDA approved. The primary objective of this literature review was to examine the existing work and identify the gaps in knowledge surrounding the current treatment protocols. A literature review was conducted through the PubMed database on November 1, 2017 yielding 21 articles that met inclusion criteria. Each article was reviewed for adherence to topic, method, results, and limitations. Overall, the nature of all the papers evaluated was generally lacking relevant details to directly compare across studies. This included missing relevant information on age and racial breakdown of patients, making it difficult to decipher if there is an age or race effect on treatment improvement by modality, and lack of information on the magnitude of the change in the key symptomatology outcome measures. However, these studies still provided valuable information to preliminarily compare their effectiveness and is a first step towards designing better trials to evaluate this problem. In conclusion, there is limited research on DMSO, with most recent findings unsupportive of the treatment. Orally administered PPS has the best-designed studies, with multiple placebo controlled, randomized clinical trials supporting the efficacy of symptom treatment, but findings indicated limited success in symptom reduction. While Onabotulinum Toxin A is considered to be a treatment that is administered at a later point of disease treatment, there is a substantial amount of published research that uses updated methods of pain and symptom evaluation which leads to a belief of efficacy. Given the stronger findings for Onabotulinum Toxin A, future research should be directed to determine if this modality should be considered as the primary intravesical treatment method of IC/BPS treatment despite its possible side effect of increasing UTIs. The public health implications of the existing and future work could allow for quicker and more effective relief of symptoms of IC/BPS for the millions of adults suffering from this painful condition.

Nancy W. Glynn, PhD

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Anna Leigh Zilinskas, MPH

University of Pittsburgh, 2017

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# preface

I would like to thank my friends and family for their unending support. I would also like to thank Dr. Martha Ann Terry and Dr. Pradeep Tiyagi for being members of my essay committee and for their patience and efforts in the process. Most of all, I would like to thank Dr. Nancy Glynn, for always believing in me, supporting me, and for never giving up, I would not be here without her.

# Introduction

## Definition of Interstitial Cystitis/Bladder Pain Syndrome

As defined by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a condition that causes discomfort or pain in the bladder and a need to urinate frequently and urgently (“Interstitial Cystitis: Medline Plus” n.d.). Symptoms of IC/BPS can vary from person to person, or throughout the individual’s experience with the disease. For example, some people may feel discomfort, pressure and struggle with urinary urgency. Other patients may experience intense pain in the bladder with a sudden need to urinate more frequently than normal (“General IC Symptoms - Interstitial Cystitis Association” n.d.). Researchers do not know the exact cause of IC/BPS, though some believe that IC/BPS could result from conditions that cause inflammation in various parts of the body (“Definition &amp; Facts of Interstitial Cystitis | NIDDK” n.d.).

## Diagnosis of IC/BPS

Patients with IC/BPS may have a presence of Hunner’s ulcers, which are not ulcers in the typical sense, but rather a distinct area of inflammation on the bladder wall. Hunner’s ulcers can lead to a definite diagnosis of IC/BPS, but are prevalent in only about 10% of diagnosed cases, and are confirmed by cystoscopy (insert IC help). Often, symptoms are more severe in the ulcerative IC/BPS than in cases lacking ulcers. Glomerulations, pin-point areas of bleeding, may be present in the bladder wall but do not lead to a definite diagnosis of IC/BPS. Health care professionals diagnose IC/BPS based on pain in or near the bladder, usually associated with urinary frequency and urgency as well as the absence of other diseases and conditions that could cause similar symptoms (“Definition &amp; Facts of Interstitial Cystitis | NIDDK” n.d.). In 1987, the NIDDK put forth a definition for diagnosis that includes 18 exclusion requirements and three inclusion requirements, one of which is Hunner’s Ulcer or glomerulations on cystoscopic exam, although diagnosis can still occur – just in non-classic type IC/BPS (“Definition &amp; Facts of Interstitial Cystitis | NIDDK” n.d.).

Diagnosing IC/BPS in women can be challenging because symptoms are consistent with other common conditions such as: overactive bladder, endometriosis, urinary tract infections, pelvic floor dysfunction pudendal neuralgia and other conditions. Women may also have one or more of these conditions in addition to IC/BPS (“General IC Symptoms - Interstitial Cystitis Association” n.d.). While the root cause of IC/BPS is still unknown, symptom flare ups can exacerbate IC/BPS and increase pain and discomfort. Women have reported symptom flares when they: are stressed/emotional with anger and sadness, have sex, have a menstrual cycle, urinate or hold urine for too long, skip meals or are dehydrated, feel changes in the seasons or weather, go through sudden or bumpy movements, inconsistent with prescribed medications, stand for long periods of time, have a pap smear, wear tight pants/undergarments, use laundry detergent with certain chemicals, complete different physical activities, such as pushing or lifting heavy objects (Sutcliffe et al. 2015).

## Epidemiology of Interstitial Cystitis/Bladder Pain Syndrome

IC/BPS is common in the United States (US). The Interstitial Cystitis Association (ICA) estimates that three to eight million women may have IC/BPS, about 3 to 6% of all women in the United States. These numbers were derived from the findings of the RAND IC Epidemiology Study (RICE), which surveyed more than 100,000 US households and was the largest IC/BPS epidemiology study ever completed (“4 to 12 Million May Have IC - ICA - McLean, VA” n.d.). The onset of IC can occur at any age, but is most commonly found in adult women. Some research suggests that women who have a history of sexual abuse or physical traumatization are more likely to develop IC/BPS (Teichman and Mayson 2009). IC/BPS can affect quality of life (QOL) significantly as patients are more likely to struggle with sleep loss, anxiety, depression and relationship struggles due to painful sex (Chuang et al. 2015; “Definition &amp; Facts of Interstitial Cystitis | NIDDK” n.d.). Other conditions that women with IC/BPS are likely to have include irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, allergies, and some autoimmune diseases (Nickel et al. 2010; “Definition &amp; Facts of Interstitial Cystitis | NIDDK” n.d.).

## Treatments for Interstitial Cystitis/Bladder Pain Syndrome

In March of 2011, the American Urological Association released clinical guidelines including a paper describing the recommended diagnosis and treatment approaches for IC/BPS recommended clinical guidelines for the diagnosis and treatment approaches of IC/BPS (Hanno et al. 2014). First-line treatments involve a relaxed approach and include education, behavioral modifications, over-the-counter medications, and stress management. Suggested second-line treatments include: physical therapy of the pelvic floor, pain management with drugs, oral medications including Elmiron/Pentosan polysulfate (PPS), and intravesical medications including dimethyl sulfoxide (DMSO). Cytoscopy and hydrodistension along with removal of Hunner’s lesions are considered to be third-line treatments. A recent study did not find any additional clinical benefit from combination of hydrodistension followed by DMSO instillation (Tomoe 2015) Fourth-line treatments include Botulinum toxin A (Onabotulinum toxin A) injections into the bladder muscle and neuromodulation (Philip M Hanno et al. 2014).

## Measurements

Clinicians and researchers use a variety of questionnaires to evaluate the severity of patients’ symptoms and assess progress (i.e., outcomes) with treatment. Some are also used to help screen patients for possible IC, although none is considered to be appropriate for diagnosis. Many researchers and clinicians use the Global Response Assessment (GRA) to measure overall improvement with therapy. This assessment is used for a primary end-point in clinical trials of therapies for IC. This seven-point scale assesses symptoms with the question, “As compared to when you started the study/treatment, how would you rate your IC/BPS symptoms now?”, ranging from markedly worse, to markedly improved (“General IC Symptoms - Interstitial Cystitis Association” n.d.).

The O’Leary-Sant questionnaire (OSS) assesses the severity of symptoms and how much of a problem the symptoms cause for the patient. The questionnaire is divided into two sections, the Interstitial Cystitis Symptom Index (ISCI), and the Interstitial Cystitis Problem Index (ICPI). Scores are evaluated separately, and in total. This method of evaluation is standard in assessing treatment, along with the GRA (“General IC Symptoms - Interstitial Cystitis Association” n.d.). Other measurements can be used, including the Quality of Life index (HRQoL), Visual Analog Scale of Pain (VAS), voiding diaries reporting the voiding history for a minimum of three days, and cytoscopic evaluation, however the OSS and GRA surveys are considered to be the primary end- point evaluators for research involving IC/BPS (“General IC Symptoms - Interstitial Cystitis Association” n.d.).

## Public health significance and Objective

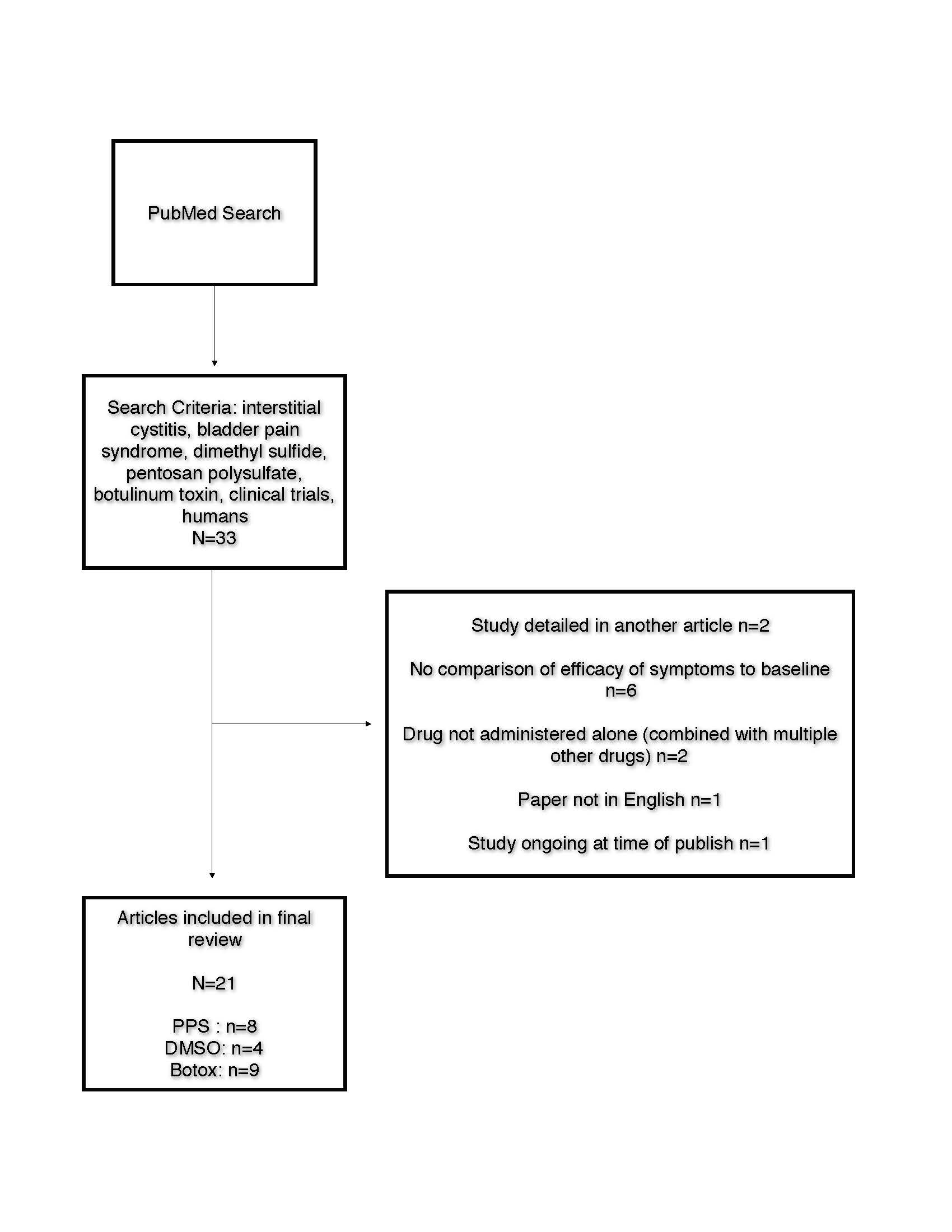
IC/BPS is highly prevalent in the population of women in the United States affecting up to 8 million women. This chronic pain condition can be extremely burdensome as symptoms are exacerbated by flare-ups associated with many aspects of life. Diet, physical activity, sexual activity, psychological state, and social interactions can all be affected and/or impacted by IC/BPS. This condition can be extremely bothersome and uncomfortable, with little immediate or long-term relief. Since there is no definitive evidence to support an autoimmune, inflammatory, structural or infectious etiology, treating patients is often challenging (“Definition &amp; Facts of Interstitial Cystitis | NIDDK” n.d.). Therefore, management of patient’s symptoms is the ultimate goal of treatment for improved quality of life. Understanding the literature surrounding the approved pharmacological treatments, as well as reviewing more recent research on newer diagnostic and treatment methods could allow for updated standards that may drastically improve the management of symptoms in patients with IC/BPS.

This paper aims to evaluate the available literature on the efficacy and management of symptoms of two FDA approved pharmacological treatments, dimethyl sulfoxide (DMSO) and Elmiron/Pentosan polysulfate (PPS) compared to Onabotulinum toxin A, a non-FDA approved pharmacological treatment for IC/BPS.

# methods

This paper is based on a literature review. Articles were located by searching online scientific resources such as PubMed and OVID databases between 1966 and October 21, 2017. The search strategy contained MeSH subheadings and word variations for IC/BPS and Methods of Treatment. Search terms included were (interstitial cystitis OR painful bladder syndrome OR bladder pain syndrome) AND (dimethyl sulfoxide OR dmso OR elmiron OR pentosane polysulfate OR botulinum toxin OR Onabotulinum toxin A OR OnabotulinumtoxinA OR botox) then filtered by “clinical trial” and “humans.” Exclusion criteria included studies that did not have measures or comparison of symptoms at baseline per treatment, research with combined therapies, and research with objectives that not include symptomatic analyses.

Figure 1 illustrates the results from the database search. In total, 33 papers were found. Nine papers were found on the treatment method of DMSO. One paper was ruled ineligible because the treatment group receiving DMSO received a dose that also included heparin and corticosteroids. Two papers were ruled ineligible because there were no comparisons to baseline, and only to other drug arms. One paper was ruled ineligible because there was no English translation. One paper from the 1970s was ruled ineligible because at the time of publishing, the study was still ongoing and there was limited data to compare to baseline. In total, four papers were included in the critical review regarding intravesical DMSO treatment. Fourteen papers were included in the initial literature review of oral PPS therapy for IC/BPS. Three papers were excluded because details of the study were reviewed in another included paper, and the retrospective analyses of these data were not evaluating the symptomatic improvement. Two studies were excluded for no comparison of symptoms to baseline, and one other paper did not include the symptomatic improvement. In total, eight papers were evaluated for the review of literature on PPS treatment of IC/BPS symptoms. For the Onabotulinum toxin A review, one paper was excluded because it did not report baseline and follow-up symptom findings. Twenty-one papers met all criteria and were included in the literature review.

**Figure 1. Literature review search strategy and selection criteria of Pubmed articles (1966-November 1, 2017) on the efficacy and management of symptoms of dimethyl sulfoxide (DMSO), Elmiron/Pentosan polysulfate (PPS), and OnabotulinumtoxinA for the treatment of Interstitial Cystitis/Bladder Pain Syndrom**e.

Excluded N=12

# results

## pentosan polysulfate

### Population and Definition of Interstitial Cystitis/Bladder Pain Syndrome

Table 1 shows the results for studies involving PPS. Six studies were completed in the United States, and one study was completed in both the US and Canada, and one exclusively in Canada. Eighty-three percent of participants were women, and 17% were men. In 1987, the National Institute of Diabetes and Digestive and ­Kidney Diseases (NIDDK) put forth a definition that includes 18 exclusion requirements, and three inclusion requirements, one of which is Hunner’s Ulcer or glomerulations on cystoscopic exam. (“Definition &amp; Facts of Interstitial Cystitis | NIDDK” n.d.). None of the papers included in the review cited the NIDDK criteria for the definition of IC/BPS in diagnosis of participants. While criteria may still have been met, for some patients, this inclusion/exclusion criteria was not the standard definition for recruiting participants, and these studies did not evaluate the difference between Hunner’s and non-Hunner’s ulcer type patients. Definition of IC/BPS was based upon recurrence and severity of symptoms in all the included papers. Nickel et al. (2015) did not take cystoscopic evaluation into consideration during recruitment of participants, and actually excluded patients, if cystoscopy was performed within four weeks of the study. All participants were over the age of 18, and could not be pregnant or lactating. Ethnic differences in population were not addressed. An early study by Nickel et al (2005) allowed participants to remain on antidepressant and antihistamine therapy throughout the duration of the PPS therapy if an already an established treatment was in place. In a subsequent study by the same authors (Nickel et al 2015), they addressed this confounding effect by excluding participants who were taking any drug that could affect IC/BPS, including antidepressants or antihistamines

### Measurements

Three of seven papers (Nickel et al 2015; Davis et al 2008; Nickel et al 2005) used the OSS, ICSI, and ICPI for evaluation of severity and symptoms (ICSI) and the bothersome burden for participants (Table 1). Four of seven papers ((Nickel et al. 2015; Davis et al. 2008; P M Hanno 1997; Parsons et al. 1993) all used the Global Response Assessment (GRA) to measure the overall symptomatic improvement. For studies prior to the development of these standardized scales, analog pain and symptom scales were used. All studies had major components of self-reporting of symptoms as a measure of efficacy of the treatments (Table 1).

### Study Design and Outcomes

Two of eight papers concluded that pentosanepolysulfate is not an efficacious treatment for IC/BPS (ref for the two papers here). Nickel et al (2015). performed a multicenter, double-blind, randomized placebo controlled study on 368 adults with IC/BPS. Participants did not undergo cytoscopic evaluations, and were considered eligible based on having a total ICSI score of 8 or greater, and a score greater than 0 on each of the 4 ICSI component items. Although researchers were expecting a 30% or greater reduction from baseline in ICSI score in those who received the drug, no statistical difference was found between the PPS and placebo group (Nickel et al. 2015). Holm-Bentzen et al 1987 also performed a prospective double-blind multicenter trial of pentosane polysulfate but divided participants into two protocols for randomization after cytoscopic evaluation. IC patients with specified histological findings (28 or more mast cells per mm squared in the detrusor muscle) were allocated to protocol A and symptomatically diagnosed participants with unspecified histological findings were assigned to Protocol B. To ensure the degree of severity in the second protocol group, participants had to have 3 or more voidings each night, and more than 10 points on the defined symptom score scale at baseline (Holm-Bentzen et al. 1987). Researchers found no difference between treatment group and placebo groups in participants allocated to both protocols with regard to symptoms, urodynamic parameters, and cystoscopic appearances. However, significant increase in the cystoscopically determined bladder capacity was found in the Protocol A treatment group. Ultimately, the findings of the study did not confirm the efficacy of PPS for the treatment of IC/BPS.

Six of eight papers reported finding PPS to be successful and effective in treating the symptoms of IC/BPS (Table 1). Nickel et al (2005) compared three dosages of PPS to evaluate symptom responses. Participants were randomized to receive either the standard dose of 100 mg oral PPS, three times daily, or 200 mg or 300 mg of oral PPS, three times daily. Results showed that mean baseline of ICSI scores improved after 32 weeks for all dosages (p<0.01), however there was no significant difference between dosage groups, therefore rejecting their hypothesis that response to treatment was dose dependent. Davis et al. (2008) saw a 46% reduction (p<0.05) in ICSI over 18 weeks, along with a significant improvement of HRQoL in those treated with oral PPS. An open-label physician’s usage study Hanno (1997) evaluated the long-term efficacy and safety of PPS for the treatment of IC/BPS symptoms. Similar to Davis et al (2008) patient assessments of overall change in IC symptoms showed that 42% to 62% experienced moderate or better improvement compared to symptoms prior to PPS therapy (P M Hanno 1997) Similar findings were reported for pain (Table 1). Length of treatment varied by participant due to the nature of this study design.

Parsons et al. (1993) conducted a randomized prospective double-blind placebo controlled study with a definition of IC/BPS based upon bladder capacity, voiding eight times per day or more, a small average voided volume and nocturia (Table 1). If a patient did not meet one or two of these inclusion criteria, they could enter the study but had to have pain and/or moderate urgency and negative urine cultures. A follow-up questionnaire was administered to confirm the efficacy of the treatment compared to placebo. After 3 months, Thirty two percent of patients taking PPS showed significant improvement compared to 16% in the placebo group (p=0.01). Further, participants receiving drug therapy also experienced at least a 50% improvement in symptoms of pain (p=0.04) and urgency p=0.01) when compared to placebo. PPS treated patients showed an average increase of more than 20 mL in voided volume than the placebo patients (p=0.02). These findings are similar to the earlier study by Parson et al (1987) where follow up was longer, but non-standardized scales were used to measure treatment efficacy (Table 1).

Lastly, Parsons and Mulholland (1987) published a multi-centered double-blind study, where patients were enrolled and treated for 3 months with PPS at the recommended dose of 100 mg oral PPS, three times daily (Table 1). At three months, there was a 26% improvement in the treatment group (p=0.03) based on the investigators review of voiding profiles, pain and urgency survey responses. Similarly, patients self-evaluated their overall improvement in symptoms as 28% (p=0.04). When evaluating pain alone, 46% of participants (p=0.07) reported improvement. (Parsons and Mulholland 1987)

## Dimethyl Sulfoxide

### Population and Definition of Interstitial Cystitis/Bladder Pain Syndrome

Table 2 shows the results of the papers evaluating DMSO for the treatment of IC/BPS. In the studies evaluating the effects of dimethyl sulfoxide (DMSO), the recruitment criteria were similar, but not entirely standard for each paper. A majority of the participants in studies were women (96%). Studies were completed in: Belgium, Italy, Sweden, and Canada – none in the US. Peeker et al (20xx) defined IC/BPS according to the NIDDK definition, and all other papers utilized their own definitions and criteria based on cytoscopic findings and symptomology. Peeker et al (20xx) was also the only group to look at a comparison of Hunner’s vs. non-ulcerative IC/BPS, and all other papers did not evaluate the differences. (Perez-Marrero, Emerson, and Feltis 1988) reported that all participants met criteria of 18 mast cells per mm squared, but no ulcers were found. (Cervigni et al. 2017) required that participants should have tried, but were unsuccessful with oral treatment of PPS, cyclosporine – A, antihistamines, antidepressant and antiepileptics, with a minimum of three months since previous treatment, authors excluded participants who had received any other type of intravesical treatment. Tutolo et al (20xx) excluded participants if they had been receiving therapies or medications that could affect IC/BPS including antidepressants, antihistamines, intravesical treatments, investigational treatments, antispasmodics or anticholinergics. (Tutolo et al. 2017) and (Cervigni et al. 2017) excluded pregnant and lactating mothers as well, because DMSO can be excreted in milk and cross the placenta.

### Measurements

All measurements of efficacy were related to the reduction of pain intensity and symptoms. Seventy-five percent of studies used the Visual Analog Scale of pain (VAS) to measure the outcome, and 50% of papers used the OSS and the GRA as well. All studies evaluated self-report voiding diaries, and video-urodynamic analyses were not performed on any patients.

### Study Design and Outcomes

The studies evaluated can be found in Table 2. The most recent study, Tutolo et al (2015) compared the effectiveness of intravesical chondroitin sulphate (CS) and DMSO in the treatment of symptoms for patients with IC/BPS. This prospective single-blind randomized multicentered trial randomized patients to receive 6 weekly instillations of CS 2% or DMSO 50%, and measured the changes from baseline in the OSS and VAS. No significant changes in any of the symptomatic or pain scales were found, and the study was halted early ended early due to the high drop-out rate of DMSO. The study concluded that DMSO should be used with caution and involve active monitoring of side effects. The three other studies that were considered for this review found DMSO to be an effective method of treatment. Cervigni et al (2017) completed a randomized open-label multicenter study for evaluating the safety and efficacy of hyaluronic acid and chondroitin sulfate versus DMSO where female participants were randomized for 13 weekly instillations of the medication. Participants were evaluated at baseline, after the final treatment at 13 weeks, and six months post treatment. Compared to baseline, a significant reduction (at least 50%) in pain intensity was observed at six months (p<0.0001). Significant improvements in urination frequency, and in all categories of the ICSI, ICPI, PUF were found at three months and six months when compared to baseline in the DMSO group (p<0.0001).

Peeker et al (2000) compared intravesical bacillus Calmette- Guerin (BCG) and DMSO for treatment of ulcerative and nonulcerative IC/BPS in a prospective, randomized double-blind study in Sweden (Table 2). Twenty-one patients randomly underwent treatments for six weeks, and if were not successful with first assigned treatment, crossed-over to the other substance after a washout period. The study found that there was no significant increase in maximal functional capacity in either subtype following DMSO, but there was a significant pain reduction (from a score of 6 to 4) measured by VAS in both classic and non-ulcer IC/BPS (p<0.05), and significant reduction in urgency in the ulcerative group. In 1985, Perez-Marrero et al. completed a controlled cross-over trial, which was the only study that evaluated DMSO at three months and six months compared with a true placebo of normal saline solution intravesically every two weeks for two sessions of four treatments each (Table 2). There was a four-week washout period in between treatments. The evaluators who provided the objective response were blinded to treatment group. When assessed subjectively, 53% of DMSO treated patients were markedly improved vs. 18% of placebo patients. When assessed objectively using voiding diaries, 93% of the DMSO group had improvement vs. 35% of placebo group. Researchers confirmed their hypothesis that DMSO was superior to the placebo in symptomatic improvement in patients with IC/BPS.

## Onabotulinum toxin a

### Population and Definition of Interstitial Cystitis/Bladder Pain Syndrome

Table 3 shows the results of the papers evaluating onabotulinum toxin A. In these studies, 90.7% of participants were women, and 9.3% of participants were men. Eighty-eight percent of studies used the NIDDK definition of IC/BPS, and three out of eight studies compared results of ulcer versus non-ulcer IC/BPS. One study was completed in the United States, one in Poland, two studies were completed in Italy, four in Taiwan, one in Australia, and one in Japan. All studies were conducted within the past 15 years. Recruitment criteria for all studies included lack of response to previous oral and intravesical treatments.

### Measurements

The GRA was used as a measure of efficacy in four of the papers reviewed (Table 3). Four studies used the OSS, ICPI and ICSI as a measure of efficacy for treatment of symptoms (Table 3). Seven studies used a VAS and all eight studies included a self-reporting voiding diary from participants. One study (Giannantoni et al 2010) also evaluated depression and other psychological functioning with administration of the Hamilton Anxiety and Hamilton Depression rating scale.

### Study Design and Outcomes

The studies evaluated can be found in Table 3. Two studies reported partially successful findings on the use of Onabotulinum toxin A as a treatment of symptoms for IC/BPS. First, Manning et al (20xx) completed a multicenter prospective randomized double-blind study on women, who were referred from medical centers to receive either hydrodistenstion and injection of normal saline, or hydrodistention and injection of Onabotulinum toxin A. If patients had no improvement to initial treatment, they could choose to withdraw themselves and have access to Onabotulinum toxin A at minimum of 3 months post-initial injection. Significant improvements (mean score change 3.64) were seen in the ICPI at three months in the Onabotulinum toxin A group in comparison to the control group. Twelve patients had a proven urinary tract infection detected and treated sometime after injection. These authors were concerned that presence of a UTI (of indeterminable origin) may have confounded the findings. Nonetheless, after excluding those with UTIs, and there was still an overall improvement in the Onabotulinum toxin A group in all measurements including total OSS score (p=0.02), ICSI (p=0.008), ICPI (p=0.08) and question 4 of the ICPI addressing the problem of bladder pain (p=0.02) (Table 3).

A paper by (Lee and Kuo 2010) evaluated the efficacy of Onabotulinum toxin A injections by diagnoses type. Participants received 4 sets of intravesical Onabotulinum toxin A injections every 6 months, and were followed in an outpatient clinic two weeks post-injection to evaluate symptoms and turn in voiding diaries. When comparing the ulcer-type group to the non-ulcer groups – improvements in the non-ulcer groups, regardless of GRA response, was significant in the OSS total score, ICSI, and ICPI (p<0.05 for all). When comparing the non-ulcer groups, the GRA success group had significant increases in the OSS (p=0.004), ICSI (p=0.007) and ICPI (p=0.016), but not the VAS (p=0.14) when compared to GRA failure. When comparing each non-ulcer group to baseline individually, both the GRA success and GRA failure group had significant improvements from baseline in OSS, ICSI, ICPI and VAS. Changes in both in day time and nighttime urinary frequency were significant when compared to baseline as well. Overall, this study found that Onabotulinum toxin A was not successful in patients with refractory ulcer-type IC/BPS, however, while half of patients with non-ulcer IC/BPS did not have significant improvement as measured by GRA, symptom scores were still significant in all non-ulcer type participants (Lee and Kuo 2010)

Akiyama et al. (2015) completed a single-center prospective open-labeled randomized comparative study, where participants were divided into two groups: immediate injection (group A) and 1-month delayed injection (group B) of Onabotulinum toxin A after allocation. At one-month analyses, the GRA (p=0.01), ICSI (p=0.04), ICPI (p=0.03), VAS (p=0.01) and QoL indexes (p=0.03) were all significantly higher in the group that had received the injection in comparison to the group that had delayed injection (Akiyama et al. 2015). Univariate analysis was completed to show that exposure to past hydrodistension more than three times, and disease duration longer than 6 years were significant factors for better response. There was no significant difference between patients with and without Hunner’s ulcers. Two studies completed in Taiwan evaluated the effects of multiple injections of Onabotulinum toxin A on IC/BPS, as measured primarily by the GRA and secondarily by the OSS, ICPI, ICSI, voiding diaries, and other clinical measures (H.-C. Kuo 2013; Hann-Chorng Kuo 2013) Methods were exactly the same in each study, one study compared the effectiveness of a single injection, and the other simply evaluated the efficacy of four repeated injections compared to baseline. Significant improvements were seen in all measurements of ICSI, ICPI, OSS, VAS and GRA when compared to baseline for both studies (p≤0.05 for all) (Hann-Chorng Kuo 2013; H.-C. Kuo 2013)

Giantonni et al (2008) evaluated the 1-year efficacy and tolerability of Onabotulinum toxin A at 1-month, 3-month, 6 month, and one-year post injection. Significant improvements in pain relief were seen in 86% of patients at three months when compared to baseline. The beneficial effect lasted about 5 months in 30% of cases, but pain had recurred in all participants at the 1-year follow-up. However, the treatment was still determined to be effective.(Giannantoni et al. 2008) In a later study by Giantonni et al (2010) improvements in psychological function in both anxiety and depression studies were also found, with the exception of weight and sleep disorders in the Hamilton Depression questionnaire (p<0.01 for all) (Table 3) (Giannantoni et al. 2010).

# Discussion

This paper compared two FDA approved pharmacological treatments for IC/BPS compared to Onabotulinum toxin A, a non-FDA approved treatment. Overall, results were mixed. Generally, the FDA approved treatments showed modest improvements in sympotology in the papers reviewed, whereas the Onabotulinum toxin A treatments seemed to confer better subjective and objective outcomes for patients impacted by IC/BPS. Comparison of the findings are difficult due to inconsistencies in reported information, differing dosages, varying outcome measures and study designs.

PPS is the FDA approved, oral medication standard for treatment of IC/BPS. However, there are some limitations to the research reviewed for this treatment. The improvement in symptoms and pain were measured using various methods. Older studies evaluating the drug and comparing to a placebo utilized symptom scales that were not directly associated with IC/BPS. Nickel et al (2015) found no significance in the use of PPS compared to a third of the dose of PPS, and a placebo group. However, the recruitment criteria were weak as the definition of IC/BPS required an ICSI total score of 8 or greater, and could not be associated to UTI. Further standardization of the diagnosis was not included.

Davis et al. (2008) compared intravesical PPS and oral PPS with oral PPS alone, with one limitation of this study being no true placebo. By double-blinding and randomizing the treatments, and having strong exclusion criteria, the strengths of this study are apparent. The methods of evaluation of symptom response were measured by the standard OSS, ICSI, ICPI and VAS pain scale. The trial also became underpowered because of the completion rate only reaching 60%, therefore lacking generalizability. In Hanno’s (1997) open-label physician usage study, the sample size was large, but the study selects out drug responders for analysis which thereby magnifies the overall response rate. This could have an effect on the conclusion that the improvement of symptoms continues throughout three years, as the responders are those who are receiving the treatment. Parsons et al. noted that patients are not all alike in the manner in which they evaluate and report individual symptoms. Some patients may report a decrease in urgency, or perhaps pain, when the number of days that these symptoms are present is significantly reduced, while other patients with similar reduction because the urgency or pain is still severe on the days that either is present This self-reporting can be a limitation of those studies that do not utilize the standardized questionnaires specifically designed for IC/BPS as they attempt to eliminate this bias by asking questions regarding the severity and timeliness of the of symptoms and problems. By choosing patients who had failed previous methods of treatment, there is a strength associated with the studies, but a better understanding of the treatment effect of PPS may be gained by studying patients at an early stage of the disease, after first-line drugs have failed.

Overall, there was only one study evaluating the effects of DMSO compared to a true placebo. (Perez-Marrero et al. 1988) As previously discussed, people self-report pain in different manners which can be a limitation of the reporting. None of the other studies evaluating DMSO had a true placebo, which limits the findings. Peeker et al. (2000) had a small sample size of 20 participants, but was double-blinded which reduced bias. Cervigni et al. (2017) required failure of other treatments for comparing the efficacy of DMSO and Chondroitin. The study had small sample size did not have a placebo or control arm and a short follow-up time. This could be due to the disease. Tutolo et al. (2017)completed a single blinded randomized trial comparing DMSO and Cervigni et. al (2017) both used the OSS, ICSI, ICPI and GRA as measures of efficacy which assist in self-reporting bias.

Overall, the literature supporting Onabotulinum toxin A as a treatment of symptoms in IC/BPS shows the strongest associations. Six out of eight articles found highly significant decreases in symptoms including bladder pain, severity of pain, urgency, and frequency of urination in participants (Table 3). The other two studies (Manning et al. 2014; Lee and Kuo 2010) significant decreases in symptoms as well. The confounding urinary tract infection skewed the data supporting the treatment in the research by Manning et al., but when removing those participants, results were significant in supporting Onabotulinum toxin A. This is not the only study that associated urinary tract infections with Onabbotulinum toxin A. Cui et. Al (2015) also found that the main side effect of onabotulinum toxin A injections was localized to urinary tract infections. (Cui et al. 2015) Lee et al. also had significant results supporting Onabotulinum toxin A as a treatment, with the exception of Hunner’s ulcer participants, who ended up removing the ulcers with laser treatment post study, and found relief from all symptoms. Ultimately, all eight reports supported the use of Onabotulinum toxin A to reduce symptoms and improve the quality of life in those suffering from IC/BPS. A primary limitation of these studies is not having a true placebo or control arm. Kuo et al. (2013) reported that the lack of placebo was due to the ethical considerations of the human subjects ethics board. Due to the lack of control arm, participants were also not randomized to treatments with the exception of Akiyama et al. randomizing a delay of injection. The inability to compare results to a comparator group rather than baseline limits the research.

A strength of Onabotulinum toxin A studies is the methods of detection, in that the majority of the studies used the standard OSS, ICPI, ICSI and GRA measurements as efficacy assessments. Research has been completed in recent years, with the oldest study in 2004. The relevance or external validity of these data could be in question because the populations studied were all refractory patients, whereas they were required to have failure in other treatment methods, likely due to the cost and lack of FDA approval for this method of treatment. Akiyama et al (2015) were the only researchers to compare groups with the delayed interjection group, but only allotted a short observational period of one month to compare groups. Double-blind, placebo controlled, multi-center randomized trials with larger sample sizes are warranted to overcome all of the study limitations. The success of the reported studies so far, and the number of studies expressing interest in this treatment method should encourage researchers to examine efficacies in other populations to provide effective and safe symptomatic relief in patients suffering from IC/BPS.

Overall, the nature of all the papers evaluated was generally lacking relevant details to directly compare across studies. This included missing relevant information on age and racial breakdown of patients, making it difficult to decipher if there is an age or race effect on treatment improvement by modality, and lack of information on the magnitude of the change in the key symptomatology outcome measures. However, these studies still gleaned valuable information to preliminarily compare their effectiveness and is a first step towards designing better trials to evaluate this problem.

In conclusion, there is limited research on DMSO, with most recent findings unsupportive of the treatment. Orally administered PPS has the best-designed studies, with multiple placebo controlled, randomized clinical trials supporting the efficacy of symptom treatment, but findings indicated limited success in symptom reduction. While Onabotulinum toxin A is considered to be a treatment that is administered at a later point of disease treatment, there is a substantial amount of published research that uses updated methods of pain and symptom evaluation which leads to a belief of efficacy. Given the stronger findings for Onabotulinum toxin A, future research should be directed to determine if this modality should be considered as the primary intravesical treatment method of IC/BPS treatment despite its possible side effect of increasing UTIs. The public health implications of the existing and future work could allow for quicker and more effective relief of symptoms of IC/BPS for the millions of adults suffering from this painful condition.

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