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Do medication prescription patterns follow guidelines in a cohort of women with interstitial cystitis/bladder pain syndrome?

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Abstract

Objective: To describe prescription patterns for women with interstitial cystitis/bladder pain syndrome (IC/BPS) and to determine whether these patterns are aligned with treatment guidelines.

Methods: We sampled female patients with an ICD-9/10 diagnosis of IC/BPS (595.1/N30.10) by querying active users of the Veterans Health Administration. Medical records were reviewed to determine whether patients met IC/BPS diagnostic criteria. A cohort of women with other pelvic pain disorders ("IC-like") was identified. Prescription patterns were compared between the two cohorts. Prescription prevalence of typical bladder pain medications was compared before and after the diagnosis of IC/BPS was made using Poisson regression.

Results: There were 641 women who met criteria for IC/BPS and 197 women with IC-like disorders. Women with IC/BPS were prescribed a pain medication more often than those with IC-like conditions (77% versus 59%, $p<0.0001$). Of the women with IC/BPS, 44% tried 3 or more pain medications. Of women with a diagnosis of IC/BPS, only 67% were prescribed an AUA-recommended medication. Prescription incidence increased after diagnosis for both pentosan polysulfate (10% to 29%, $p<0.0001$) and hydroxyzine (17% to 40%, $p<0.0001$), but not for amitriptyline or cimetidine. Amitriptyline was prescribed to 223 women with IC/BPS, only 125 of which (56%) had a documented history of depression.

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Conclusions: Many women with IC/BPS required multiple bladder prescriptions, highlighting the difficulty in finding an effective treatment for IC/BPS. PPS and hydroxyzine were preferred IC/BPS medications. Our next step will be to analyze treatment patterns in those patients who did not receive medications.

Keywords

Interstitial cystitis; bladder pain syndrome; pentosan polysulfate; hydroxyzine; amitriptyline

Introduction:

While it is difficult to estimate the true prevalence of interstitial cystitis/bladder pain syndrome (IC/BPS), likely due to underreporting and difficulty in diagnosis, a telephone survey administered by the RAND Interstitial Cystitis Epidemiology (RICE) study estimated a population prevalence of between 2.7% (high specificity definition) and 6.5% (high sensitivity definition) of United States women. However, only 9.7% of the women who met the study's diagnostic criteria for IC/BPS reported being diagnosed with IC/BPS.[1] IC/BPS is most often diagnosed in the fifth decade of life, affecting women in their prime reproductive and workplace productivity years.[2] When matched with non-IC controls, patients with IC/BPS had $7,223 higher total health care costs in the first twelve months after diagnosis.[2]

The American Urological Association (AUA) updated their most recent guidelines for the treatment of IC/BPS in 2014. These guidelines provide a framework for treatment for IC/BPS patients, while recognizing that IC/BPS has a wide array of clinical presentations that respond variably to different treatments. They outline first-line through sixth-line treatments with increasing levels of invasiveness. Medications were designated as a second-line therapy after first line therapies, which include behavioral modifications and stress management. Based on the available evidence, there was enough information to recommend the following four medications as options for patients with IC/BPS: pentosan polysulfate (PPS), hydroxyzine, amitriptyline, and cimetidine.[3,4]

Our goal was to gain a better understanding of how these medications are being prescribed by sampling a national cohort of women with IC/BPS. We hoped that, by further examining treatment patterns, we can learn more about this complex disease and help target more effective treatments for patients.

Methods and Materials:

After obtaining institutional approval (Durham VAMC IRB#1936) the Veterans Affairs Informatics and Computing Infrastructure (VINCI) was queried for all female active users of the Veterans Health Administration (VHA) to obtain a random sample of patients with an ICD-9/10 diagnosis of IC/BPS (595.1/N30.10). Chart review was then performed to confirm that the patients identified truly had IC/BPS. The inclusion criteria were: two visits complaining of bladder-centric pain in the absence of positive urine culture at least six weeks apart, or a history of bladder pain/irritative symptoms with one additional visit complaining of bladder-centric pain. These criteria are consistent with the recommended diagnostic criteria of the AUA.[3]

Next, it was determined which patients received prescriptions for typical bladder pain medications by extracting this information for the entire duration of time that the patient received care at the VHA. The medications investigated were tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, nortriptyline), H2 blockers (cimetidine, ranitidine), hydroxyzine, methenamine, pentosan polysulfate, and phenazopyridine. Acknowledging that many women with IC/BPS likely have comorbid pain conditions, and that it could not be determined with certainty that the bladder pain medication was indeed prescribed for bladder pain, a control group of women with other pelvic pain disorders was identified. For this group VINCI was queried using ICD-9/10 codes for dyspareunia (625.0/N94.1), vaginismus (625.1/N94.2), vulvodynia (625.7/N94.81), and vulvar vestibulitis (625.71/N94.81). The group was designated as the “IC-like” cohort.

For the IC/BPS cohort, prescription prevalence for the medications listed above was compared before and after the diagnosis of IC/BPS. This included the four oral medication options recommended by the AUA (PPS, hydroxyzine, amitriptyline, and cimetidine).

Means of continuous variables were compared using student’s t-test. Categorical variables were compared using chi-squared analysis. Poisson regression was used to determine the number of prescriptions per patient, with time followed as an offset. Data were considered significant where two-tailed p-values were less than 0.05. Analyses were performed using SAS v9.4 software.

Results:

A total of 641 women were sampled who met criteria for our IC/BPS cohort. Subjects had been diagnosed between October 2004 to July 2016. The control group of “IC-like” patients totaled 197 women. The two groups did not differ with respect to mean age at diagnosis or BMI, but there were more Hispanic women in the IC/BPS group and the “IC-like” group had a higher proportion of women who described their race as “other/unknown”. The total time followed was not different between groups, with an overall average of 84 +/− 57 months. Both groups had prescription data in the medical record for at least seven years after diagnosis: 83.7 months for the IC/BPS group and 86.0 months for the “IC-like” group ($p=0.6309$). Women with IC/BPS were prescribed a pain medication more often than those with IC-like conditions (77% versus 59%, $p<0.0001$). Of the women with IC/BPS, 44% tried 3 or more pain medications (Table 1).

Out of the 641 women with a diagnosis of IC/BPS, 307 (48%) were prescribed a bladder pain medication at some point prior to diagnosis, while 457 (71%) were prescribed a bladder pain medication at some point after diagnosis. The prescription incidence for any of the AUA-recommended oral medications increased after diagnosis from 33% to 60% ($p<0.0001$). Prescription incidence increased after diagnosis for both PPS (10% to 29%, $p<0.0001$) and hydroxyzine (17% to 40%, $p<0.0001$). However, prescription prevalence did not increase for amitriptyline (17% to 24%, $p=0.6025$) or cimetidine (2% to 2%). Prescription incidence also increased for phenazopyridine (19% to 36%, $p=0.0009$) (Table 2). It was noted that 223 women (34.7%) received prescriptions for amitriptyline at some

point during treatment, with only 125 of those women (56%) having an ICD-9/10 diagnosis of depression (296.3/F32.9).

While 494 women (77%) with IC/BPS received a prescription for a bladder pain medication at some point, 23% of women with IC/BPS never received a prescription for any of the medications on our list and 33% never tried one of the AUA-approved medications.

Discussion:

There are many treatment “options” available for patients with IC/BPS but no scientific consensus on which treatments are most effective and well-tolerated in clinical practice. Numerous studies have been undertaken to find the most efficacious treatments for IC/BPS and have determined the most beneficial oral therapies to include AUA-recommended treatments such as amitriptyline, cimetidine, hydroxyzine, and PPS, and additional medication options suggested by the Canadian Urologic Association such as cyclosporine A and gabapentinoids.[3–5] However, in clinical practice these are not always the treatment options that patients find most effective. In one patient survey, amitriptyline was described as moderately effective, while cimetidine, hydroxyzine, and PPS were categorized as mildly effective. That survey found that, based on patient reports, the most effective medications were opioids, alkalinizing agents, and phenazopyridine. This illustrates the difficulty in applying recommended IC/BPS treatments into clinical practice.[6]

Hydroxyzine was the most prescribed medication in this cohort of IC/BPS patients. One randomized control trial demonstrated improvement when treated with hydroxyzine compared to placebo, although the difference was not statistically significant, with few side effects.[7] An observational study demonstrated improvement in symptoms, with a better response in a subset of patients with systemic allergies.[8] Hydroxyzine may also be prescribed for anxiety, nausea, and urticaria. While there are multiple indications for prescription of hydroxyzine, there was a statistically significant increase in prescriptions after diagnosis of IC/BPS, suggesting that hydroxyzine was a preferred medication for the treatment of IC/BPS. The nature of this analysis prevented us from determining if practice patterns reflected true efficacy of hydroxyzine in this population.

Phenazopyridine is an azo dye which has an analgesic effect on urinary tract mucosa through an unknown mechanism. It was the second most prescribed medication and prescription incidence increased after patients were diagnosed with IC/BPS. In our literature search, we did not find a randomized control trial examining IC/BPS response to phenazopyridine. On a web-based survey of women with a self-reported diagnosis of IC/BPS, 61.1% of women who tried phenazopyridine thought it improved their symptoms, making it one of the most effective medications according to the survey results.[6] On another patient survey, 57% of women who tried phenazopyridine reported that it improved their symptoms.[9]

Prescriptions for PPS more than doubled in this cohort after the diagnosis of IC/BPS. Currently, PPS is the only FDA-approved oral therapy for the treatment of IC/BPS. There is mixed evidence on the efficacy of PPS for treatment of IC/BPS. Several randomized placebo-controlled studies have demonstrated that PPS is efficacious in treating IC/BPS

when compared to placebo.[10] However, a Cochrane review performed in 2020 found no evidence that PPS use led to improvement of pain, frequency, or nocturia or increased likelihood of cure when compared to controls.[11] Recent studies (2018–2021) have identified a dose-dependent risk of maculopathy with prolonged PPS exposure that may persist after discontinuation.[12] The association of PPS with maculopathy was not identified until 2018, and so it is not reflected in this study. We may see prescription patterns for PPS change over the next several years.

While amitriptyline is one of few medications to have been shown in multiple studies to significantly reduce symptoms in patients with IC/BPS,[13] it comes with a significant side effect profile. One prospective, open label study reported an 84% rate of side effects including dry mouth in 79% and weight gain in 59%, with side effects contributing to dropout in 25 of the 94 participants.[14] More than one-third (35%) of the IC/BPS patients in this cohort received a prescription for amitriptyline at one point during the study period, only half of whom had a diagnosis of depression, suggesting that amitriptyline was commonly prescribed for other indications, including pain. However, amitriptyline prescriptions did not increase after a patient was diagnosed with IC/BPS in our study, indicating that it was not a preferred treatment for IC/BPS by the providers in the VHA. Future studies might determine whether providers were deterred by the side effect profile.

Our study was limited in that missing data was assumed to be a negative response. However, there is unlikely to be significant amounts of data missing, as the data we extracted was not reliant on manual entry. Also, these patients may have been receiving additional care outside of the VHA that was not accounted for in our database. Veterans may differ in how they present with pain and depression; therefore, these results may not be generalizable to other populations. Data were abstracted from both prior to and after the publication of the AUA IC/BPS guideline, and so we are unable to assess whether the guidelines had an influence on prescribing patterns.

The strengths of this study were that it was a national cohort study with a large sample size. VHA patients typically receive most of their medical care through the VHA, reducing the potential for missing data.

In this population of female VHA patients with IC/BPS, almost half tried three or more different bladder pain medications, highlighting the difficulty in finding an effective and well-tolerated oral medication for IC/BPS. Patients were more likely to be prescribed one of the AUA-recommended IC/BPS medications once a diagnosis of IC/BPS had been made. The provider-preferred medications to treat IC/BPS were pentosan polysulfate and hydroxyzine. Prescription of amitriptyline and cimetidine did not increase for patients once a diagnosis of IC/BPS was made. One-third of women with a diagnosis of IC/BPS were not prescribed any of the AUA-recommended IC/BPS medications within the study period. Our next step will be to analyze treatment patterns in those patients who did not receive oral medication.

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References:

1. Berry SH, Elliott MN, Suttorp M, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol. 2011;186(2):540–544. doi:10.1016/j.juro.2011.03.132 [PubMed: 21683389]
2. Tung A, Hepp Z, Bansal A, et al. Characterizing health care utilization, direct costs, and comorbidities associated with interstitial cystitis: a retrospective claims analysis. J Manag Care Spec Pharm. 2017;23(4):474–482. doi:10.18553/jmcp.2017.23.4.474 [PubMed: 28345436]
3. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185(6):2162–2170. doi:10.1016/j.juro.2011.03.064 [PubMed: 21497847]
4. Hanno PM, Erickson D, Moldwin R, et al. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol. 2015; 193: 1545. doi:10.1016/j.juro.2015.01.086 [PubMed: 25623737]
5. Cox A, Golda N, Nadeau G, et al. CUA guideline: Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. Can Urol Assoc J. 2016;10(5–6):E136–E155. doi:10.5489/cuaj.3786 [PubMed: 27790294]
6. Lusty A, Kavaler E, Zakariasen K, et al. Treatment effectiveness in interstitial cystitis/bladder pain syndrome: Do patient perceptions align with efficacy-based guidelines?. Can Urol Assoc J. 2018;12(1):E1–E5. doi:10.5489/cuaj.4505 [PubMed: 29173267]
7. Sant GR, Propert KJ, Hanno PM, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003; 170: 810–5. doi:10.1097/01.ju.0000083020.06212.3d [PubMed: 12913705]
8. Theoharides TC, Sant GR. Hydroxyzine therapy for interstitial cystitis. Urology. 1997;49(5A Suppl):108–110. doi:10.1016/s0090-4295(97)00182-9
9. Hill JR, Isom-Batz G, Panagopoulos G, et al. Patient perceived outcomes of treatments used for interstitial cystitis. Urology. 2008;71(1):62–66. doi:10.1016/j.urology.2007.09.011 [PubMed: 18242366]
10. van Ophoven A, Vonde K, Koch W, et al. Efficacy of pentosan polysulfate for the treatment of interstitial cystitis/bladder pain syndrome: results of a systematic review of randomized controlled trials. Curr Med Res Opin. 2019;35(9):1495–1503. doi:10.1080/03007995.2019.1586401 [PubMed: 30849922]
11. Imamura M, Scott NW, Wallace SA, et al. Interventions for treating people with symptoms of bladder pain syndrome: a network meta-analysis. Cochrane Database Syst Rev. 2020;7(7):CD013325. doi:10.1002/14651858.CD013325.pub2
12. Paredes Mogica JA, De EJB. Pentosan polysulfate maculopathy: What urologists should know in 2020. Urology. 2021;147:109–118. doi:10.1016/j.urology.2020.08.072 [PubMed: 33045286]
13. Di XP, Luo DY, Jin X, et al. Efficacy and safety comparison of pharmacotherapies for interstitial cystitis and bladder pain syndrome: a systematic review and Bayesian network meta-analysis. Int Urogynecol J. 2021;32(5):1129–1141. doi:10.1007/s00192-020-04659-w [PubMed: 33638677]
14. van Ophoven A, Hertle L. Long-term results of amitriptyline treatment for interstitial cystitis. J Urol. 2005;174(5):1837–1840. doi:10.1097/01.ju.0000176741.10094.e0 [PubMed: 16217303]
15. Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. Urology. 1994;44(4):614–616. doi:10.1016/s0090-4295(94)80074-x [PubMed: 7941209]

Table 1.

Comparison of IC/BPS and "IC-like" Cohorts

	IC (n=641)		IC-Like (n=197)		p-value*
Age at Diagnosis, mean±SD	47.1±12.7		46.6±11.6		0.5747[a]
Race					
White	408	64%	127	64%	
Black	163	25%	45	23%	**0.0102**[b]
Hispanic	39	6%	5	3%	
Other/Unknown	31	5%	20	10%	
BMI, mean±SD	28.2±5.9		27.6±6.1		0.2483[a]
Ever Prescribed any AUA-recommended Rx	431	67%	78	40%	**<0.0001**[b]
Among Cases with Rx					
Months Prior to Diagnosis for First AUA-recommended Rx, mean±SD	14.9±65.0		16.9±70.2		0.8072[a]
Any Medications from Table 2	494	77%	116	59%	**<0.0001**[b]
# Medications per Patient, median (IQR)	2 (1, 4)		1 (0, 2)		**<0.0001**[c]
Medication Counts per Patient (Table 2)					
0	147	23%	81	41%	
1	100	16%	45	23%	
2	112	17%	43	22%	
3	105	16%	15	8%	
4	88	14%	6	3%	**<0.0001**[c]
5	62	10%	6	3%	
6	21	3%	1	1%	
7	5	1%	0	0%	
8	1	0%	0	0%	

*P-values computed from (a) Student's t-test, (b) Chi-square test, or (c) Poisson regression.

Table 2.

Typical bladder pain medications and their prescription prevalence overall, prior to and after diagnosis in the IC/BPS cohort

	Overall		Pre-IC Dx		Post-IC Dx		Pre vs Post p-value*
Tricyclic antidepressant:	305	48%	176	27%	219	34%	0.0663
Amitriptyline	223	35%	111	17%	156	24%	0.6025
Desipramine	10	2%	8	1%	2	0%	0.4399
Doxepin	73	11%	36	6%	45	7%	0.5819
Imipramine	32	5%	16	2%	19	3%	0.6207
Nortriptyline	87	14%	44	7%	54	8%	0.4399
H2 Blocker:	231	36%	124	19%	177	28%	0.7484
Cimetidine	21	3%	13	2%	10	2%	0.1029
Ranitidine	220	34%	116	18%	169	26%	0.5699
Antihistamine:							
Hydroxyzine	297	46%	109	17%	258	40%	**<0.0001**
Acidifier							
Methenamine	16	2%	0	0%	16	2%	*non est.***
Protective coating:							
Pentosan polysulfate (PPS)	206	32%	61	10%	183	29%	**<0.0001**
Analgesic:							
Phenazopyridine	285	44%	123	19%	230	36%	**0.0009**
Any AUA-approved treatments	431	67%	211	33%	383	60%	**<0.0001**
(Amitriptyline, cimetidine, hydroxyzine, pentosan polysulfate (PPS))							
ANY medication from this list	494	77%	307	48%	457	71%	0.1400

*P-values computed from Poisson regression.

**Could not estimate due to no sample size in Pre-IC Dx group