**Real World Use of Oral Treatments in Interstitial Cystitis/Bladder Pain Syndrome in the UK: A Cross-Sectional Study**

**Abstract**

**Background**: To describe the oral treatments people living with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) are using to treat their urologic condition in the UK.

**Method**: A questionnaire hyperlink encompassing current and previous medications taken for IC/BPS with other sociodemographic and diagnostic indices was available to the Bladder Health UK website. Interested and fully consented individuals accessed and completed the survey.

**Results**: A total of 601 accessed the questionnaire of whom 173 participants responded (response rate: 28.7%) with a mean ± SD O’Leary/Sant scores of 20.12 ± 9.38. A sample size of 171 was estimated to be used in the survey. A fifth of the participants were not on any treatment at all. Amitriptyline was the most prevalent medication in use both alone and in combination. A shift in the use of unapproved (for IC/BPS) antidepressant, smooth muscle relaxant, opioids, gabapentenoids and antibiotics was observed in the sample. There were no significant differences between the mean (SD) O’Leary/Sant scores of cohorts currently taking oral medications and those not taking it. More than two-thirds of the participants had been diagnosed with the disease more than five years. Just under a half (47.4%) of participants reported a history of allergy.

**Conclusion**: Our study provides contemporary evidence that the treatments used for managing IC/BPS encompass a broad range of medications both recommended and not recommended by current guidelines. The latter suggests patients are willing to try novel treatments when more conventional ones are ineffective.

**Key words**: Oral Treatments, Amitriptyline, Interstitial Cystitis/Pain Bladder Syndrome, Comorbidity

**INTRODUCTION**

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a poorly understood disorder of the urinary bladder. Despite affecting millions of people around the world, there is no known cure. 1,2 The difficulty in both understanding and diagnosing the disease is partly due to the varying symptoms under which it may present. These, in turn, are a direct consequence of the different types of aetiologies held to be responsible for the disease. 3

As a consequence, pharmacotherapy is often broad; mostly consisting of different drug classes, each addressing a particular symptom(s) or possible aetiology(ies). Glycosaminoglycan (GAG) replacement therapy, mast cell modulators, antidepressants and immunosuppressant therapies have been used with varied outcomes, but overall treatment outcomes remain unsatisfactory. 4,5 Nevertheless, pharmacotherapy is an important component in the treatment algorithm for IC/BPS; being used when more conservative interventions are ineffective. 6

The role of pharmacotherapy in the management of IC/BPS is emphasised in the management guidelines for most professional bodies in urology with slight variations in the grades of evidence and recommendations on how and when each member drug is to be used. 7,8 Rovner, et al. 9 reported in the Interstitial Cystitis Database (ICDB) Study the existence of 183 treatments for IC/BPS. However, little is known regarding oral medications which occupy a central position in the treatment algorithm.

Cross sectional surveys are used to monitor treatment programs inter alia. 10 In particular, patient reported outcomes have been used to provide insight into the quality of life, dietary habits and other experiential domains of IC/BPS sufferers. 11 In view of this, it is reasonable to identify the proportions of IC/BPS cohorts who are on oral therapy and in particular the specific treatments they are using with a view to give a clear description of this population.

In this study, we aimed to collect and describe the use of oral treatments for IC/BPS in the UK with the view to providing baseline data that could generate plausible hypotheses for the role of IC/BPS oral pharmacotherapy.

**METHODS**

**Questionnaire content and development**

The questionnaire consisted of items pertaining to sociodemographic variables, diagnostic procedures used in establishing diagnosis, medication history and dietary consumption pattern of the participants. Participants were presented with a list of guideline-recommended IC/BPS oral treatments and asked to indicate in a multiple response manner whether they have used/were using any of these medications. In addition, an open-ended item was included for them to include any other treatment they had used/were using for their bladder condition. Moreover, enquiries relating to length of time since IC/BPS was diagnosed and disease type in the cohort were made. Participants who had received a clinical diagnosis of IC/BPS also completed the O’Leary/Sant questionnaire to help confirm that they fulfilled the criteria for a diagnosis of IC/BPS thereby justifying their inclusion in the study.

**Sample and questionnaire administration**

Data were collected from a convenience sample of members of Bladder Health UK - a bladder focused charity in the UK. Approval for the study was obtained from the Faculty of Medicine ethics committee at the University of Southampton, United Kingdom. Those members with a prior clinical diagnosis of IC/BPS were approached. The only inclusion criterion was age between 18 and 80 years. The questionnaire hyperlink was made available at the charity’s website between February 2019 and March 2019. Interested and consented members accessed and completed the survey. Based on the Confidence Interval (CI) width of 0.15, CI of 0.5% and a planning proportion of 0.5, a sample size of 171 was deemed suitable for statistical purposes (precision of findings).

**Statistical analysis**

Data were collected using isurvey software and result transformed into IBM SPSS statistics for windows version 26.0 (IBM Corp., Armonk, N.Y., USA) for analysis. Data were presented as means (SD) and percentages. Responses to questions were structured in multiple response pattern. Thus, multiple response analysis was used as applicable. A student t test was used to compare means between two numerical groups and the value of p was set at 0.05 (2-tailed).

**RESULTS**

A total of 173 participants completed the survey out of the 601 members that accessed the survey hyperlink producing a response rate of 28.7%. The mean (SD) age of the participants was 56.13 (15.39) years and 93.1% of the participants were females as shown in table 1.

Table 1 shows that more than 90% of the participants have been living with their condition for more than 2 years and have no family history of the disease. In terms of care providers, 59% indicated they are being managed by a urologist while only 5.8% are being seen by a gynaecologist. Almost half of the participants reported a history of allergy, although specific allergens were not recorded. There was no significant difference between the O’Leary/Sant scores of those with allergy 19.41 (10.02) and those without it 20.76 (8.76).

Regarding beverages, 54.3, 38.7% and 39.9% consumed tea, coffee and alcohol respectively. Only 4.6% and 1.7% smoked cigarettes or vaped e-cigarette, respectively. There were no significant differences between the O’Leary/Sant scores of those drinking 18.78 (10.02) and not drinking 20.97 (8.89) coffee and of those drinking 19.24 (9.46) and not drinking tea 21.16 (9.23). However, there were significant differences in the mean O’Leary/Sant scores of cohorts smoking 27.13 (9.28) and not smoking cigarettes 19.78 (9.28); and those drinking 17.17 (8.98) and not drinking alcohol 22.13 (9.15).

From Table 2: Participants mostly underwent more than 1 diagnostic procedure to confirm their diagnosis. Cystoscopy under anaesthesia appeared to be the commonest procedure used either alone or in combination. Only a very small number of participants had no idea as to the type of procedure they had undergone.

Endometriosis, vulvodynia and asthma were the commonest comorbidities in the sample in descending order of frequency of cases. Systemic Lupus Erythematosus was the least reported comorbid condition (Table 3). The relationship between presence/absence of specific comorbid condition and O’Leary/Sant scores was run using an independent t test. Only vulvodynia and chronic fatigue syndrome showed a significant difference. This underscores the finding that other chronic conditions often co-exist with IC/BPS. The mean (SD) O’Leary/Sant cores of those having and not having vulvodynia were 24.09 (10.24) and 19.51 (9.12) p=0.029, respectively. Similarly, the scores for those having and not having chronic fatigue syndrome were 26.79 (5.32) and 19.53 (9.44) p=0.05, respectively.

From table 4, (sample size is 173), it can be seen that the per cent cases is 214.7 because some participants had taken more than one drug in the past and were allowed to have multiple responses to include both past and current drug usage. A fifth of participants reported being on no treatment at the time of the survey.

Respondents previously on recommended medications by current guidelines for IC/BPS had an O’Leary Sant score of 20.48 ± 9.49, whilst those who had not used recommended medications had a score of 17.68 ± 8.36 (p=0.193) .

Similarly, table 5 has a cases greater than the sample size indicating some participants were taking more than one. Of note, amitriptyline was a widely used medication either alone or in combination while L-arginine was the least used. Participants currently on any recommended medication and those who had not use alternative medication had mean ± SD O’Leary/Sant scores of 20.76 ± 9.38 and 18.98 ± 9.34 (p=0.234), respectively.

**DISCUSSION**

This is, to our knowledge, the first cross-sectional study to look at oral treatments in IC/BPS sufferers. Strikingly, the majority of participants were not on any oral treatment despite elevated O’Leary/Sant scores (moderate symptoms). This serves to underline the fact that for many participants the available oral treatments lack efficacy. It is also imperative to highlight the fact that a higher attrition rate (Tables 4 and 5) was observed for participants on no-medications which further strengthened this view.

From the survey, amitriptyline was the most frequent drug used for symptom control in the participants. Our finding is consistent with the outcome of the Interstitial Cystitis Database Study that also reported amitriptyline to be the most widely prescribed medication for IC/BPS 9. The frequency of usage in the latter study was 16%, whilst in the current study it was 20.5%, figures that are in broad agreement. This widespread use of amitriptyline can be explained by the fact that the drug has a multiplicity of actions in addition to its known antidepressant action. Thus, it also has a smooth muscle relaxant effect, mast cell stabilising actions, provides relief of neurogenic pain and is a sedative; 12 all actions which help aid pain relief and improve sleep in IC/BPS. It is to be noted that amitriptyline is the only recommended (by guidelines) antidepressant for IC/BPS use due to a supportive evidence base. 13 Although the use of the antidepressant’s nortriptyline, fluoxetine, duloxetine and imipramine were also noted in the cohort, these were based on ‘’off-label’’ use. The reason for this statement being that the studies in support of their use in IC/BPS were inadequately powered, flawed, non-randomised or performed on non-IC/BPS patients. For instance, van Ophoven and Hertle 14 reported a non-significant change in global response assessment from baseline when using duloxetine in IC/BPS patients in a non-randomised-non-controlled prospective study. Likewise, a randomised control trial of nortriptyline showed a significant (p≤0.05) reduction in mean pain scores in the nortriptyline arm. However, the study population were chronic pelvic pain (CPP) sufferers rather those with a diagnosis of IC/BPS. 15

With respect to gabapentenoids, the rationale for their use in IC/BPS stems from modest improvements in pain seen when they are used to treat neuropathic pain, vulvodynia and related conditions where there is plausible Central Nervous System involvement. 3,16 Gabapentin is thought to act via increasing the inhibitory neurotransmitter (Gamma-aminobutyric acid) at post synaptic fibres and also inhibiting calcium currents. 17 Gabapentin had shown significant reductions in visual analogue scale pain scores at both 12 and 24 weeks from baseline, when compared to placebo in a randomised double blind control trial of CPP patients.18 The fact that it has not been trialled in IC/BPS makes the evidence anecdotal.

Regarding opioids, a paradigm shift in the increased consumption of opioids was observed in the cohort (Tables 4 and 5). Recently, Zillioux, et al. 19 reported an upsurge in opioid consumption amongst IC/BPS patients. This, together with our findings, suggests an unmet need in pain management in this patient group. Whilst the use of opioids in non-cancer patients especially those with IC/BPS is still open to debate, 20 there is a clear desire to optimise non-opioid pain management in IC/BPS using existing or novel (e.g. cannabinoids) drugs. Although our study is limited by the fact that participants were not questioned further on how long they had been on opioids, given that IC/BPS is a chronic disease, the possibility of chronic usage cannot be excluded. This raise concerns relating to tolerance, addiction, and misuse.

Whilst smooth muscle relaxants (anti-cholinergic) such as solifenacin have been tried in overactive bladder with modest outcomes, 21 there is no good evidence to justify their use in IC/BPS. Similarly, antibiotic use in the cohort cannot be supported because they are neither indicated for IC/BPS nor any of the comorbid condition the participants have identified to be suffering from. Nevertheless, such drugs are not uncommonly used for symptom control in IC/BPS.

Overall, there was a trend towards the use of guidelines-not-recommended medications to treat this frustrating urologic condition. This suggests a dissatisfaction on the part of caregivers with recommended drugs who need to address the pain experienced by the patients under their care. The minimum we should be doing is to try to provide an evidence base for the use of such treatments using randomised controlled trials where this is possible or well-designed observational studies where this is not so.

Tea, coffee and alcoholic drinks have been long identified as triggers for the worsening of IC/BPS symptoms. 22 Whether these items should be entirely avoided is still a subject of debate due to the individual nature of their impact on IC/BPS patients. However, in this sample, the non-significant difference in the O’Leary/Sant scores of those drinking and not drinking tea and coffee does not support any correlation between their use and IC/BPS symptoms. Conversely, a significant decrease in O’Leary Sant scores of those drinking alcohol compared to non-alcoholic drinkers was observed. This is highly unexpected considering the diuretic effect of alcohol could mean frequent urination with attendant elevation of the problem domain of the O’Leary/Sant scale. Alternatively, IC/BPS individuals in the cohort could be aware of the adverse effects of alcohol and choose to avoid it, this being most marked in those with worse symptoms.

The fact that only 4.6% of our cohort smoked cigarettes compared to 87.9% in the snapshot study reported by Kleier 23 suggests good lifestyle measures are being adopted in this patient sample. Tobacco smoke and its constituents have deleterious effects in most bodily systems and organs with well-known adverse effects on the cardiovascular system, respiratory system and the bladder. Given this, it is hard to conclude that the cumulative benefits of smoking cessation would have any effect other than to improve bladder function.

One of the limitations of our study is that data were collected directly from the participants and not retrieved from their clinical records which could be a source of recall bias. However, given that the option was provided for participants to choose from a list of drugs in the questionnaire minimises this risk. In addition, there was a free text option to describe any other medication they might be using, thereby providing a more complete capture of their treatments.

Another possible limitation is that the sample population was pooled from an IC/BPS charity rather than directly from a medical setting which could lead to concern regarding the accuracy of their IC/BPS diagnosis. However, participants were all originally diagnosed by medical personnel and the use of O’Leary/Sant scores to screen patients offers an additional layer of diagnostic security. The geographically diverse nature of the participants from the charity helps to strengthen the validity of our findings and counteract bias arising from the convenience sampling design.

**CONCLUSION**

We have in this study provided a snapshot of the oral treatments currently being offered to and used by individuals with IC/BPS in the UK. The complexity of the disease is reflected in the diversity of drugs classes being used in attempt to treat this difficult condition. A substantial proportion of the sample are still on medications not commonly used to treat the disease, as reflected by frequency of “others”.

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**LEGENDS TO TABLES**

**Table 1:** Description of the sample (n=173).

**Table 2:** Diagnostic procedures undertaken by participants for IC/BPS diagnosis by multiple response analysis (n=173).

**Table 3:** Distribution of comorbidity in the sample using multiple response analysis (n=173).

**Table 4:** Proportions of previous medications consumed by participants using multiple response analysis (n=173).

**Table 5:** Proportions of current medications used by the participants using multiple response analysis (n=173).

**Table 1:**

| **Variable** | **N (%)** | **Mean (SD)** |
| --- | --- | --- |
| Age  | 56.13 (15.39) |
| Gender | Female | 161 (93.1) |  |
| Male | 12 (6.9) |
| IC/BPS | Ulcer | 35 (20.2) |
| Non-ulcer | 76 (43.9) |
| Don’t know | 62 (35.8) |
| O’Leary/Sant score  | 20.12 (9.38) |
| Period of time since diagnosis of IC/BPS  | >6months<1year | 3 (1.7) |  |
| >1year<2years | 14 (8.1) |
| >2years<5years | 38 (22.0) |
| >5years | 118 (68.2) |
| Healthcare professional managing IC/BPS | Urologist | 102 (59.0) |
| Gynaecologist | 10 (5.8) |
| Nurse | 17 (9.8) |
| Don’t know | 23 (13.2) |
| \*Others | 21 (12.1) |
| Family members with IC/BPS | Father/Mother | 4 (2.3) |
| Grandfather/Grandmother | 1 (0.6) |
| Brother(s)/Sister(s) | 0 (0.0) |
| Children/Grandchildren | 3 (1.7) |
| Uncle(s)/aunt(ies) | 1 (0.6) |
| \*\**Cumulative family members with IC/BPS* | 9 (5.2) |
| Allergy | 82 (47.4) |
| Cups of coffee drunk in a day | None | 106 (61.3) |
| 1-2 | 57 (32.9) |
| 3-4 | 9 (5.2) |
| 5-6 | 1 (0.6) |
| Cups of tea drink in a day | None | 79 (45.7) |
| 1-2 | 47 (27.2) |
| 3-4 | 30 (17.3) |
| 5-6 | 17 (9.8) |
| Units\*\*\* of alcohol consume in a week | None | 104 (60.1) |
| 1-5 | 48 (27.7) |
| 5-10 | 16 (9.2) |
| > 10 | 5 (2.9) |
| Number of cigarettes smoked in a day | None | 165 (95.4) |
| 1-5 | 1 (0.6) |
| 5-10 | 3 (1.7) |
| > 10 | 4 (2.3) |
| Vape e-cigarettes |  | 3 (1.7) |

\*Include pain specialist, nutritionist and non-response by participants,

\*\*\*Represent total family members with the disease

**Table 2:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Diagnostic procedure** | **Frequency** | **% responses** | **% of cases** |
| Cystoscopy under AE\* | 114 | 35.6 | 65.9 |
| Cystoscopy awake | 47 | 14.7 | 27.2 |
| Hydrodistension | 60 | 18.8 | 34.7 |
| Bladder biopsy | 52 | 16.3 | 30.1 |
| Clinical history | 44 | 13.8 | 25.4 |
| Don’t know | 3 | 0.9 | 1.7 |
| Total | 320 | 100 | 185.0 |

\*Anaesthesia

**Table 3:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Comorbid disease** | **Frequency** | **% responses** | **% of cases** |
| Vulvodynia | 23 | 20.0 | 30.7 |
| Endometriosis | 25 | 21.7 | 33.3 |
| Asthma | 22 | 19.1 | 29.3 |
| Fibromyalgia | 21 | 18.3 | 28.0 |
| Chronic Fatigue Syndrome | 14 | 12.2 | 18.7 |
| Systemic Lupus Erythematosus | 3 | 2.6 | 4.0 |
| Sjogren’s syndrome | 7 | 6.1 | 9.3 |
| Total | 115 | 100.0 | 153.3 |

**Table 4:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Medication status** | **Frequency** | **% responses** | **% of cases** |
| Pentosan polysulphate | 33 | 9.0 | 19.4 |
| Amitriptyline | 100 | 27.4 | 58.8 |
| Cimetidine | 57 | 15.6 | 33.5 |
| L-arginine | 10 | 2.7 | 5.9 |
| Cyclosporine | 9 | 2.5 | 5.3 |
| Hydroxyzine | 34 | 9.3 | 20.0 |
| Prednisolone | 15 | 4.1 | 8.8 |
| None | 22 | 6.0 | 12.9 |
| \*Others | 75 | 20.5 | 44.1 |
| Don’t know | 10 | 2.7 | 5.9 |
| Total | 365 | 100.0 | 214.7 |

Missing cases: 3

\*Other drugs used previously include: antibiotics (Cefradine, flucloxacillin, trimethoprim, doxycycline, fluroquinolones) nortriptyline, solifenacin, mirabregon, duloxetine, tamsulosin, diclofenac, gabapentin, pregabalin, paracetamol, naproxen, uribel, ranitidine, tramadol, hydroxychloroquine, desmopressin and anticholinergics.

**Table 5:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Medications status** | **Frequency** | **% responses** | **% of cases** |
| Pentosan polysulphate | 16 | 7.3 | 9.4 |
| Amitriptyline | 45 | 20.5 | 26.5 |
| Cimetidine | 11 | 5.0 | 6.5 |
| L-arginine | 2 | 0.9 | 1.2 |
| Hydroxyzine | 13 | 5.9 | 7.6 |
| Prednisolone | 3 | 1.4 | 1.8 |
| None | 62 | 28.3 | 36.5 |
| \*Others | 63 | 28.8 | 37.1 |
| I don’t know | 4 | 1.8 | 2.4 |
| Total | 219 | 100.0 | 128.8 |

Missing cases: 3

\*Others currently in use viz: Antibiotics (cefradine, flucloxacillin, cephalexin, nitrofurantoin); Smooth antispasmodics (solifenacin, oxybutynin, tamsulosin); Proton pump inhibitors (ranitidine, lansoprazole); Antidepressants (nortriptyline, imipramine, fluoxetine, duloxetine); Opioids (morphine, paracetamol and codeine, phenazopyridine, naltrexone, oxycodone, hydromorphone, tramadol); NSAIDs (celecoxib) Gabapentenoids (pregabalin, gabapentin); heparin, hexamethylenetetramine, cannabis oil and herbal tea.