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# Contemporary Management of the Painful Bladder: A Systematic Review

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**Abstract**

***Context:*** Different types of behavioural, dietary, interventional, pharmacologic, and surgical therapies have been used to treat painful bladder syndrome/interstitial cystitis (PBS/IC). Because of the paucity of randomised placebo-controlled studies on different treatments, an evidence-based management approach has not yet been developed.
***Objective:*** To critically review and synthesize data from a wide range of current therapeutic approaches to PBS/IC, to quantify the effect size from randomised controlled trials (RCTs), and to reach clinical agreement on the efficacy of treatments for PBS/IC.
***Evidence acquisition:*** We performed a systematic review of the literature to identify articles published between 1990 and September 2010 on the management of PBS/IC. We included articles restricted to the English language published since 1990 to date that reported on oral and intravesical treatment, multimodal or combined treatment, and surgical treatment. For all RCTs, standardised mean differences (SMDs) were extracted and combined in a meta-analysis applying a random-effect model that incorporated the heterogeneity of effects. The four outcomes assessed in all studies were a change in the Interstitial Cystitis Symptom Index (ICSI), pain, urgency, and frequency. Non-RCTs (nRCTs) were analysed with a narrative synthesis of the evidence from all research designs.
***Evidence synthesis:*** We included 7709 adult patients from 29 RCTs and 57 nRCTs. Meta-analysis of RCTs showed that only cyclosporine A provided a simultaneous great effect size of SMD on ICSI, pain, and frequency. Amitriptyline at different dosages showed a great effect size of SMD on pain and urgency or on ICSI and frequency. The remaining RCTs showed sporadic significant changes in only one of the four considered parameters. The attributed levels of evidence for treatments reported in RCTs were 1b; grades of recommendations ranged from A to C. According to the Jadad score, 11 RCTs were high-quality studies. Meta-analysis of RCTs showed a great heterogeneity in the applied methodologies, clinical outcomes assessed, and the obtained results in different studies. The results from the nRCTs showed that the most frequently adopted treatment is oral pentosan polysulfate and that the use of botulinum A toxin intradetrusorial injections in PBS/IC is increasing. A high heterogeneity in drugs and treatment modalities, clinical outcomes, and obtained results was also found for nRCTs.
***Conclusions:*** Limited evidence exists for the few treatments for PBS/IC. The lack of definitive conclusions is due to the great heterogeneity in methodology, symptoms assessment, duration of treatment, and follow-up in both RCTs and nRCTs.


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## 1. Introduction

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a poorly defined clinical condition characterised by pelvic pain and urinary storage symptoms (eg, urinary urgency and frequency). The European Society for the Study of Interstitial Cystitis (ESSIC) [1] suggested the term *PBS/IC,* which is strictly consistent with the taxonomy guidelines of the European Association of Urology (EAU) [2]. In the ESSIC proposal, PBS/IC is defined as "chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder, with at least one other urinary symptom such as persistent urge to void or urinary frequency." The phrase "persistent urge to void" should replace the term *urgency* because it better describes urinary urgency experienced by patients with PBS/IC. In addition, confusable diseases as the cause of the symptoms have to be excluded [1]. The American Urological Association (AUA) guidelines recently provided a modified definition for the diagnosis and treatment of PBS/IC: "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes" [3].

There is no general agreement about the physiopathology of the disease, which has prevented identification of an objective marker and development of a clinical diagnostic protocol. Thus how patients are identified for epidemiologic studies differs greatly [4,5]. The close diagnostic criteria proposed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) can miss about 60% of patients and thus are only recommended for research purposes [6]. The EAU guidelines on chronic pelvic pain recently proposed an algorithm for diagnosing and treating PBS/IC that should help properly identify and treat patients with the disease [2].

The O'Leary-Sant Symptom and Problem score (Interstitial Cystitis Symptom Index [ICSI] and Problem Index [ICPI]) has been recognized as one of the most reliable and valid instruments to identify the most prominent voiding and painful symptoms in patients with PBS/IC and the extent of the perceived problem [7].

Treatment and management approaches vary widely, and different types of behavioural, dietary, interventional, pharmacologic, and surgical therapies have been used. This diversity reflects both the complexity of the condition in terms of aetiology and pathogenesis and the lack of clear diagnostic criteria for the disease. The Interstitial Cystitis Data Base study reported on >180 treatment modalities, with unsatisfactory results in most cases [8]. In addition, the lack of high-quality randomised placebo-controlled studies on different treatments has not permitted the development of an evidence-based management approach. To date, there is general agreement on the use of some agents, orally or intravesically administered, as indicated by the EAU guidelines on chronic pelvic pain and the AUA Guidelines for the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome [2,3], particularly for amitriptyline, hydroxyzine, and pentosan polysulfate sodium (PPS) [2,3].

Our aim was to critically review and synthesise data from a wide range of current therapeutic approaches to PBS/IC, to quantify the effect size from randomised controlled trials (RCTs), and to reach clinical agreement on treatment efficacy for PBS/IC.

## 2. Evidence acquisition

### 2.1. Literature search

We performed a systematic review of the literature to identify articles published between 1990 and September 2010 on the management of PBS/IC. We conducted a Medline search using the search terms *painful bladder syndrome, interstitial cystitis, hypersensitive bladder, oral treatment, intravesical treatment, multimodal or combined treatment,* and *surgical treatment.* We also surveyed the references of review articles to identify any missed articles.

### 2.2. Inclusion and exclusion criteria

We included only articles in the English language published from 1990 to date. Then we included all original research and excluded review articles, abstracts, case reports, and nonhuman studies. Antonella Giannantoni and Silvia Proietti reviewed each title and, if unclear, the full article applying the inclusion and exclusion criteria. We excluded studies and articles with <10 patients.

### 2.3. Assessment of results

We previously analysed outcomes assessed in each individual study. Because the outcomes assessed in all studies were change in the ICSI index, pain, urgency, and frequency, each of the mentioned outcomes was assessed in all studies.

We decided to include urgency in the evaluation of the outcomes for PBS/IC despite recent observations that suggested leaving it out of the description of patients with PBS and considering "persistent urge to void," which better describes urinary urgency in patients with PBS/IC [3]. Even if urgency is the key symptom of overactive bladder syndrome, which is considered a major confusable disease for PBS/IC, it still remains in its original meaning one of the most frequently assessed outcomes to evaluate therapies.

For all RCTs, we attempted to abstract the data as a standardized mean difference (SMD). This produces measures of effect for each treatment trial on a similar metric.

The SMD is obtained by dividing the difference in mean outcome between two groups with the pooled standard deviation of the measurement. These effect sizes indicate the mean difference between two variables expressed in standard deviation units. A score of 0 represents no change, and effect size scores can be negative or positive. The result of this calculation is that the outcome is measured in standard deviation units. This can be difficult to interpret, and the following rule of thumb has been suggested: A SMD of 0.2 standard deviation units is considered a small difference between the intervention groups; a SMD of