



## Platinum Priority – Editorial and Reply from Authors

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# The Future of Pharmacologic Treatment for Bladder Pain Syndrome/Interstitial Cystitis: Lessons From a Meta-Analysis

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The paper by Giannantoni et al in this issue of *European Urology* [1] is certainly an important scientific document, but it also provides overwhelming evidence for urgent profound reflection on the direction of study of bladder pain syndrome/interstitial cystitis (BPS/IC) treatment. It is timely because, fortunately, there is increasing interest in uncovering the pathophysiology of and an effective treatment for this mysterious disease. It gives readers comprehensive information about the literature on BPS/IC. For investigators new to this area, easy access to a complete review on the topic may help identify new paths to explore and new research priorities. In addition, this manuscript shows that a consensus about the definitions to be used in the next round of BPS/IC randomized controlled trials (RCTs) must be urgently established.

A fundamental step in the understanding of BPS/IC is agreement on a single, clear definition. This has not been possible in the past as different definitions were advanced by the International Continence Society Terminology Committee [2], by the European Society for the Study of Interstitial Cystitis (ESSIC) [3], and, more recently, by the American Urological Association [4]. The possible inclusion of urgency in the BPS/IC symptom complex is major issue around which a consensus should be built, particularly if, in the minimal work-up required for diagnosis, cystoscopy with hydrodistention is to be omitted. A significant overlap between BPS/IC and overactive bladder (OAB) might occur, bringing unnecessary noise to the trials' patient cohorts. In this respect I believe that a plea for a consensus around the classification forwarded by ESSIC [3], based on cystoscopic findings after bladder hydrodistention and on the biopsy report given by a trained pathologist, could be a fundamental step for

categorizing BPS/IC patients. A similar approach to define stepwise approaches to malignancies proved highly successful in oncology.

Though I found that the comprehensive literature review is the strength of this manuscript [1], I have some reserves about the utility of the meta-analysis performed. A meta-analysis based upon studies of limited quality will not elevate the level of the evidence for the variables at stake. Assessing primary and secondary outcomes in a meta-analysis is disputable: The studies are usually powered for the former, and not the latter. By analyzing each symptom individually, the meta-analysis concluded that bacillus Calmette-Guérin (BCG), resiniferatoxin, hydroxyzine, or amitriptyline can be effective for some BPS/IC symptoms despite the fact that the few high-quality RCTs available for each of those compounds were consistently negative. Moreover, I believe that symptoms like frequency and nocturia should not be analyzed separately from pain. Also difficult to understand is the fact that urgency was analyzed individually, since, as already stressed, it causes an immediate undesirable confusion with OAB.

The authors correct possible misinterpretations of the meta-analysis with a well balanced discussion that dissects in depth the most important and well designed RCTs involving patients with BPS/IC. And the discussion clearly highlights to me the current disappointing situation of pharmacologic treatment of BPS/IC.

Based on unambiguous studies that followed good scientific methods, pentosan polysulfate sodium (PPS) is the only effective and safe treatment we can offer to our patients so far. BCG [5], resiniferatoxin [6], and hydroxyzine [7] did not survive the test of well controlled trials. Post hoc subanalysis suggests that amitriptyline may be effective in a small group of patients, but high doses must be used, with

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obvious inconvenience [8]. Cyclosporine was compared to PPS in an well designed pilot study [9]. Cyclosporine was significantly superior to PPS in reducing frequency, nocturia, pain intensity, and in increasing voided volume per micturition. Unfortunately, adverse events were severe and the high withdrawal rates (close to 25%), combined with the excessive costs of the treatment, prevent the use of cyclosporine as a first option [9]. Tanezumab, a nerve growth factor-sequestering molecule, was assayed in a pilot placebo-controlled study, but pain reduction was modest and adverse events potentially very severe [10].

Such a negative scenario can also be seen from a positive side, however, as it suggests great opportunities for research and drug development. Many investigators have been repeatedly studying old drugs over the years, with new trials frequently supported by inconclusive data provided by previous low-quality studies. It is time to wipe out all those old options from the research field and initiate a new period of investigation looking for another set of compounds.

Pain and bladder inflammation will be the most important targets for new drugs. Pain is most probably the driving symptom for a patient to void at progressively low volumes of bladder filling, leading to frequency and nocturia. Therefore, pain will be the primary outcome of several studies in the near future. Interesting drugs that are potentially useful in controlling bladder pain include cannabinoid receptor (CB1) agonists, TRPV1 antagonists, and purinergic receptor antagonist compounds. Botulinum toxin type A has well known analgesic properties and proved effective in small case series [11,12]. It is probable that after the approval of onabotulinum toxin type A for the treatment of incontinence in patients with neurogenic bladder dysfunction, a RCT will study the toxin in BPS/IC patients. It would be interesting if such a trial included the evaluation of trigonal versus whole-bladder technique of injection, as trigonal injections carry with them a lower risk of urinary retention. Eventually new types of botulinum toxins specific for nociceptive fibers will come into clinical use, offering additional opportunities to combat bladder pain.

Gene therapy using virus vectors to transport genes that synthesize opioids or other analgesic proteins may also be an interesting concept when considering the role of bladder injections to treat pain. More effective anti-inflammatory compounds with fewer adverse events will certainly be an object of clinical trials now that cyclosporine [9] and tanezumab [12] have paved the way in the field of anti-inflammatory therapy. Last, but not least, the antiproliferative factor protein [13] may prove to be an important therapeutic target, in addition to its possible role as a urine biomarker for disease diagnosis and monitoring.

**Conflicts of interest:** Francisco Cruz is a consultant for Allergan, Astellas, and Recordati and has received honoraria for speaking for Allergan, Astellas, Recordati, and AMS.

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