# Current Status of Intravesical Therapies for Bladder Pain Syndrome (BPS): A Narrative Review of Emerging Evidence

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Bladder pain syndrome (BPS) is a complex condition, which can have debilitating sequelae for patients. Many elements of BPS remain poorly understood including pathophysiology, diagnosis and treatment. Navigating patient care can therefore be challenging for the clinician. Management mandates a multidisciplinary and symptom-based approach. Intravesical treatments such as instillation therapies remain a cornerstone of most treatment algorithms and there are a range of agents that can be selected. This review offers an up-to-date evaluation of the evidence for these intravesical treatments. UROLOGY 156: e48–e57, 2021. © 2021 Elsevier Inc.

Bladder pain syndrome (BPS) is a disease of prevalence and chronicity. Population based studies estimate it affects 6-11% and 2-5% of adult women and men in the United States (US) respectively.[1] It is defined by the International Continence Society (ICS) as 'persistent or recurrent chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as an urgent need to void or urinary frequency'.[2] Standardisation of terminology has led to the recommendation to adopt the term BPS, which reflects a symptom-based diagnosis, rather than previous nomenclature such as interstitial cystitis (IC).[3] BPS is now classified as a subdivision of chronic pelvic pain according to European Association of Urology (EAU) guidelines.[4] Uncertainty persists, regarding the underlying pathophysiology and multiple theories exist related to urothelial dysfunction, neural 'cross-talk' and hypersensitivity among others [5] A difficult condition to conceptualise, the natural history of BPS is widely accepted to be progressive and multifactorial in aetiology. The sequelae are far reaching and can impact all domains of daily life. Lack of pathognomonic investigations renders the diagnosis to be largely one of exclusion. The multifaceted effects of this disease demand a holistic treatment approach, based on a biopsychosocial model, which reflects the non-specific phenotypes. A plethora of therapies exist in current clinical practice and these range from conservative approaches to reconstructive surgery.[6,7] Among this treatment catalogue, exists intravesical therapies, which typically represent the next step in the treatment algorithm when conservative measures and pharmacotherapy have failed. While a large body of research now exists for this treatment strategy, critical appraisal remains under reported. Furthermore, such is the complexity of this disease process as well as the heterogenous patient profile, it can be difficult for the healthcare professional to navigate the treatment pathway [8] This review aims to evaluate the evidence basis for these intravesical therapies.

## MATERIALS AND METHODS

A comprehensive search of world literature was performed in order to identify studies investigating intravesical therapies for BPS. Given the large body of evidence on the wide topic, our review only evaluated findings from randomised trials, the highest level of evidence for an original study according to the Oxford Centre for Evidence Based Medicine (OCEBM).[9] All randomised trials assessing an intravesical therapy were considered. These could either use an alternative agent as the comparator or a placebo control. The studies did not have to include any specific outcome measure(s). Studies investigating the following therapies were eligible for inclusion: lidocaine, dimethyl sulfoxide (DMSO), chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate sodium (PPS) and Botulinum Toxin type-A (BoNT-A). Bibliographic databases searched included Medline, Google Scholar, CINAHL, Cochrane Library and clinicaltrials.gov. Search terms included 'bladder pain syndrome' 'painful bladder syndrome', 'interstitial cystitis', 'intravesical', 'instillation', 'randomised' and 'trial' (see Supplementary Appendix for full list of Medical Subject Headings (MeSH)). Boolean operators (AND, OR) were incorporated to augment the search. In order to identify recent evidence, a time restriction since 2000 was set. Presentation of the findings is in a narrative format was determined most suitable due to their heterogeneity.

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## RESULTS

Overall, 15 studies satisfied the inclusion criteria. Breakdown of number of studies for each intervention was as follows: lidocaine ($n$ = 2), heparin ($n$ = 0), lidocaine/heparin combination ($n$ = 2) HA ($n$ = 1), CS ($n$ = 2), HA/CS combination (n = 2), PPS ($n$ = 1), DMSO ($n$ = 1) and BoNT-A ($n$ = 4).

## INSTILLATION THERAPIES

### Lidocaine

Lidocaine, a non-selective sodium channel blocker, is a well-known and powerful local anaesthetic agent owing to its ability to block pain but allow the patient to remain conscious (Table 1).[10] It has been used as a treatment strategy for BPS since the first description in 1989.[11] When alkalinisation of Lidocaine is performed, a greater proportion of the drug is stabilised into its non-ionised form and the resulting pharmacokinetic profile provides improved bladder permeability, thus allowing the drug to reach the submucosal plexus of the bladder.[10] Consequently, peak concentrations of lidocaine are achieved much faster.[12] In 2001, Henry et al first demonstrated this in a non-randomised comparative study ($n$ = 24) and since this time studies investigating lidocaine for BPS have exclusively used alkalinised preparations (Table 2).[13] Of note alkalinisation of lidocaine also prevents drug precipitation if it is combined with heparin. In 2009, Nickel reported findings from a multi-centre randomised trial.[14] 102 patients received daily instillation of either alkalinised lidocaine or placebo and were followed up one month later. Peak concentrations of <2 micrograms/ml were reported (toxicity occurs >5 micrograms/ml) and subjects receiving lidocaine reported significantly greater symptom improvement (30% and 9.6%, $P$ = 0.012). The latter was measured using a 7-point Likert scale from 'markedly worse' to 'markedly improved'. In 2019, Offiah et al reported findings from the only other randomised study reported since 2000.[10] 24 participants were assigned to receive either 20ml of 2% alkalinised lidocaine ($n$ = 16) or 20ml of normal saline ($n$ = 8) for 20 minutes. In the former group, more than half (11/16) responded well to lidocaine as determined by a significant increase in maximum bladder capacity (192ml vs 262ml, $P$ = 0.005). This was measured using urodynamics. Pain scores, measured using the Central Sensitisation Inventory (CSI) before and after the procedure, revealed significant reduction in pain for the lidocaine group but no difference for the saline group. No changes in maximum bladder capacity were recorded after saline instillation. However, 5/16 participants in the lidocaine group did not respond to this treatment as determined by the lack of improvement in maximum bladder capacity and furthermore, pain scores were significantly worse. Lidocaine instillation has been reported for use as a diagnostic test for BPS to promote exploration of alternative causes for symptoms in non-responders. However, another theory is that BPS can be due to both peripheral and central pain signaling.[10] In a proportion of patients with BPS, it is believed that central sensitivity syndromes (CSS) dominate and non-response to lidocaine instillation may be explained by this theory.

### Dimethyl Sulfoxide (DMSO)

First discovered as a byproduct during wood pulp production, DMSO is an organic solvent, which holds analgesic properties and displays high membrane penetration.[15] Yoshimura reported the largest randomised study investigating effects of DMSO and the only one to satisfy our inclusion criteria.[16] Across 24 centres, 96 patients were enrolled in a 12-week treatment course. Of note, all patients received lidocaine instillation for 15 minutes before this was drained and either DMSO or placebo (normal saline) was administered. The DMSO group were found to have significantly greater improvement in O'Leary Symptom Index (OSI) score (-5.2 vs -3.4, $P$ = 0.00188), a validated patient reported outcome measure (PROM) with items on bothersome urinary symptoms and pain.[17] However, DMSO did not demonstrate superiority over placebo at the end of the treatment course. 69.4% ($n$ = 34) of the treatment arm experienced an adverse event (AE), however the majority (67.3%) of these were mild in nature. A characteristic associated with DMSO is garlic odour (metabolic by-product), which 4% ($n$ = 2) of the group reported. Additional disadvantages of DMSO include the possible temporary symptom flare and the requirement for ophthalmologic surveillance due to risk of lens opacification (Table 1). However, this has only been recorded in animal studies.[18]

### Glycosaminoglycan (GAG) Layer Treatments

In 1975, Parsons et al identified the GAG layer, a mucous barrier, which covers the bladder urothelium.[19] The importance of this "barrier effect" is considered paramount in engineering therapeutic solutions.[20] Natural constituents of this layer include heparin, CS and HA. "Replenishment" strategies aim to restore these architectural components.

### Heparin

Heparin is administered with the aim of enhancing the native urothelial environment .[21] In clinical practice, it is commonly combined with lidocaine. Best known for its application in medicine as an anticoagulant, intravesical heparin does not reach the systemic circulation and no effect on coagulation is incurred. While there have been no recent randomised trials investigating the role of heparin as a monotherapy, there have been randomised studies comparing combined effect of lidocaine and heparin. In 2012, Parsons et al used placebo (sodium carbonate) as a comparator.[22] 36 patients were recruited and post treatment evaluation using Global Assessment Response (GAR) revealed improvement in symptoms compared to placebo (50 vs 30%, $P$ = 0.013). 36% recorded minor AEs such as pain and dizziness. In a subsequent study, the same intravesical combination was compared against lidocaine monotherapy.[23] The former significantly reduced bladder pain (38% versus 13%, $P$ = 0.029) and urgency (42% versus 8% $P$ = 0.003).

**Table 1.** Overview of available intravesical therapies

| *Therapy* | *Lidocaine* | *Heparin* | *HA* | *CS* | *PPS* | *DMSO* | *BoNT-A* |
|---|---|---|---|---|---|---|---|
| *Mechanism of action* | Anaesthetic | Replenish GAG layer | Replenish GAG layer | Replenish GAG layer | Replenish GAG layer | Anti-inflammory<br>Muscle relaxant | Reduction of dysfunctional muscle hyperactivity |
| *Dosage* | 10-20ml of 2% (2-400mg) + alkalinization (Urolieve®/ PSD597/ USP®) | 10-50 000 units | 40mg/50ml (Cystistat ®) | 20ml of 2% (Uracyst ®) | 200mg in 30ml saline (Elmiron ®) | 50 mL of 50% solution (Rimso-50 ®) | 50-200 units (Dysport®/ BOTOX®) |
| *Instillation time (mins)* | 30-45 | 30-60 | 30 | 30 | 20 | 10-20 | n/a |
| *Common regimes* | Once weekly for 6 weeks + Monthly maintenance as required | Up to 3 times a week for 2-12 weeks Monthly maintenance as required | Once weekly for 4-6 weeks + Monthly maintenance as required | Once weekly for 4- 6 weeks + Monthly maintenance as required | Once weekly for 4- 6 weeks + Monthly maintenance as required | Once weekly for 6-8 weeks Monthly maintenance as required | 10-40 injections per procedure. No consensus on frequency thereafter. |
| *Common Combinations* | Lidocaine + heparin (Urigen®) | | HA +CS (iAluril ®) | | + lidocaine (no pre-formulated version available) | + heparin (no pre-formulated version available) | Nil |
| *Possible side effects* | Pain,<br>Irritation<br>UTI | Pain,<br>Irritation<br>UTI | Pain,<br>Irritation<br>UTI | Pain,<br>Irritation<br>UTI | Pain,<br>Irritation<br>UTI<br>Headache<br>Hair loss | Pain<br>Irritation<br>UTI<br>Dizziness<br>Flare ups<br>Transient chemical cystitis | Pain<br>Irritation<br>UTI<br>Haematuria<br>Urinary retention<br>Sepsis<br>Bladder ulceration<br>Reactive arthritis |
| *Advantages* | Rapid onset | Minor side effects | More favourable side effect profile<br>No additional checks needed<br>Self-administration possible | | Self-administration possible | Self-administration possible<br>Only agent with FDA approval | Offers another line of treatment to patients beyond instillation and less invasive than reconstructive surgery |
| *Disadvantages* | Short half life<br>Short duration of effect | Optimal dosing not known | >70% patients experienced minor adverse events in trials<br>Not approved in USA | | Headache<br>Ophthalmology checks required<br>No RCT | Pain if instillation time >20 mins<br>Garlic odour (urine, skin, breath) | Patient needs to learn self catheterisation<br>More invasive - Injection required |

*Continued*

**Table 1.** Continued

| *Therapy* | *Lidocaine* | *Heparin* | *HA* | *CS* | *PPS* | *DMSO* | *BoNT-A* |
|---|---|---|---|---|---|---|---|
| | | | | | investigating monotherapy use | Hypersensitivity reaction reported<br>Need for 6 monthly blood checks including liver and renal function tests and ophthalmology exam<br>Rapid instillation induces spasm<br>Not suitable in patient with known urothelial malignancy as it can cause vasodilation | to breach bladder urothelium<br>Drug leakage outside bladder<br>May require general anaesthetic<br>Serious adverse events reported e.g., sepsis/reactive arthritis |
| *Shared disadvantages* | Allergy to drug or catheter<br>Catheter irritation<br>Very limited cost data<br>Frequent hospital visits for treatment<br>May not improvement of symptoms | | | | | | |
| *Safe in pregnancy?* | Likely the safest and not excreted in breast milk | Likely safe but not truly known known but does not cross placenta. | Not known | Not known | Not known but very similar structure to heparin | No. Teratogenic in animal studies | Not known |
| *EAU recommendation* | Yes | Yes | Yes | Yes | Yes | NR | Yes |
| *AUA recommendation* | Yes | Yes | NR | NR | Yes | Yes | Yes |

UTI = urinary tract infection.
HA = Hyaluronic Acid
CS = Chondroitin Sulfate
PPS = Pentosan polysulfate sodium
DMSO = Dimethyl sulfoxide
BoNT-A = Botulinum Toxin type-A
USA = United States of America
RCT = Randomised controlled trial
FDA = Food and Drug Agency

**Table 2.** Overview of randomised trials published since 2000.

| Author/Country | Year | Comparator | Sample size | Formulation | Outcome assessed | Result | Adverse events | Follow up (months) |
|---|---|---|---|---|---|---|---|---|
| | | | | *Lidocaine (alkalinised)* | | | | |
| Nickel/ Canada[14] | 2009 | Placebo* | 102 | 50 mL of 50% | GRA<br>Pain<br>Urgency<br>Frequency | Significant improvement**in overall symptoms | Fatigue ($n$ = 4)<br>UTI ($n$ = 1) MSK pain ($n$ = 2), Dizziness ($n$ = 4), Headache ($n$ = 2), Pain ($n$ = 10) | 1 |
| Offiah/ Republic of Ireland[10] | 2019 | Placebo* | 24 | 20ml of 2% | Pain<br>Bladder capacity | 11/16 receiving lidocaine had improvement in both pain **and capacity**<br>5/11 receiving lidocaine had worse pain** and no change in capacity | NR | NR |
| | | | | *Heparin* | | | | |
| | | | | None reported | | | | |
| | | | | *HA* | | | | |
| Gülpınar/ Turkey[25] | 2018 | CS | 42 | 50 mL/120 mg | Pain<br>Frequency<br>Nocturia<br>ICSI | CS yielded greater improvement in 24h frequency and nocturia**<br>Both improved pain** | Nil | 6 |
| | | | | *CS* | | | | |
| Nickel/ Canada[26] | 2010 | Placebo* | 65 | 20ml of 2% | Pain<br>Urgency<br>Voiding frequency<br>OSI | No significant** improvement compared to control group | 70.4% experienced atleast one adverse event. No further details given | 3 |
| Nickel/ Canada[27] | 2012 | Placebo* | 98 | 20ml of 2% | Pain<br>Urgency<br>Voiding frequency<br>OSI | No significant** improvement compared to control group | 76.9% experienced atleast one adverse event. No further details given | 2.75 |
| | | | | *PPS* | | | | |
| Davis/ USA[31] | 2008 | Placebo* | 41 | 400mg mixed with 30ml saline | OSI<br>Pelvic pain<br>Urgency<br>Quality of life | Significant improvement** in quality of life score in treatment group<br>No differences (**) in adverse events between groups | Headache ($n$ = 14)<br>Hair loss ($n$ = 3) | 4.5 |
| | | | | *DMSO* | | | | |
| Yoshimura/ Japan[16] | 2021 | Placebo* | 96 | 50 ml 50% DMSO | OSI<br>Voids/24hrs<br>Pain | Significant improvement in OPSI<br>No different in pain between DMSO and placebo | Chest infection ($n$ = 6)<br>Contusion ($n$ = 3)<br>Pain ($n$ = 4)<br>Bladder irritation ($n$ = 4)<br>Urethral irritation (7)<br>Femur fracture ($n$ = 1)<br>Vertigo ($n$ = 1) | 3 |

*Continued*

**Table 2.** Continued

| Author/Country | Year | Comparator | Sample size | Formulation | Outcome assessed | Result | Adverse events | Follow up (months) |
|---|---|---|---|---|---|---|---|---|
| | | | | *BoNT-A* | | | | |
| Kuo/ Taiwan[34] | 2009 | Placebo* | 67 | 100-200 units | OSI<br>Voids/24hrs<br>Pain<br>Bladder capacity | Only BoNT-A produced significant improvement in pain and bladder capacity** | Haematuria ($n$ = 3), UTI ($n$ = 3), dysuria (n = 10), large PVR ($n$ = 7), AUR ($n$ = 3), CUR ($n$ = 2) | 3 |
| Gottsch/ USA[37] | 2011 | Placebo* | 20 | 50 units | Pain<br>Stress<br>AUA-SI | No improvements in any parameters | Nil | 3 |
| Kuo/ Taiwan[35] | 2016 | Placebo* | 60 | 100 units | Pain<br>Voiding frequency<br>Bladder capacity | Improvement in pain and bladder capacity** | Dysuria ($n$ = 16)<br>UTI ($n$ = 2)<br>AUR($n$ = 1)<br>Haematuria ($n$ = 1) | 2 |
| Manning/ Australia[36] | 2014 | Placebo | *50* | 100 Units | OSI<br>Bladder capacity | Significant improvement** in OLS | UTI ($n$ = 7) | 3 |
| | | | | *Combination* | | | | |
| Parsons/ USA[22] | 2012 | Lidocaine + Heparin vs Sodium bicarbonate | 36 | 50000 units + 200mg in 15ml | Pain<br>Urgency<br>GRA | Pain reduction over 12 hours (42%, $P$ = 0.036).<br>Reduction in urgency | 30% experienced adverse event.<br>Breakdown not provided | NR |
| Parsons/ USA[23] | 2015 | Lidocaine + Heparin vs lidocaine | 14 | 50000 units + 200mg in 15ml | Pain<br>Urgency | Combination significantly reduces** pain and urgency and GRA outcome | Nil | NR |
| Cervigni/ Italy[28] | 2016 | HA/CS vs DMSO | 88 (2:1) | 1.6%/2% vs 50% | Pain<br>Voiding<br>OSI<br>Bladder capacity | HS/CS ad DMSO both gave improvement** in all outcome measures but no superiority between them | HA/CS: $n$ = 52<br>DMSO: $n$ = 39 | 6 |
| Özkıdık/ Turkey[29] | 2019 | HA vs CS vs HA/CS | 72 | NR | Pain<br>Voiding<br>OSI | Significant improvement** in quality of life assessment when combination therapy used | UTI ($n$ = 5)<br>Haematuria ($n$ = 3) | 24 |

* =normal saline
** =statistically significant ($P$ <0.05)OSI = O'Leary Symptom IndexGRA = Global Assessment ResponseMSK = MuskuloskeletalAUA-SI = American Urological Association- Symptom IndexBCG = Bacillus Calmette GuerinHA = Hyaluronic AcidCS = Chondroitin SulfatePPS = Pentosan polysulfate sodiumDMSO = Dimethyl sulfoxideBoNT-A = Botulinum Toxin type-AUSA = United States of America

### Hyaluronic acid (HA) and chondroitin sulfate (CS)

These agents act to proliferate the GAG layer and restore this protective coating. While both receive a status of recommendation among EAU guidelines, they do not hold approval by the US Food and Drug Agency (FDA) and they are not recommended by the AUA guidelines.[4,24] There exist limited studies investigating their use. Gülpinar et al randomised 42 patients to receive either one of these agents.[25] At 6 months follow up, both agents were shown to significantly reduce pain ($P$ <0.001), however CS was superior in regard to reducing 24-hour frequency ($P$ <0.001) and was the only agent to significantly improve nocturia ($P$ <0.001). No AEs were recorded in either treatment arm. Overall, the authors concluded that CS yielded greater clinical improvement for patients. One theory for this may be that CS constitutes a higher proportion (26%) of the integral proteins, which make up 80-90% of the natural GAG layer. Nickel et al reported findings from two consecutive multi-centre studies investigating CS as a monotherapy.[26,27] However, in both studies, none of the improvements observed for outcomes related to pain, frequency and urgency were statistically significant. 70.4% of the treatment group experienced at least one AE and 16.3% discontinued the treatment during the study. The authors determined that if patients are counseled, they will have a 38% chance of clinical response to CS. As these studies were carried out across more than 10 centres, they may be interpreted to reflect a more 'real life' clinical experience with CS. There have been two subsequent studies, which have investigated the outcomes associated with a combined HS/CS instillation.[28,29] Cervigni et al randomised 88 women to either receive HA/CS or DMSO.[28] Significant improvements were yielded for both treatment arms for voiding frequency, pain and bladder capacity; however, no superiority was found to favour either one of these treatments. Özkıdık et al randomised 72 patients to receive either HA, CS or combined HA/CS and they were followed up over the 24-month treatment course.[29] The greatest improvement in pain was recorded in the HA/CS group although it was not significantly better than either of the other treatment arms ($P$ = 0.15). However, improvement in both urgency and Health Related Quality of Life (HRQoL) score were significantly better in the former treatment group ($P$ = 0.04 and $P$ = 0.02 respectively).

### Pentosan Polysulfate Sodium (PPS)

PPS is a semi-synthetic agent, which also serves to repair the damaged GAG layer. Most studies on PPS investigate the oral form. However, a limitation of this administration method is that only 1-3% reaches the bladder and a six-month course is required.[30] Application was therefore trialed intravesically in order to increase the potential therapeutic efficacy. By directly targeting the "diseased organ", higher drug concentrations can be administered while minimising the risk of systemic toxicity. However, there has only been one randomised trial on intravesical PPS in the past twenty years and this was in a small sample ($n$ = 41).[31] Oral and intravesical PPS were compared against oral PPS and intravesical placebo. At week 12, there was significantly greater improvement in median OSI score compared to placebo group (-46% vs -24%, $P$ = 0.04). Of note, a significant reduction in voiding frequency was only recorded among placebo group. Also, all subjects experienced AEs during the trial (range 2-15 per person) and the commonest was headache ($n$ = 14, 66.7%). PPS associated maculopathy has been reported elsewhere and therefore ophthalmological checks are mandated according to use also.[24]

## INJECTION THERAPIES

### Intra-detrusor injection of Botulinum Toxin type-A (BoNT-A)

The first urological application of BoNT-A was described in 1988 for use in spinal cord injury patents with detrusor −sphincter dyssynergia.[32] As well as manipulate detrusor contractility, it has been found in rat models to affect sensory transmission and display anti-inflammatory effects[33] The high molecular mass of this neurotoxin (150 kDA) means that it cannot penetrate the bladder urothelium.[33] Cystoscopy and injection are therefore required to deliver it to the submucosal nerve plexus.

In 2009, Kuo et al randomised 67 patients who had previously failed conventional treatments, to receive either hydrodistension and BoNT-A (100-200 units(U)) or hydrodistension alone.[34] Only treatment in the BoNT-A arm rendered significant improvement in bladder capacity and reduction in pain scores. Dosage increase from 100U to 200U did not yield any additional benefit. 3/44 patients experienced acute urinary retention (AUR). The need for patients to potentially self-catheterise is a recognised disadvantage. Later, the same author group repeated the study (fixed dose of 100U), but the placebo group received sub-urothelial injections of normal saline.[35] Improvements in pain (VAS) and bladder capacity (ml) were significantly greater in the treatment arm compared to placebo (-2.6 vs 0.9, $P$ = 0.021 and +67.8 vs -45.4, $P$ = 0.020). Manning et al recruited patients with chronic BPS to a similar study and while there was a significant improvement in a small number of patients, there was no overall improvement in outcome measures associated with BoNT-A.[36] Gottsch et al randomised patients to BoNT-A or injection with a placebo (normal saline).[37] Injections in this study were placed peri-urethrally, in order to block urethral sensory (afferent) fibres, which mediate sensory signals and add to the detrusor reflex. However, no improvements were reported across any of the outcome measures. Great variation in success achieved with BoNT-A has therefore been reported. Evans et al demonstrated no difference in efficacy when trigone placement of BoNT-A injections was compared to a standard, trigone sparing template.[38]

## NON RECOMMENDED THERAPIES

Several intravesical therapies are not recommended. While BCG has been investigated, its superiority for

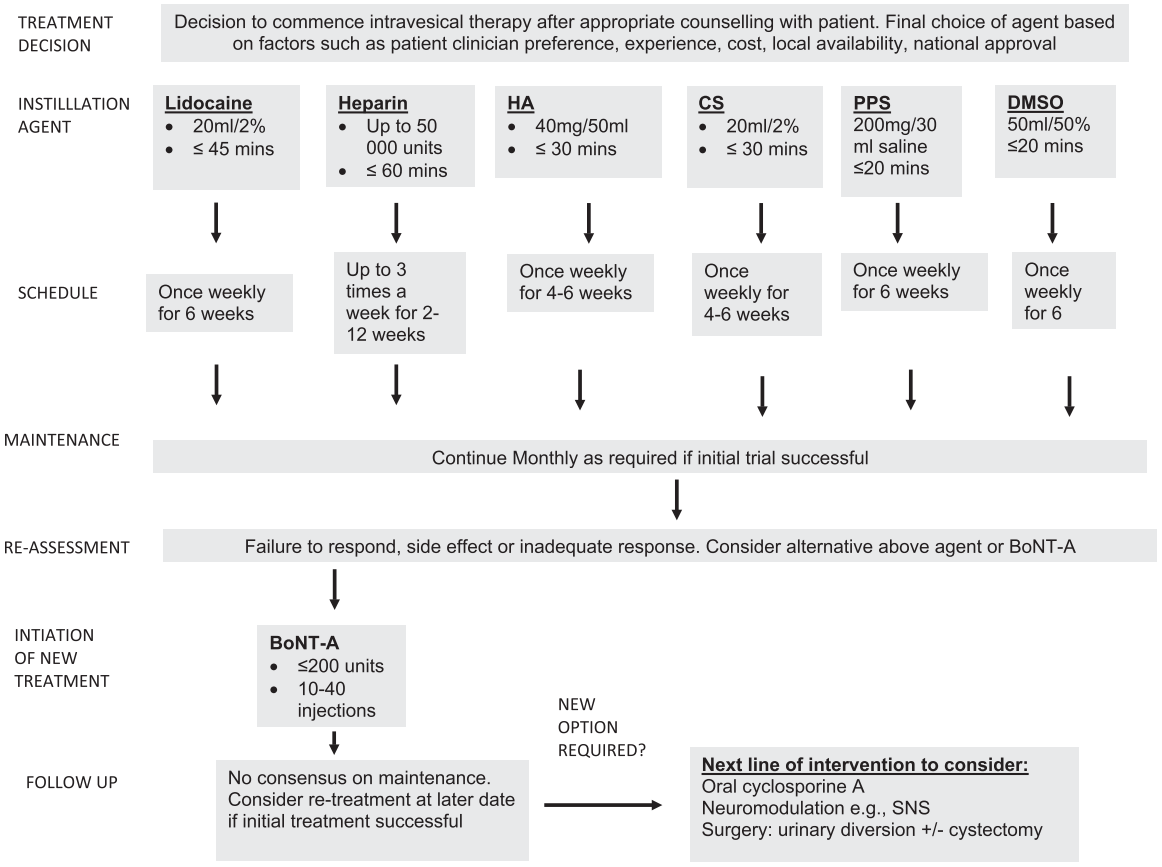


**Figure 1.** Suggested BPS treatment algorithm

improving BPS symptoms has not been demonstrated.[39] Moreover, any benefits of its use do not outweigh the potentially serious adverse events. Resiniferatoxin (RTX) is a vanilloid receptor and ultrapotent capsaicin analogue, which desensitize C fibres transmitting pain.[40] Despite promising results in animal studies, this has not been reproduced in humans. High pressure (>80 to 100 cm $H_20$), long duration (>10 minutes) hydrodistension is also recommended against given both the limited evidence demonstrating clinical benefit but also because of serious adverse events reported in observation studies performing it e.g., bladder rupture [24] However, low pressure (< 80 cm $H_20$) and short duration (<5 minutes) hydrodistension does remain a safe option in current clinical practice. An example of possible treatment pathway for intravesical therapies is given in Figure 1.

## FUTURE THERAPIES

As the quest for more efficacious treatments for BPS continues, new agents and delivery methods are the subject of continued research. Characteristics of an optimal intravesical therapy would be high penetration of the urothelium, long duration of effect and a strong morbidity profile. Ease of administration and cost efficiency are also important considerations. However, it is a challenge because the urothelium is naturally highly impermeable and urine creates a hostile environment, which destabilises many agents.[31]

A major limitation of most instillations is the short duration of benefit. A pivotal approach to overcome this has been the development of a novel drug delivery systems (DDS), which is implanted into the bladder and obviates the need for repeat catheterisation and provides longer drug exposure. One example is a continuous lidocaine releasing intravesical system (LiRIS) to deliver the drug over a 2-week period.[41] Despite the theoretical advantages of such a system, which employs elastomeric polymers, few clinical studies have demonstrated its success. While the advent of BoNT-A has provided an additional treatment option, the need for injection renders it more invasive and painful for the patient. Recently, delivery of "injection free" intravesical BoNT-A has been developed. Liposomes (LPs), lipid vesicles with a phospholipid bilayer surrounding an aqueous core, appear to display the necessary properties to serve as a drug carrier.[42] In 2017, Chuang et al performed a randomised trial comparing LP mediated BoNT-A (Lipo-BoNT-A) with standard BoNT-A delivery.[43] While the former did improve pain and OSI scores, these were not significant compared to standard BoNT-A delivery. However, none of the patients receiving treatment with Lipo-BoNT-A experienced AUR.

Tacrolimus, a potent immunosuppressive, is the latest drug to receive attention as a treatment option for BPS.[44]

## LIMITATIONS AND IMPLICATIONS FOR PRACTICE

The complex nature of BPS results in key limitations shared by all available studies. Challenges include older studies National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) criteria to determine inclusion.[24] However, the definitions outlined in this earlier tool are more restrictive than recent symptom-based criteria. The varying results achieved across studies despite at times is likely in part due to the heterogenous phenotypes among BPS. Dosages and treatment protocols also vary widely. Furthermore, parameters to evaluate treatment response are not standardised and no BPS specific core outcome set is available. Development of an universal tool would provide a platform for future research. There is a paucity of randomised trials on these different therapies, which leads to guidelines largely relying on limited evidence and older studies in order to establish recommendations. These studies often have short follow up periods and small sample sizes. Future randomised trials are therefore required, which are designed with these shortcomings in mind. These will be of paramount importance in re-writing the next chapter of BPS treatment.

## CONCLUSION

BPS is a complex disease, and this is mirrored in the management pathway. Intravesical therapies are an integral part of the treatment strategy. A number of these exist in clinical practice, each with their respective advantages and disadvantages. Further randomised studies employing standardised outcome measures are warranted in order to ameliorate the available evidence basis.

## FINANCIAL DISCLOSURES

Nil

## CONSENT

Not applicable

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2021.05.042.

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