Systematic Review of Oral Therapy for the Treatment of Symptoms of Bladder Pain Syndrome: The Brazilian Guidelines*

*Revisão sistemática sobre terapia oral para tratamento dos sintomas da síndrome da bexiga dolorosa: as diretrizes brasileiras**

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Abstract

Interstitial cystitis (IC), including bladder pain syndrome (BPS), is a chronic and debilitating disease that mainly affects women. It is characterized by pelvic pain associated with urinary urgency, frequency, nocturia and negative urine culture, with normal cytology. In 2009, the Society for Urodynamics and Female Urology (SUFU) defined the term IC/BPS as "an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than 6 weeks duration, in the absence of infection or other identifiable causes." This is the definition used by the American Urological Association (AUA) in the most recent guidelines on IC/BPS. Interstitial cystitis may be sufficiently severe to have a devastating effect on the quality of life, but it may also be associated with moderate symptoms whose effects are less debilitating. Although there are several clinical trials to assess oral and intravesical therapies, the treatment for IC remains far from ideal. This systematic assessment evaluates published randomized clinical trials on oral medications used to treat symptoms of BPS. This study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) method. Two independent reviewers screened the studies to determine their inclusion or exclusion and to perform the methodological analysis. The inclusion criteria included randomized studies published between April of 1988 and April of 2016 that used oral medications to treat symptoms of BPS or IC. According to the systematic review

Keywords
- bladder pain syndrome
- interstitial cystitis
- oral therapy

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performed, we should consider pentosan polysulfate as one of the best options of oral drugs for the treatment of BPS symptoms. However, this drug is not an available option in Brazil. Orally administered amitriptyline is an efficacious medical treatment for BPS, and it should be the first treatment offered.

Resumo

Cistite intersticial (IC), incluindo a síndrome da bexiga dolorosa (SBD), é uma doença crônica e debilitante que afeta principalmente mulheres. É caracterizada por dor pélvica associada à urgência miccional, frequência urinária, noctúria e exame cultural de urina negativo, com citologia normal. A cistite intersticial pode ser suficientemente severa para ter um efeito devastador na qualidade de vida, mas também pode estar associada a sintomas moderados e menos debilitantes. Embora existam vários ensaios clínicos para avaliar terapias orais e intravesicais, o tratamento para IC permanece longe do ideal. Esta revisão sistemática avaliou ensaios clínicos randomizados publicados sobre medicamentos orais usados para tratar sintomas de SBD. Este estudo foi realizado de acordo com o método *preferred reporting items for systematic reviews and meta-analyses* (PRISMA). Dois revisores independentes examinaram os estudos para determinar sua inclusão ou exclusão e para realizar a análise metodológica. Os critérios de inclusão foram: ensaios clínicos randomizados publicados entre abril de 1988 e abril de 2016 que usaram medicações orais no tratamento dos sintomas da SBD ou CI. De acordo com a revisão sistemática realizada, a melhor opção de medicação oral para o tratamento dos SBD é o pentosano polissulfato sódico. No entanto, esta droga não está disponível no Brasil. A amitriptilina administrada por via oral é um tratamento eficaz para SBD e deve ser oferecida como primeira escolha.

Descritores

- síndrome da bexiga dolorosa
- cistite intersticial
- terapia oral

Introduction

Interstitial cystitis (IC), including bladder pain syndrome (BPS), is a chronic and debilitating disease that mainly affects women. It is characterized by pelvic pain associated with urinary urgency, frequency, nocturia and negative urine culture, with normal cytology.[1,2] There is no consensus on the physiopathology, etiology and IC classification, resulting in diagnoses made by clinical exclusion rather than by objective measures. Physiopathological alterations may result in a process of epithelial cell dysfunction, C nerve fiber activation and mast cell proliferation, ultimately leading to a worsening condition and tissue damage, scarring, fibrosis and neuropathic pain.[2] The IC diagnosis presents several clinical phenotypes, most likely with different combinations of etiologies, symptom complexes and associated comorbidities.[3] Interstitial cystitis may be sufficiently severe to have a devastating effect on the quality of life, but it may also be associated with moderate symptoms whose effects are less debilitating.[4–6]

Some studies have shown that women with IC may have a higher prevalence of several organisms in the urinary microbiota of the lower urinary tract, even with negative culture (for bacteria). In addition, the reports of a decrease in symptoms following the administration of antibiotics in some cases of IC suggest that bacteria may have a role in the symptoms of this disease.[7]

Although there are several clinical trials to assess oral and intravesical therapies for the syndrome, the treatment for IC remains far from ideal.[6] Moreover, many of the existing oral treatments are ineffective in patients with IC, and patients might require multimodal treatment to relieve symptoms.[4]

Recent studies have suggested that nitric oxide (NO) may play a role in the etiology of IC. Nitric oxide is the product of L-arginine oxidation and has many physiological functions, but two are considered important in the bladder and, potentially, in IC. First, it acts as an antagonist of smooth muscle contraction, promoting muscle relaxation; and second, it seems to inhibit the degranulation of mast cells, decreasing the associated inflammatory reactions. Women with IC have significantly less NO synthesis activity in their urine than normal control subjects.[8,9]

Amitriptyline is an option frequently used to treat patients with IC. It has at least three major pharmacological actions. It has central and peripheral anticholinergic action, and it blocks the active transport system in the presynaptic nerve ending, which is responsible for the reuptake of serotonin and noradrenaline. The sedative properties may be related to its antihistaminic properties and may explain the potential benefits observed in patients with IC.[6]

Other drugs, such as gabapentin, are being studied with a specific focus on pain treatment. Pentosan polysulfate sodium (PPS) is the only FDA-approved oral therapy for IC. The mechanism of action for PPS is not completely understood, but a widely accepted theory is that it replaces the damaged segments of the glycosaminoglycan layer, which protects the bladder against the corrosive effects of urine and bacteria. It is believed that intravesical therapy, compared with oral therapy alone, may provide the benefit of establishing a higher drug

concentration directly into the bladder, with a minimal risk of systemic side effects. Thus, the PPS instilled directly into the bladder could accelerate the resolution of IC symptoms.[4]

The objective of this systematic review is to evaluate published randomized clinical trials on oral medications used to treat symptoms of BPS, analyzing group of patients, interventions, comparisons and outcomes of each study.[5]

Methods

A systematic review was performed using the PubMed, Embase and Lilacs databases. The following terms were used to search clinical trials that included female patients: *interstitial cystitis* or *painful bladder syndrome* or *bladder pain syndrome* or *pelvic pain* and *pharmacological treatment*.

This study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[10] Two independent reviewers screened the studies to determine inclusion or exclusion and to perform the methodological analysis.

The inclusion criteria comprised randomized studies published between April of 1988 and April of 2016 that used oral medications to treat symptoms of BPS or IC. We included trials that compared an oral treatment for BPS versus another oral, intravesical or placebo treatment. The oral medication must have been used in at least one arm of the study and the methodology must have been clearly described.

Studies that were not published in English, Portuguese or Spanish and studies that did not show results related to the symptoms of BPS or IC were excluded.

The articles were subdivided into groups according to the drug used. The results of each group were assessed by comparing the initial assessment to the final clinical outcome data.

All articles were scored according to the Jadad scale.[11] The Jadad scale consists of three topics, which are directly related to bias reduction and are centered on internal validity. All questions have a yes/no option. The Jadad Scale has a five-point quality scale: three single points for "yes" responses and two additional points for appropriate methods of randomization and allocation concealment.[11]

Results

Initially, 45 articles were identified in the database search. Twenty publications were fully analyzed, and from these studies, 13 randomized studies were selected for inclusion. The studies were divided into subgroups, according to the drug studied: 5 studies assessed PPS, 2 studies assessed amitriptyline, 2 studies assessed L-arginine, and 4 studies assessed other drugs (sildenafil, antibiotics, cyclosporine, dimethyl sulfoxide [DMSO] and PD-0299685). The study selection process is illustrated in a PRISMA flowchart presented in ►**Fig. 1**.

L-Arginine

Two studies that used L-arginine to treat BPS were found. Korting et al[2] tested a dose of 1,500 mg daily for 3 months compared with placebo. The four primary outcome measures used to assess the effect of L-arginine treatment on IC symptoms were a voiding diary, a secondary outcome measure, a symptom score and a Likert scale. According to the intention-to-treat

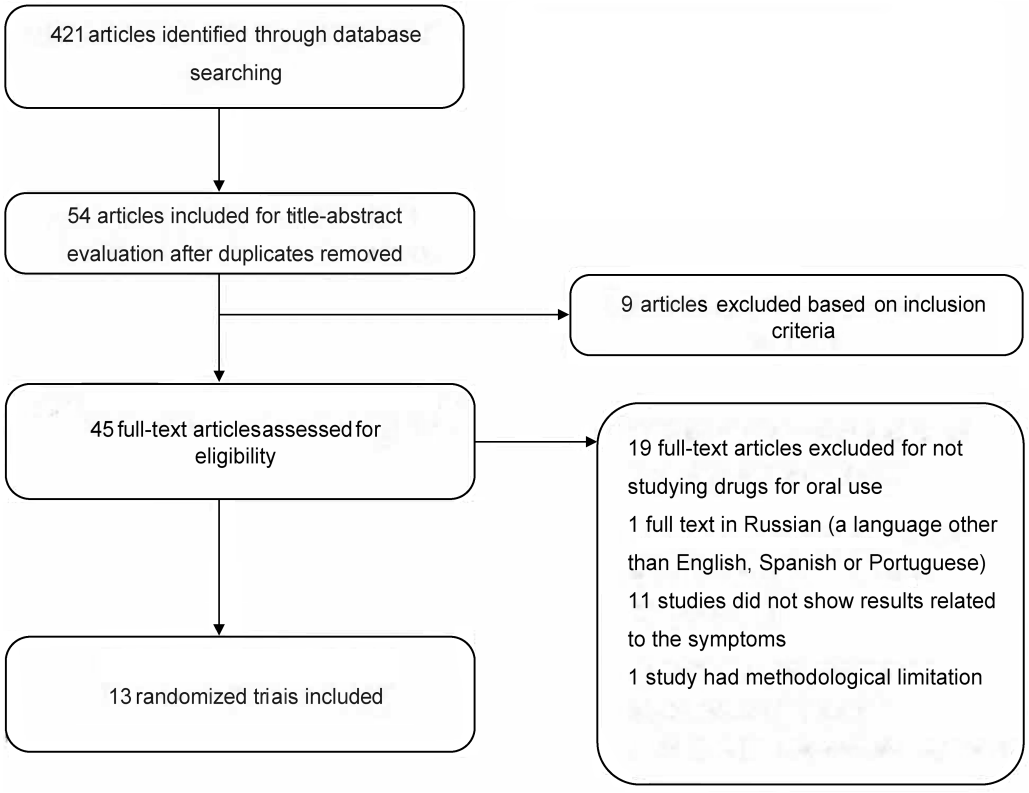

Fig. 1 Flowchart demonstrating the process of searching, screening, and selecting eligible studies.

(ITT) analysis, 22% of the patients (6 of 27) in the L-arginine group, and 12% (3 of 26) of the ones in the placebo group were clinically improved at the end of the trial ($p = 0.31$). The ITT analysis showed no significant differences between the groups in the voiding diary results evaluating frequency and nocturia, secondary outcome measure, symptom score or the Likert scale. The trial was completed by 21 of 27 patients in the L-arginine group, and 25 of 26 in the placebo group. According to the protocol analysis, 29% (6 out of 21) of the patients in the L-arginine group and 8% (2 out of 25) of those in the placebo group were clinically improved by the end of the trial ($p = 0.07$). A Likert scale showed greater global improvement in the L-arginine group (48%, 10 of 21) compared with the placebo group (24%, 6 of 25) at 3 months ($p = 0.05$), with a decrease in pain intensity ($p = 0.041$), and tendency toward improvement in urgency ($p = 0.06$) and frequency of pain ($p = 0.09$). Using an ITT analysis of the outcome measures, there were no significant differences between the groups after the initiation of L-arginine or placebo. According to the per-protocol analysis, the Likert scale showed significant improvement in the L-arginine group compared with the placebo group. As per the Likert scale, the L-arginine group had significantly greater improvement in pain intensity and in all symptoms combined (global improvement) at 3 months. The ITT analysis includes all patients, regardless of withdrawal from the trial for assigned group analysis. The per-protocol analysis includes only those patients who adhere to the protocol during the study. According to the per-protocol analysis, the use of L-arginine significantly decreased the IC pain intensity ($p = 0.04$) and the global scores on a Likert scale ($p = 0.05$) (►**Table 1**).[2]

Cartledge et al[8] tested a daily dose of 2,400 mg of L-arginine for 4 weeks and compared the results with those of placebo. The primary endpoint of the study was a change in the IC symptoms index (ICSI) score. There was no difference between the group receiving L-arginine and the placebo in the studied outcomes (ICSI score, symptoms score and voiding diary). The ICSI score recorded from patients after 4 weeks of L-arginine use was 7.5% lower than the mean value calculated at baseline ($p < 0.05$). Although lower than the mean ICSI score recorded from patients on placebo, the difference was not significant ($p = 0.16$), and even though the improvement in the ICSI score over baseline after 4 weeks of treatment with L-arginine was statistically significant, the effect was not considerably better than that with placebo (►**Table 1**).[8]

Other Drugs

The following four treatments were tested: PD-0299685, cyclosporine A, sildenafil and multiple antibiotics.

The PD-0299685 is an agonist of the α2-delta subunit of the voltage-dependent calcium channel. The α2-delta subunit of voltage- gated calcium ion channels mediates afferent pain fibers and is implicated in chronic pain. There is a small number of uncontrolled reports suggesting that, as the α2-delta ligand may have efficacy in refractory genitourinary pain and IC/BPS.

Nickel et al[3] tested PD-0299685 at daily doses of 30 and 60 mg and compared the results to those of the placebo group for a 12-week period; PD-0299685 failed to show a significant benefit over the placebo and presented poor tolerability (►**Table 2**).[3]

Sairanen et al[9] compared a cyclosporine A (CyA) dose of 1.5 mg/kg, twice per day, with 100 mg of PPS, 3 times per day for 6 months. Cyclosporine A was superior to PPS in all clinical studied outcome parameters measured at 6 months. The micturition frequency in 24 hours was significantly reduced in the CyA arm compared with the PPS arm. The clinical response rate (according to global response assessment) was 75% for CyA compared with 19% for PPS ($p < 0.001$). There were more adverse events in the CyA arm than in the PPS arm. (►**Table 2**).[9]

Chen et al[12] tested sildenafil at daily doses of 25 mg and compared these results to those of a placebo for a 3-month period. Sildenafil showed significant superiority over the placebo on all studied outcomes (►**Table 2**).[12]

Warren et al[7] tested the combination of using a 300 mg per day dose of rifampicin for 18 weeks with a sequential therapy of antibiotics, 3 weeks each, using the following doses: 100 mg doxycycline twice per day; 250 mg erythromycin four times per day; 500 mg metronidazole four times per day; 300 mg clindamycin four times per day; 500 mg amoxicillin three times per day and 250 mg ciprofloxacin twice per day in comparison to placebo. The treatment did not significantly improve the symptoms, compared with placebo, and showed significant increase in dropout and side effects (►**Table 2**).[7]

Amitriptyline

Two studies using amitriptyline to treat BPS were included (►**Table 3**). Foster et al[6] performed a study with 271 participants, in which both groups received information on behavioral modifications, and compared amitriptyline versus placebo. The medication was increased on the sixth week from 10 to 75 mg/day. The primary outcome was the assessment of the

Table 1 Outcomes of L-arginine in the treatment of painful bladder syndrome

First Author/Year	n	Groups	Outcomes Measured	Results	Significance between groups	Jadad Scale[11] score
Cartledge et al (2000)[8]	16	L-arginine x placebo	ICSI score Voiding Diary	Significant improvement compared with initial assessment. No difference between groups.	$p = 0.16$	3
Korting et al (1999)[2]	53	L-arginine x placebo	Symptoms Score Likert Scale Voiding Diary	No difference between groups.	$p = 0.31$ (intention to treat)	5

Abbreviation: ICSI, interstitial cystitis symptoms index.

Table 2 Outcomes of Amitriptyline in the treatment of painful bladder syndrome

First Author/Year	Drug tested	n	Groups	Outcomes Measured	Results	Significance between groups	Jadad Scale[11] score
Nickel et al (2012)[3]	PD-0299685	161	PD-0299685 30 mg x PD-0299685 60 mg x placebo	ICSI score severity score of pain worsening	No difference between groups and placebo.	$p = 0.08$	2
Sairanen et al (2005)[9]	Cyclosporine A	64	Cyclosporine A x Pentosan polysulfate	daily micturition frequency Volume voided Nocturia Scale of pain GRA	Significant improvement in parameters regarding pentosan polysulfate	$p < 0.01$	3
Chen et al (2014)[12]	Sildenafil	48	Sildenafil x Placebo	Voiding diary ICSI score ICPI Visual analog scale Urodynamic parameters Symptoms global improvement rate	Significant improvement in parameters regarding placebo.	$p < 0.05$	3
Warren et al (2000)[7]	Antibiotics	50	Antibiotics x Placebo	Semi-quantitative assessment of bladder pain	No significant difference in global improvement between groups.	$p = 0.14$	1

Abbreviations: GRA, global response assessment; ICPI, Interstitial Cystitis Problem Index; ICSI, interstitial cystitis symptoms index.

Table 3 Outcomes of other drugs in the treatment of painful bladder syndrome

First Author/Year	n	Groups	Outcomes Measured	Results	Significance between groups	Jadad Scale[11] score
van Ophoven et al (2004)[1]	50	Amitriptyline 25 to 100 mg/day x Placebo	ICSI Visual pain scale	Significant improvement in pain symptoms and urgency intensity scores.	$p = 0.05$ (score) $p < 0.001$ (pain/urgency)	4
Foster et al (2010)[6]	271	Amitriptyline 10 to 75 mg/day x Placebo	GRA, ICSI SF-36, FSFI	Group using Amitriptyline, at least 50 mg/day, had significant improvement.	$p < 0.01$ (for dose of at least 50 mg/day)	3

Abbreviations: DMSO, dimethyl sulfoxide; FSFI, female sexual function index; GRA, global response assessment; ICSI, interstitial cystitis symptoms index; SF-36, health related quality of life index.

global response based on the improvement of symptoms after 12 weeks of treatment. The subgroup of patients that received a dose of at least 50 mg amitriptyline demonstrated a significantly higher response than that obtained with placebo ($p < 0.01$).[6]

Van Ophoven et al[1] tested amitriptyline at a dose of 25 to 100 mg and compared these effects to placebo. There was significant change in the symptoms score, and a significant improvement in pain and urgency was observed when the treated group was compared with placebo. The use of amitriptyline for 4 months was considered safe and effective for the treatment of IC.[1]

Pentosan Polysulfate Sodium

Five randomized studies assessed the use of PPS in the treatment of symptoms of IC/BPS, and their most relevant results are described in ►**Table 4**.

The studies included a total of 1,084 patients. The largest series was published by Nickel et al,[4] in 2005, and included 380 cases. Three doses of PPS were tested (300, 600 and 900 mg) for 32 weeks. The ICSI score average improved significantly during the 32 weeks for all dosages. Thus, there was relevant clinical improvement with the three dosages. However, the treatment duration appeared to be more important than the dosage.[4]

Mulholland et al[13] compared the results of PPS use to those of placebo over 3 months of treatment. Global improvement higher than 25% was reported by 28% of patients treated with PPS and by only 13% of patients who received placebo ($p = 0.03$). In this study, PPS was considered as safe and more effective than placebo.[13]

Sant et al[14] published a study designed to assess PPS and hydroxyzine. The primary outcome was the global response assessment. The treatment response rate with hydroxyzine was 31% and there was a 20% response for the untreated group ($p = 0.26$). With PPS, the response was 34% and in the untreated group it was 18% ($p = 0.064$). The low global response rate to PPS and hydroxyzine suggests that none of these therapies can provide benefits to most patients with IC.[14]

Nickel et a.[15] tested doses of 100 and 300 mg of PPS and compared these effects to those of the placebo group for 24 weeks. There was no difference between the groups receiving PPS and placebo regarding the primary outcome (30% of reduction of ICSI total score from the initial to final assessment).[15]

David et al[16] assessed 41 women diagnosed with IC who received intravesical PPS associated with oral PPS or placebo associated with oral PPS for 6 weeks. The use of intravesical PPS combined with oral PPS was the safest and most effective therapeutic option.[16]

The studies included were scored according to the Jadad Scale. Only three studies received the maximum score on this scale, which showed high quality; nine studies scored three or lower and one study scored four.

Discussion

The product of L-arginine oxidation is NO. Although NO may have a potential effect on the etiology of BPS, the clinical results of L-arginine in the treatment of this pathology were no better than placebo.[2,8] Among the drugs with very few studies in the

Table 4 Outcomes of pentosan polysulfate in the treatment of painful bladder syndrome

First Author/Year	n	Groups	Outcomes Measured	Results	Significance between groups	Jadad Scale[11] score
Nickel et al (2014)[15]	368	PPS 100 mg x PPS 300 mg x Placebo	PORIS ICSI GRA	No significant difference in symptoms.	$p > 0.08$	2
Mulholland et al (1990)[13]	110	PPS 300 mg x placebo	Voiding diary. Pain and urgency scales.	PPS was more effective than placebo.	$p = 0.03$	5
Sant et al (2003)[14]	121	Combined therapy (PPS + hydroxyzine) x PPS alone x hydroxyzine alone x placebo	GRA The University of Wisconsin Symptom Score ICSI	1. PPS + Hydroxyzine: lower urinary frequency. 2. Hydroxyzine x No Hydroxyzine: no significant difference. 3. PPS × no PPS: better response trend in the PPS group.	1. $p = 0.0036$ 2. $p = 0.26$ 3. $p = 0.064$	2
Nickel et al (2005)[4]	380	PPS 300 mg × 600 mg × 900 mg/day	ICSI PORIS	All dosages had significant clinical response. Efficacy: no significant difference between dosages.	$p < 0.001$	1
Davis et al (2008)[16]	41	Intravesical PPS + oral PPS x intravesical placebo + oral PPS	ICSI PUF SF-36	The change in total ICSI score and improvement in quality of life was significantly higher in the group treated.	$p = 0.04$ $p \leq 0.001$	5

Abbreviations: GRA, global response assessment; ICSI, interstitial cystitis symptoms index; PORIS, patient's overall rating of symptoms index; PPS, pentosan polysulfate; PUF, pelvic pain and urgency/frequency questionnaire; SF-36, health related quality of life index.

management of BPS, sildenafil at a low dose and CyA showed promising initial results, but these results need to be verified by further studies with larger groups of individuals.[9,12]

According to Foster et al,[6] amitriptyline plus an education and behavioral modification program did not significantly improve the symptoms. The adverse effects were acceptable, but the adherence to treatment with higher doses was low. The study also suggests that amitriptyline may be beneficial just in the group that can achieve a daily dose of 50 mg/day, although this subgroup comparison was not specified in advance.[6] In the study performed by van Ophoven et al,[1] there was an improvement in symptoms, and it was also confirmed that amitriptyline showed a significant improvement in the urinary urgency symptom. These authors describe that, based on the results of this study, they recommended using amitriptyline as a first-line therapy for IC in their institution.[1]

With regard to PPS assessment, the studies showed heterogeneous outcomes. Three series included a dose of 300 mg/day in their assessments. In two of the series, this dose was compared with placebo, and the results were conflicting. In the study performed by Nickel et al (2014),[15] there was no difference between the group that received 300 mg/day of PPS and the group that received placebo on the primary outcome, which was defined in this study as a 30% reduction of the ICSI total score from the initial to final assessment. In the series published by Mulholland et al,[13] with the same dose of 300 mg/day, PPS was more effective than placebo.[13,15]

However, due to the limitations caused by the study design, early termination, inclusion criteria and high dropout rate, Nickel et al (2014)[15] reported that they do not believe that their study can be used to justify the abandonment of one of the few medications with significant clinical trials in the treatment of IC/BPS They also report that PPS is most likely the best component of an overall therapeutic strategy as described in the American Urological Association (AUA) guidelines.[15]

Although antihistamines are widely used in the treatment of BPS, studies that assess their exclusive use were not found in our search. Only one study evaluating hydroxyzine was found.

It was not possible to perform a meta-analysis based on the assessed clinical trials due to the heterogeneity of the published studies.

Conclusion

According to the systematic review performed, we should consider PPS as one of the best options of oral drugs for the treatment of BPS symptoms. However, this drug is not an available option in Brazil. Orally administered amitriptyline is an efficacious medical treatment for BPS and should be the first treatment offered.

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