







Daily low dose of tadalafil improves pain and frequency in bladder pain syndrome/interstitial cystitis patients

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Abstract

Objective: Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic disease, with consequent high morbidity. Increasing evidence suggests that bladder afferent hyperexcitability, through neurogenic bladder inflammation and urothelial dysfunction, plays a key role in the pathophysiology of BPS/IC. The rationale of using phosphodiesterase type 5 inhibitors (PDE5i) would be to decrease bladder afferent hyperactivity. Detrusor relaxation, improvement of microcirculation, and a decrease in adrenergic nociceptive overactivity would be other effects in bladder tissue. We aimed to evaluate the efficacy, tolerability, and safety of a daily low dose of 5 mg tadalafil in refractory BPS/IC patients.

Material and methods: A total of 14 refractory BPS/IC female patients, previously evaluated with a physical examination, bladder diary, bladder-pain related visual analogue score, O'Leary-Sant Scores (OSS) for symptoms and problems, and quality of life (QoL) question from International Prostate Symptom Score, were treated with 5 mg of tadalafil, for 3 months. Re-evaluations occurred at 4 and 12 weeks. Adverse events were assessed and recorded.

Results: Urinary frequency, OSS, and QoL were significantly improved at 1-month follow-up (10 ± 2.5 , 21.9 ± 4.1 , and 4 ± 1.5 , respectively, $P < .05$). Pain intensity and volume voided were significantly improved at a 3-month follow-up (3.5 ± 2 and 266.7 ± 60.5 , $P < .05$). Patients referred to urinary frequency as the most important parameter improved at 4 weeks, and pain at 3 months. No differences between ulcerated and nonulcerated patients were observed. Two patients dropped out due to unsatisfactory results and two due to persistent headache and/or tachycardia, but both events were resolved after discontinuing the drug.

Conclusion: Daily low-dose tadalafil is an easy, well-tolerated, and effective treatment for refractory BPS/IC in women.

Keywords: Cystitis; drug therapy [E02.319]; interstitial [C12.777.829.495.500]; phosphodiesterase 5 inhibitors [D27.505.519.389.735.500]; tadalafil [D03.633.100.473.155.500].

Introduction

Bladder pain syndrome (BPS) was defined in 2008's consensus from International Continence Society (ICS), as a chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the bladder, accompanied by at least one other urinary symptom such as a persistent urge to void or frequency.¹ The term interstitial cystitis (IC) should be reserved for a specific phenotype in cystoscopy and histologic features: the presence of

Hunner's lesions (HLs).^{2,3} During a transition period, International Society for the Study of Bladder Pain Syndrome (ESSIC) has agreed to include IC in the overall term (BPS/IC) to facilitate the transition of terminology.¹ BPS/IC has an overall prevalence of 10.6/100,000, affecting more women (6:1) than men.^{4,5}

According to the American Urologic Association (AUA) guidelines, the impact of BPS/IC on psychosocial health and quality of life (QoL) is so severe that it could ultimately ruin work-

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life, psychological well-being, personal relationships, and general health.⁶ All the guidelines agree that the initial step should be the assessment and management of pain.⁶⁻⁹ The following steps are still controversial. According to ESSIC, the second step should be bladder biopsies with hydrodistention, while the AUA suggests undergoing this invasive procedure only in more complex or refractory cases.^{1,6} The findings in the urothelium during bladder hydrodistention (normal vs glomerulations vs the presence of HL) and the findings from the biopsied urothelium are needed to phenotype according to the ESSIC criteria.¹⁰ The two phenotypes are with HL (used for IC, or ESSIC classification 3X) and the non-HL or BPS.

When referring to the physiopathology of these conditions, little is known but one of the main actors in nociception seems to be the L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway.^{11,12} This pathway is responsible for signal transduction both in the central and peripheral nervous systems being especially responsible, through the activation of protein kinase G (PKG), for the inhibition of the nervous pain signaling.¹³ The mechanism of action seems to be directly related to the effect of PKG in stimulating the opening of ATP-sensitive K⁺ channels, and the consequent restoring of the nociceptor threshold.¹⁴ cGMP, the final product of the L-arginine-NO pathway, seems to be utterly important for the regulation of the nociceptor fibers threshold. The enzymes phosphodiesterase (PDE) 5, 6, and 9 inhibits the GMP degradation to 5-GMP, potentially favoring their antinociceptive effect, being PDE 5 the most relevant enzyme.¹⁵

According to the AUA guidelines, most treatments are targeted at symptom control and no treatment works overtime for the majority of patients.⁶ The treatment approach should be therefore patient-tailored to optimize life quality.^{7,8}

A previous multicentric, double-blinded, randomized controlled trial evaluated the efficacy and safety of low-dose silde-

nafil, improved in terms of urinary frequency complaints, both daytime and nocturn, although the results in terms of pain were not significant.¹⁶ Following a previous study, we aimed to assess the efficacy, tolerability, and safety of an oral daily low dose of tadalafil (5 mg) in refractory BPS/IC patients, once tadalafil presents a better pharmacokinetic profile, with and half-life of approximately 24-36 hours.¹⁷

Material and Methods

Patients

After obtaining clearance from the local ethics committee (Protocol number 40-20: Papel do tadalafil na Cistite Intersticial), 14 females, previously diagnosed with BPS/IC, according to ESSIC criteria, and refractory to previous medical and intravesical therapy, entered this single-arm trial, during 2019 Centro Hospitalar e Universitário de São João, Porto, Portugal. Patients were asked if they accepted to take tadalafil as an off-label treatment for this kind of Lower Urinary Tract Symptoms (LUTS) and if they consent to have their data analyzed and shared at the end of the 12 weeks of treatment.

Patients were aware of the type of drug and the possible adverse events (AEs). The subjects were subdivided, during the analyses of the results, according to the presence or absence of the HL. Patients have been previously advised to change their negative lifestyle choices, such as excessive drinking and quitting smoking before starting this trial.

Study Design

This was a single-arm exploratory trial. Patients who accepted to participate received an oral daily low dose of tadalafil (5 mg) for 12 weeks. There was no dose titration option. The evaluation of symptoms and complaints was performed at baseline, in the 4th week, and the 12th week.

Evaluation

The evaluation compromised a 3-day bladder diary to evaluate functional bladder capacity (CC) the week previous to the appointment; and during the appointment, the investigators evaluated: bladder-pain related visual analogue score (VAS) from 0 to 10 points representing the perception of mean pain during the period since last evaluation, O'Leary-Sant Scores (OSS) for symptoms and problems from 0 to 43 (with 43 representing being the worst symptoms possible), and QoL was evaluated through the last question from International Prostate Symptom Score (from 0 to 6 points, being 6 the worst QoL imaginable). Urinary tract infections and other AE were also screened.

Statistical Analysis

Data analysis was performed with a Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM SPSS Corp.;

Main Points

- BPS/IC patients usually underwent several lines of therapy before reaching the best therapeutic approach (mono or multimodality).
- Tadalafil, an inhibitor of the phosphodiesterase 5, seems to act in the pain pathway.
- In patients' refractory to previous modalities of treatment, tadalafil 5 mg seems to have positive results in the pain and urinary frequency symptoms.
- The already known adverse events of this drug can be limiting and should be carefully explained to these patients.

Table 1. Patient's Demographics

	n/HL	HL
Age	39 ± 9	48 ± 16
N	7	7
Previous local therapies	2	6
Compatible histology (ESSIC class C)	2	6
>6 months disease time	7	7

N/HL, non-Hunner's lesion; HL, Hunner's lesion.

Armonk, NY, USA). Data evaluation at two-time points was deltas against the baseline and presented as mean and standard deviation. Differences were assessed by appropriate exact parametric testing: T-test when normality was observed and non-parametric Mann-Whitney U test ($P < .05$ was considered statistically significant). The relative reduction was calculated by a simple comparison between the two evaluations, in percentage.

Results

Demographics

The trial included 14 female patients, with a mean age of 46 ± 15 years. Seven patients presented HLs, being six of them classified as 3C according to ESSIC classification and one patient had an inconclusive biopsy and was classified as 3B. The remaining patients were classified as 2C. Regarding previous treatments, all were refractory to systemic and/or intravesical therapies. Eight patients who had received an intratrigenal injection of 100 units of onabotulinum toxin A and decided to participate in the trial had the injection at least 12 months apart from the beginning of the trial. Patients' demographics are presented in Table 1.

Outcomes (VAS/Frequency/OSS/CC/QoL)

The improvements in all measured outcomes are represented in Table 2. At baseline, pain intensity in VAS was 6.7 ± 1.4 , OSS was 25.7 ± 4.3 , and day and night frequency were 12.6 ± 5.2 and 4.4 ± 2.7 , respectively. Functional bladder capacity was 185.7 ± 56.9 mL, and QoL score (0-6) was 5.0 ± 1 .

Pain intensity was majorly improved at the 12th week, with a reduction of 6.7 ± 1.4 to 3.5 ± 1.9 (relative reduction of 48%) and was statistically significant at that time point ($P < .01$). At 3 months, eight of the 10 patients had a reduction in VAS of more than two points, the other two patients maintained the same score.

OSS decreased through the 3 months' study, from 25.7 ± 4.3 to 17.8 ± 5.9 (reduction of 31%), and the difference was statistically significant in the transition between baseline and week 4 with a relative reduction of 15% ($P = .01$), and at week 12 ($P < .01$), with a relative reduction from baseline of 31%.

Compared with baseline, the urinary frequency was significantly improved at week 4 with a reduction of 16.9 ± 7 to 9.9 ± 2.6 (relative reduction of 42%). At week 12, the mean urinary frequency was 8.3 ± 2.6 , with a relative risk reduction of 51% from baseline. This trend toward reduction was maintained at the 12th week. Differences were statistically significant between baseline and week 4 and week 12 ($P < .01$, in both). At the 3rd month, all 10 patients reduced the number of micturitions. The minimum reduction was from 13 to 8, and the maximum difference was from 36 to 13 micturitions per day.

QoL scale presented a gradual improvement, from 5.1 ± 0.9 to 4.1 ± 1.5 at week 4 (relative reduction of 20%), with a final score of 3 ± 1.3 (relative reduction of 42%) at 12 weeks, and differences were statistically significant along with the trial ($P = .01$ and $P < .01$, respectively).

Table 2. Study Results

	Baseline	W4	RR (Base-W4)	P value (Bas-W4)	W12	RR (Base-W12)	P value (Bas-W12)
VAS	6.7 ± 1.4	5.3 ± 1.9	21%	.056	3.5 ± 1.9	48%	.001
Freq	16.9 ± 7.2	9.9 ± 2.5	42%	.01	8.3 ± 2.6	51%	.001
CC	185.7 ± 56.9	238.9 ± 48.6	28%	.07	266.7 ± 60.5	43%	.01
QoL	5.1 ± 0.9	4.1 ± 1.5	20%	.01	3 ± 1.3	42%	.001
OSS	25.7 ± 4.3	21.9 ± 4.1	15%	.01	17.8 ± 5.9	31%	.001

W4, week 4; W12, week 12; RR, relative reduction; base, baseline; VAS, visual analogue scale; Freq, frequency; CC, functional bladder capacity; QoL, quality of life; OSS, O'Leary-Sant.

CC, evaluated through micturition in the 3-day bladder diary, also experienced a major improvement, with an increasing volume of voided urine per micturition (185.7 ± 56.9 to 266.7 ± 60.5). This difference was only statistically significant at week 12 ($P = .01$), with a relative increase in 43%.

When comparing patients with and without HL at baseline, no statistical differences between the groups were noted except the QoL score, significantly worse in the HL group.

A more pronounced improvement in nonulcer patients, when compared with HL patients, is seen, but this difference is not statistically significant in all variables measured ($P > .05$ when compared to the different values). Frequency improvement was always statistically significant in non-HL patients ($P < .05$), while it was only statistically significant at 3 months of follow-up on ulcer patients ($P = .04$). VAS and OSS improvements were statistically significant only at 3 months of follow-up, in both phenotypes. CC improved with a statistical significance in non-HL, while in ulcerated patients, this improvement was not significant—expected given the fibrotic course of this specific phenotype. At 3 months, none of the particular phenotype seems to benefit more than the other.

According to patients, while the urinary frequency was the most important reported parameter improved at 1-month follow-up, the pain improvement was the most important at 3 months.

Adverse Effects

After 1 month in therapy, four patients (30% of the participants) dropped out of the study: two (15%) due to the lack of symptom improvement—treatment failure, and two (15%) had a persistent headache and/or tachycardia. Both of the patients presented minor AEs, not life-threatening, and were resolved after tadalafil discontinuation without the need of consulting a doctor for this purpose.

Discussion

The absence of unanimous guidelines in terms of which therapeutic escalation should be used, allied to a large number of patients who do not respond to the usual first lines (analgesic, amitriptyline, and pentosane sulfate), explains the reason why pain control is usually achieved after experimenting several drugs, usually with a massive burden of pain-killers. This motivates us to search for off-label treatments. 5PDE-i(s) were initially used for pulmonary hypertension and, after observing their AEs, began to be used for erectile dysfunction given their vasodilator effect. Later, it was observed that this class of

drugs could improve LUTS, and tadalafil was the drug with a more favorable (longer) half-lifetime. Nowadays, its use in voiding and storage LUTS are official as European Association Urology Guidelines demonstrate.¹⁸

The first and only placebo-controlled trial evaluating tadalafil in BPS/IC patients was published in 2014 by Chen et al¹⁶ The group evaluated the efficacy of daily sildenafil (25 mg) for 3 months. The authors concluded that sildenafil improved the OSS and the urodynamic index (first desire to void, strong desire to void, and functional bladder capacity). No significant change in the VAS score was observed between the two groups, except at week-12 in the treatment group.

Although pain is the hallmark symptom of BPS/IC and it can be located anywhere in the pelvis or external genitalia, most patients experience urgency and/or urinary frequency.¹⁹

The primary outcomes in our trial were pain and urinary frequency. Our patients reported urinary frequency as the most important reported parameter improved at 1-month follow-up, and pain the most important at 12-week follow-up. No significant differences were registered in terms of improvement between ulcerated and nonulcerated patients in these parameters.

Jain et al¹⁵ conducted a preclinical trial exploring the role of the NO-cGMP pathway in nociceptive conditions. Peripheral nociception was assessed chemically while central nociception was assessed by tail-flick and hot-plate methods. In this trial, the use of sildenafil, a member of the PDE5i drug class like tadalafil, induced a dose-dependent antinociception. This analgesia was blocked by methylene blue, a guanylate cyclase inhibitor (inhibits the formation of cGMP) as tadalafil.

Minagawa et al²⁰ showed that tadalafil dose-dependently decreased single afferent activities in both A δ and C-fibers during intravesical saline instillation. Tadalafil inhibited the acrolein-induced hyperactivity of both fibers, showing that systemic administration of tadalafil reduces mechanosensitive afferent activities. A long way must be walked to understand the real function of PDE5i in bladder nociception. Nevertheless, our hypothesis relies on PDE5i as a new possible drug to control pain in BPS/IC patients' refractory to other therapies. Tadalafil is commercially available in low-dose, 5-mg, with an optimal half-life of approximately 17 hours (the reason for being the only PDE5i licensed for male LUTS) and is the ideal drug to start the experimentation in these patients.¹⁸

BPS/IC patients also experience urinary frequency and urgency. In our study, the urinary frequency was the parameter with a higher improvement in the 4th-week evaluation.

This symptom can be caused by increased sensitivity of detrusor muscle due to elevated urinary potassium or adrenergic nociceptive overactivity.^{21,22} These are probably mediated by an increased RhoA/Rho-kinase (ROCK) signaling, and it is known that this pathway, in the vascular soft muscle, is disabled by the GMPc-protein kinase G. Fibbi et al²³ investigated the PDE5 tissue distribution and activity in human lower urinary tract tissues (urethra, prostate, and bladder), concluding that the highest expression and biological activity of PDE5 were found in the bladder. Morelli et al²⁴ demonstrated that the increase in GMPc in the bladder, by the use of a PDE5i, can block ROCK signaling. Bittencourt et al²⁵ showed sildenafil-induced smooth muscle relaxation, demonstrating that there is a dependence of the NO and GMPc formation pathways for bladder relaxation.

Vasquez et al²⁶ showed that bladder overcontraction caused by deficient bladder vascularity in the setting of endothelium dysfunction could be reverted with the use of 5PEDI. It was also shown that sildenafil can modulate the number of endothelium progenitor cells, which can explain the effects of this drug on endothelium repair and normal function.

From all these preclinical and clinical studies, it seems that tadalafil mechanisms of action can be related to BPS/IC symptoms. The relaxation of the bladder detrusor muscle, improvement of microcirculation, and reabsorption of excessive potassium in the bladder (by inhibiting the cGMP-G-RhoA/Rho-kinase pathway and NO-cGMP pathway) can explain part of the BPS/IC symptoms, namely, pain and frequency.

Our decision to perform a subanalysis based on patients with HL and without was based on a previous Van Moh et al's²⁷ work. The group compared the characteristics between patients with and without HL, concluding that participants without HL reported more pain.²⁷ Contrarily, Killinger et al²⁸ conducted assessed pain characteristics in women grouped by IC/BPS subtype and no difference in pain distribution or characteristics in ulcerative and nonulcerative groups. Braunstein et al²⁹ also concluded no significant differences between symptom duration, history of gross hematuria, history of comorbid disease, or VAS score between the two groups.

The worst QoL of patients with HL observed in our study was previously described by El Khoudary et al³⁰ The higher rate of frequency and a lower bladder capacity were observed and seem to be the reason for the worst QoL baseline.

Although it is tempting to assume that probably there are significant overlaps in symptomatology between the two groups, the origin of both phenotypes could be different, and particular

treatments can be more effective in one group. That was not the case in our study, the results evidenced that there were no statistical differences between ulcer and no ulcer patients. This suggests that cystoscopy is needed to accurately identify patients with HL since the clinical evaluation is insufficient to distinguish the two groups. However, more research is needed in larger samples to determine whether differences exist.

The characteristics of our study (single-arm study, with low sample size, without a control group) make us impossible to take safe conclusions. Additionally, the elevated number of dropouts did not favor the paper. More clinical studies, namely, placebo controlled, should be promoted. The lack of patient compliance was also a limitation in our study.

In this context, and because tadalafil appears to have a quick effect on frequency and pain, it seems to be a drug with a possible role in a subset of refractory patients.

In conclusion, daily low-dose tadalafil could be an effective, simple, and well-tolerated therapy for BPS/IC patients' refractory for first-line therapies. Further randomized, controlled, multicenter trials with a larger population and a longer follow-up period are warranted to confirm these results and, if possible, to tailor this treatment for a specific phenotype of patients.

Ethics Committee Approval: Ethical committee approval was received from the local ethics committee (Protocol number 40-20: Papel do tadalafil na Cistite Intersticial).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.A.M., R.P.; Design - P.A.M., R.P.; Supervision - P.A.M., P.D., F.C., R.P.; Analysis and/or Interpretation - P.A.M., N.D., R.P.; Literature Search - P.A.M., N.D., F.C., R.P.; Writing Manuscript - P.A.M., R.P.; Critical Review - P.A.M., N.D., P.D., F.C., R.P.

Conflict of Interest: The authors have no conflicts of interest to declare.

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References

1. van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. *Eur Urol*. 2008;53(1):60-67. [\[CrossRef\]](#)

2. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the international continence society. *Urology*. 2003;61(1):37-49. [\[CrossRef\]](#)
3. Pinto R, Lopes T, Frias B, et al. Trigonal injection of botulinum toxin a in patients with refractory bladder pain syndrome/interstitial cystitis. *Eur Urol*. 2010;58(3):360-365. [\[CrossRef\]](#)
4. Clemens JQ, Meenan RT, Rosetti MCO, et al. Prevalence and incidence of IC in a managed care population. *J Urol*. 2005;173(1):98-102. [\[CrossRef\]](#)
5. Clemens JQ, Link CL, Eggers PW, et al. Prevalence of painful bladder symptoms and effect on quality of life in black, hispanic and white men and women. *J Urol*. 2007;177(4):1390-1394. [\[CrossRef\]](#)
6. Hanno PM, Erickson D, Moldwin R, et al. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. *J Urol*. 2015;193(5):1545-1553. [\[CrossRef\]](#)
7. Engeler D, Baranowski AP, Berghmans B, et al. EAU guidelines on chronic pelvic pain. In *EAU Guidelines Edn Presented at the EAU Annual Congress Milan, 2021*: 681-689.
8. Malde S, Palmisani S, Al-Kaisy A, et al. Guideline of guidelines: Bladder pain syndrome. *BJU Int*. 2018;122(5):729-743. [\[CrossRef\]](#)
9. Homma Y, Akiyama Y, Tomoe H, et al. Clinical guidelines for interstitial cystitis/bladder pain syndrome. *Int J Urol*. 2020;27(7):578-589. [\[CrossRef\]](#)
10. Fall M, Peeker R. Classic interstitial cystitis: Unrelated to BPS. *Curr Bladder Dysfunct Rep*. 2015;10:95-102. [\[CrossRef\]](#)
11. Ventura-Martínez R, Déciga-Campos M, Díaz-Reval MI, et al. Peripheral involvement of the nitric oxide-cGMP pathway in the indomethacin-induced antinociception in rat. *Eur J Pharmacol*. 2004;503(1-3):43-48. [\[CrossRef\]](#)
12. Thippeswamy T, McKay JS, Quinn JP, et al. Nitric oxide, a biological double-faced Janus—Is this good or bad? *Histol Histopathol*. 2006;21(4):445-458.
13. Paiva-Lima P, Bakhle YS, Francischi JN. Dual effects of rho-kinase inhibitors on a rat model of inflammatory pain. *Pain Res Manag*. 2014;19(6):e172-e178. [\[CrossRef\]](#)
14. Cury Y, Pico G, Gutierrez VP, et al. Pain and analgesia: The dual effect of nitric oxide in the nociceptive system. *Nitric Oxide*. 2011;25(3):243-254. [\[CrossRef\]](#)
15. Jain NK, Patil C, Singh A, et al. Sildenafil-induced peripheral analgesia and activation of the nitric oxide-cyclic GMP pathway. *Brain Res*. 2001;909(1-2):170-178. [\[CrossRef\]](#)
16. Chen H, Wang F, Chen W, et al. Efficacy of daily low-dose sildenafil for treating interstitial cystitis: Results of a randomized, double-blind, placebo-controlled trial—treatment of interstitial cystitis/painful bladder syndrome with low-dose sildenafil. *Urology*. 2014;84(1):51-56. [\[CrossRef\]](#)
17. Gupta M, Kovar A, Meibohm B. The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol*. 2005;45(9):987-1003. [\[CrossRef\]](#)
18. Gravas S, Cornu JN. MGCGRWHCMMRMJKAOTGAM-KIKSMVSRU EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) 2021.
19. McKernan LC, Walsh CG, Reynolds WS, et al. Psychosocial comorbidities in interstitial cystitis/bladder pain syndrome (IC/BPS): A systematic review. *Neurourol Urodyn*. 2018;37(3):926-941. [\[CrossRef\]](#)
20. Minagawa T, Aizawa N, Igawa Y, et al. Inhibitory effects of phosphodiesterase 5 inhibitor, tadalafil, on mechanosensitive bladder afferent nerve activities of the rat, and on acrolein-induced hyperactivity of these nerves. *BJU Int*. 2012;110(6b):E259-E266. [\[CrossRef\]](#)
21. Filippi S, Morelli A, Sandner P, et al. Characterization and functional role of androgen-dependent PDE5 activity in the bladder. *Endocrinology*. 2007;148(3):1019-1029. [\[CrossRef\]](#)
22. Oger S, Behr-Roussel D, Gorny D, et al. Signalling pathways involved in sildenafil-induced relaxation of human bladder dome smooth muscle. *Br J Pharmacol*. 2010;160(5):1135-1143. [\[CrossRef\]](#)
23. Fibbi B, Morelli A, Vignozzi L, et al. Characterization of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. *J Sex Med*. 2010;7(1):59-69. [\[CrossRef\]](#)
24. Morelli A, Filippi S, Sandner P, et al. Vardenafil modulates bladder contractility through cGMP-mediated inhibition of RhoA/rho kinase signaling pathway in spontaneously hypertensive rats. *J Sex Med*. 2009;6(6):1594-1608. [\[CrossRef\]](#)
25. Bittencourt JAF, Tano T, Gajar SA, et al. Relaxant effects of sildenafil on the human isolated bladder neck. *Urology*. 2009;73(2):427-430. [\[CrossRef\]](#)
26. Vasquez E, Gava A, Graceli J, et al. Novel therapeutic targets for phosphodiesterase 5 inhibitors: Current state-of-the-art on systemic arterial hypertension and atherosclerosis. *CPB*. 2016;17(4):347-364. [\[CrossRef\]](#)
27. Van Moh F, Vetter J, Lai HH. Comparison of urologic and non-urologic presentation in interstitial cystitis/bladder pain syndrome patients with and without Hunner lesions. *Neurourol Urodyn*. 2018;37(8):2911-2918. [\[CrossRef\]](#)
28. Killinger KA, Boura JA, Peters KM. Pain in interstitial cystitis/bladder pain syndrome: Do characteristics differ in ulcerative and non-ulcerative subtypes? *Int Urogynecol J*. 2013;24(8):1295-1301. [\[CrossRef\]](#)
29. Braunstein R, Shapiro E, Kaye J, et al. The role of cystoscopy in the diagnosis of Hunner's ulcer disease. *J Urol*. 2008;180(4):1383-1386. [\[CrossRef\]](#)
30. El Khoudary SR, Talbott EO, Bromberger JT, et al. Severity of interstitial cystitis symptoms and quality of life in female patients. *J Women's Heal*. 2009;18(9):1361-1368. [\[CrossRef\]](#)