Review

Pharmacological treatment of bladder stent symptoms

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Abstract

Background: Ureteric stenting is a ubiquitous procedure, but it is associated with symptoms that affect psychological well-being and quality of life. While many factors are linked to worse symptomatology, some innovative modifications to the stent's structure, as well as treatments, have been studied to reduce their clinical impact. Pharmacotherapy is a well-evaluated treatment modality derived from the treatment of lower urinary tract symptoms not related to stents. **Objective:** This review focuses on these pharmacological treatments. Several drug classes have been trialed to treat stent-related symptoms. Most of these studies investigated adrenoceptor modulators (both alpha-blockers and beta-3 agonists), muscarinic receptor antagonists, phosphodiesterase-5 inhibitors, as well as novel pharmacological modalities. Most trials and subsequent meta-analyses support treatment over placebo and controls, and some drugs are better at treating certain symptom domains, such as phosphodiesterase-5 inhibitors working on sexual issues. Furthermore, a combination therapy with alpha-blockers and muscarinic receptor antagonists appears to be superior to monotherapy with either of them. Treatments are also well tolerated. **Conclusion:** However, initiating pharmacotherapy should be part of a shared decision-making approach that balances the severity of symptoms and the duration the stents will remain *in situ* against potential side effects.

Keywords: Pharmacotherapy, Stent symptoms, Ureteric stent

1. INTRODUCTION

Ureteric stents are essential in maintaining ureteric patency in obstruction or following procedures of the upper urinary tract. However, stent-related symptoms (SRS), namely, lower urinary tract symptoms (LUTSs), hematuria, and loin pain are associated with impairments to psychological health and quality of life (QoL) [1]. Several factors contribute to worse symptomatology. Stent length and crossing the midline [2,3], as well as wider stent diameter, are linked to worse SRS [4]. Non-silicone polymer and "harder" stents elicit worse SRS compared to thier silicone ("soft") counterparts [5]. Different treatments have been considered, such as drug-eluting stents, for example, with the antimicrobial triclosan [6]. Their clinical utility beyond maintaining ureteric patency, however, remains to be seen. Another innovative solution is a suture stent, which has improved SRS compared to conventional stents, where a proximal coil bypasses the obstruction. The bladder contains only sutures to facilitate removal, which means there is no distal stent coil irritating the bladder [7]. Periureteric botulinum toxin A injection was associated with improvements in stent-related pain, but not LUTSs [8]. A comparison of intravesical oxybutynin, alkalinized lidocaine, or ketorolac versus saline solution (placebo) found that ketorolac, a non-steroidal anti-inflammatory, was associated with improvements in SRS compared to other solutions [9]. Intravesical glycosaminoglycans (GAGs) also elicited similar improvements in SRS in one trial [10]. Pharmacotherapy for SRS has been extensively investigated for its clinical utility, revealing several options that are translated from its use in the treatment of non-stent-related LUTS. This review examines the literature on the pharmacological treatment options for SRS.

2. THE LITERATURE ON PHARMACOLOGICAL MONOTHERAPY OF SRSs

2.1. Adrenergic receptor modulators (alpha-1 adrenoceptor antagonists)

Modulation of adrenergic receptors has been used in the treatment of LUTS due to their ubiquitous expression in

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the smooth muscle of the ureters down to the lower urinary tract [11], and thus, has been used to treat SRS. Alpha-1 receptors mediate bladder neck and urethral contraction, and thus, their blockade reduces urinary tract smooth muscle tone. These include tamsulosin, alfuzosin, doxazosin, terazosin, silodosin, and naftopidil, among others (Table 1).

Three trials, two of which were placebo-controlled [12,13], evaluated the effect of tamsulosin monotherapy on SRS [14]. The findings indicated statistically significant improvements in LUTS, pain, and QoL compared to controls. However, one placebo-controlled trial did not identify statistically significant differences in outcomes with tamsulosin treatment [15]. Similar findings were highlighted with trials on alfuzosin [16-18]. However, one of these trials did not identify differences in QoL with treatment [16]. Monotherapy with terazosin [19] and doxazosin [20] also elicited improvements in urinary and pain symptoms, but not with naftopidil [21]. Dellis *et al.* [22] compared tamsulosin and alfuzosin against controls in 150 patients, reporting statistically significant differences in the ureteral stent symptom questionnaire (USSQ; $P = 0.001$) and QoL measures with alpha-blockers versus placebo ($P = 0.28$); alfuzosin scores were better than those with tamsulosin. Meta-analyses favored alpha-blockers concerning LUTS, pain, and QoL [1,23-25]. However, there is conflicting evidence on their impact on sexual symptoms [24,25]. Liu *et al.* [26] have elucidated a pathophysiological mechanism for SRS and its treatment in their placebo-controlled trial with alfuzosin in 70 patients, where they also serially measured urinary GAGs over a 3-week treatment period and the 3 weeks after stent removal. There were statistically significant reductions in symptom and biochemical measures at all weekly time points ($P < 0.05$). Interestingly, urinary GAGs dropped to equivalent levels 3 weeks post-stent removal. Furthermore, GAG levels were strongly positively correlated with urinary symptoms ($R^2 = 0.65$; $P < 0.001$) and pain scores ($R^2 = 0.33$, $P < 0.001$). A commonly reported side effect (SE) is postural hypotension and related symptoms (Table 1).

2.2. Adrenergic receptor modulators (beta-3 adrenoceptor agonists)

Beta receptors are also important in bladder and urethral relaxation, particularly beta-2 and beta-3 subtypes. Mirabegron is the main beta-3 adrenoceptor agonist that has been trialed, particularly for bladder overactivity and SRS (Table 2). A retrospective case review [27], and two untreated control studies have found benefits with mirabegron [28,29], while only one trial did not identify any therapeutic benefit [28]. A meta-analysis of five studies on mirabegron for SRS concluded that low-quality studies point to symptomatic relief with treatment [30]. A meta-analysis on 546 patients aggregated from five trials evaluating mirabegron for SRS identified that it outperformed controls in eliciting symptom and QoL improvements [31]. Mirabegron was also associated with reduced adjunctive analgesia and hospital readmissions and was well-tolerated with no significant differences in SEs.

2.3. Muscarinic receptor antagonists

Anti-muscarinic drugs used for managing LUTS act by blocking cholinergic signaling at the M2 and M3 receptor subtypes and commonly include oxybutynin, solifenacin, tolterodine, and trospium. These drugs reduced bladder contractility and overactivity, making them viable treatments for SRS (Table 2). A case–control study of solifenacin 10 mg once daily (od) for SRS in 70 patients found significant improvements in all domains of the USSQ ($P < 0.05$) [32]. One trial compared solifenacin and trospium, with treatment eliciting significant improvements in USSQ scores compared to placebo ($P = 0.001$); solifenacin was superior to trospium in terms of urinary symptoms, while trospium yielded better results for pain relief [33]. Treatment with tolterodine for 1 month was associated with improvements in urinary symptoms and pain compared to placebo, but not with tamsulosin versus placebo or tolterodine versus tamsulosin in 125 patients [15]. Predictably, anticholinergic SEs were observed but were well tolerated.

2.4. Phosphodiesterase-type 5 (PDE5) inhibitors

PDE5 inhibitors (*e.g.*, sildenafil and tadalafil) are ubiquitously utilized for erectile dysfunction. They increase intracellular cyclic mononucleotides by preventing PDE5-mediated degradation, resulting in urinary tract smooth muscle relaxation, which may help treat SRS (Table 2) [34]. Treatment with sildenafil produced reductions in USSQ domains compared to the untreated controls ($P < 0.001$) [35]. A meta-analysis of 352 patients from four randomized controlled trial (RCTs) evaluating the effect of PDE5 inhibitors on SRS indicated that sildenafil and tadalafil were associated with improvements in the sexual health domain ($P < 0.00001$), urinary symptoms ($P = 0.03$), body pain ($P = 0.008$), and general health ($P < 0.0001$) [34]; the PDE5 inhibitor treatment was well-tolerated.

3. THE LITERATURE ON PHARMACOLOGICAL COMBINATION THERAPY OF SRSS

Combination therapies help identify which drugs may be more effective for SRS or specific SRS symptom domains (Table 3). A placebo-controlled trial comparing different treatments evaluated solifenacin, trospium, the antispasmodic hyoscine butyl bromide, and alfuzosin for 2 weeks in 200 patients [36]. There were significant differences in the USSQ urinary symptoms domain between

Table 1. Trials and meta-analyses on alpha-1 adrenoceptor antagonist pharmacotherapy for stent-related symptoms

Study	Trial characteristics	Efficacy	Side effects
Damiano *et al.* [14]	*n*=75 (38 on tamsulosin at 0.4 mg od for 2 weeks; 37 as controls)	Tamsulosin was associated with statistically significant improvements in USSQ, including urinary symptom and pain domains, other pain measures, and QoL at 4 weeks	
Wang *et al.* [12]	*n*=154 (75 on placebo; 79 on tamsulosin at 0.4 mg od for 2 weeks)	Statistically significant improvements in urinary symptoms on USSQ and IPSS, and voiding pain with tamsulosin at 4 weeks; more patients in the placebo group required adjunctive analgesia	
Wang *et al*. [13]	*n*=146 (71 on placebo; 75 on tamsulosin at 0.4 mg od for 2 weeks)	Tamsulosin was associated with lower IPSS and VASP scores compared to placebo at 2 weeks (P<0.0001)	Transient hypotension, asthenia, syncope, palpitations; no discontinuation
Deliveliotis *et al.* [16]	*n*=100 (50 on alfuzosin at 10 mg od for 4 weeks; 50 on placebo)	Statistically significant improvements in USSQ urinary symptoms, pain, and general and sexual health domains with alfuzosin treatment versus placebo at 4 weeks; there were no statistically significant differences in QoL scores between groups	Dizziness, headache, hypotension, and syncope; no discontinuation
Beddingfield *et al.* [17]	*n*=52 (26 on alfuzosin at 10 mg od; 26 on placebo)	Statistically significant improvements in urinary symptoms, flank pain, and QoL with alfuzosin treatment compared to placebo at 3 days; no differences in analgesic use	Orthostatic hypotension, upper respiratory tract infection, headache, and fatigue; no discontinuation
Nazim and Ather [18]	*n*=130 (65 on alfuzosin at 10 mg od; 65 on placebo)	Total USSQ (particularly the urinary symptom and QoL domains) were statistically significantly better with alfuzosin versus with placebo at week 1 (P<0.001); pain as reported on the VAS was also significantly lower with alfuzosin versus placebo	Postural hypotension with alfuzosin (*n*=5) versus placebo (*n*=2)
Liu *et al.* [26]	*n*=70 (35 on alfuzosin at 10 mg od for 3 weeks; 35 on placebo)	IPSS and VASP scores were significantly lower in the alfuzosin group versus placebo at weekly time points (P<0.05); urinary GAG was equivalently raised at baseline and post-stent insertion, sequentially reduced over a 3-week period with alfuzosin treatment versus placebo (P<0.05) and plateaued in the placebo group; GAG levels dropped to equivalent levels 3 weeks post-stent removal; GAG levels were strongly positively correlated with IPSS (R^2=0.65; P<0.001) and VASP scores (R^2=0.33; P<0.001)	
Mokhtari *et al.*[19]	*n*=73 (37 on terazosin at 2 mg od; 36 on placebo)	Terazosin produced statistically significant improvements in IPSS and VASP scores at 4 weeks (both P<0.001)	Headache, fatigue, and orthostatic dizziness; no discontinuation
Zhang *et al.* [20]	*n*=239 (112 on doxazosin at 4 mg od for 4 weeks; 107 on placebo)	Doxazosin was associated with statistically significant improvements in USSQ domains, QoL, and analgesic requirements versus placebo No differences after stent removal	Dizziness, and orthostatic hypotension in three patients, of whom, 2 discontinued treatment
Oh *et al.* [21]	*n*=100 (50 on placebo; 50 on naftopidil at 75 mg od for the duration of stenting)	No statistically significant differences in USSQ, IPSS, and analgesic requirement with naftopidil treatment versus placebo	
Dellis *et al.*[22]	*n*=150 (50 on tamsulosin at 0.4 mg for 4 weeks; 50 on alfuzosin 10 mg od; 50 as controls)	Statistically significant differences in USSQ (P=0.001) and QoL with treatment versus placebo (P=0.28); scores for both were better with alfuzosin than with tamsulosin	Treatment was well-tolerated and did not prompt discontinuation.
Lamb *et al.* [1]	Meta-analysis of *n*=461 patients from five trials evaluating tamsulosin and alfuzosin	Alpha-blockers (tamsulosin and alfuzosin) were associated with reductions in USSQ and pain scores versus placebo.	
Yakoubi *et al.* [23]	Meta-analysis of *n*=341 patients from four trials evaluating tamsulosin and alfuzosin	Statistically significant improvements in USSQ urinary, pain, and general health domains with alpha-blocker treatment versus controls	
He *et al.*[24]	Meta-analysis of *n*=1489 patients from 16 trials on tamsulosin, alfuzosin, doxazosin, and terazosin	Alpha-blocker treatment produced statistically significant improvements in the urinary symptoms, pain, general and sexual health domains of the USSQ, and QoL (all P<0.0001)	
Zhang *et al.* [25]	Meta-analysis of *n*=14 trials on tamsulosin, alfuzosin, doxazosin, and terazosin	Alpha-blocker treatment was associated with favorable outcomes on urinary tract symptoms, pain, and QoL, but not sexual health	Predominantly dizziness, headache, and hypotension

GAG: Glycosaminoglycans; IPSS: International prostate symptom score; od: Once daily; QoL: Quality of life; USSQ: Ureteral stent symptom questionnaire;VASP: Visual analog scale for pain; VAS: Visual analog scale.

Table 2. Trials and meta-analyses on mirabegron, muscarinic receptor antagonist, and phosphodiesterase-type 5 inhibitor pharmacotherapy for stent-related symptoms

Study	Trial characteristics	Efficacy	Side effects
Cinar *et al.* [27]	Retrospective case review of 145 patients treated with mirabegron 50 mg od for at least 3 weeks	Mirabegron was associated with improvements in all USSQ symptom domains and QoL (all $P<0.001$)	
Tae *et al.* [28]	n=96 (48 on mirabegron at 50 mg od; 48 as controls)	Statistically significant reductions in USSQ pain scores with mirabegron versus placebo (P=0.007); no difference in the USSQ urinary symptom domain	Gastrointestinal disturbance
Galal *et al.* [29]	n=210 (105 as controls; 105 on mirabegron at 50 mg od)	Statistically significant improvements in urinary symptoms, bodily pain, and QoL (all $P<0.05$); reduced analgesic use with mirabegron (P=0.005)	Constipation and dry mouth
Van Besien *et al.* [30]	Meta-analysis of five trials on mirabegron	Low-quality studies pointed to beneficial effects on stent symptoms with mirabegron.	
Li *et al.* [31]	Meta-analysis of 546 subjects from 5 trials on mirabegron	Mirabegron outperformed controls in eliciting improvements in urinary and general health domains of the USSQ and IPSS, as well as the QoL; mirabegron was also associated with reduced adjunctive analgesia and hospital readmission.	Well-tolerated; no differences in adverse events
Lee *et al.* [32]	Case–control study of 70 patients treated with solifenacin 10 mg od for 2 weeks; 70 as age-matched and sex-matched controls (patients)	Statistically significant improvements in all USSQ domains with solifenacin versus controls ($P<0.05$)	7.1% with solifenacin (retention in 1, dry mouth, and constipation); no discontinuation
Abdelhamid *et al.* [33]	n=210 (70 on solifenacin at 10 mg od for 2 weeks; 70 on trospium at 60 mg od; 70 on placebo)	Treatment was associated with statistically significant improvements in USSQ scores versus placebo (P=0.001); solifenacin was superior in terms of urinary symptoms; trospium superior in terms of pain symptoms.	Treatment was associated with constipation, dry mouth, and headache; no difference with either drug; no discontinuation
Tharwat *et al.* [35]	n=94 receiving stent post-procedure (46 as controls; 48 on sildenafil at 50 mg od for 2 weeks)	Improvement in all USSQ symptom domains with sildenafil treatment versus controls ($P<0.001$)	Dyspepsia, flushing, and rhinitis; no discontinuation
Zhang *et al.* [34]	Meta-analysis of 352 subjects from four trials on sildenafil and tadalafil	PDE5 inhibitors were associated with better improvements in sexual health ($P<0.00001$), urinary symptoms (P=0.03), body pain (P=0.008), and general health ($P<0.0001$)	Gastrointestinal and respiratory side effects

IPSS: International prostate symptom score; Od: Once daily; PDE5: Phosphodiesterase-type 5; QoL: Quality of life; USSQ: Ureteral stent symptom questionnaire; VASP: Visual analogue scale for pain.

groups, with trospium displaying superiority over other groups ($P < 0.01$). There was constipation in 46.7% of patients taking solifenacin and in 33.3% of patients on trospium versus other groups ($P = 0.048$). Dry mouth was a statistically significant SE with anti-muscarinic treatment ($P = 0.005$). Bhattar *et al.* [37] carried out a comprehensive placebo-controlled trial in 335 stented patients, investigating silodosin, solifenacin, and tadalafil monotherapies, as well as dual and triple therapies. All treatments were associated with statistically significant reductions in USSQ domains, QoL, and analgesic requirements compared to placebo (all $P < 0.001$). Silodosin and solifenacin in combination performed well across domains compared to other combinations. Chandna *et al.* [38] compared mirabegron, solifenacin, and tamsulosin in 150 patients, but no statistically significant differences were observed among groups. A large meta-analysis on alpha-blockers, antimuscarinics, and PDE5 inhibitors for SRS found that all treatments were associated with improvements in symptoms and QoL compared to placebo (Table 4) [39]. Alpha-blockers in combination with antimuscarinics were superior to monotherapy of either drug class. Treatments with PDE5 inhibitors were associated with improvements in sexual health domains, and, importantly, non-inferior in terms of other symptom domains and QoL. However, a controlled study examining the effects of multiple treatments (the non-steroidal anti-inflammatory diclofenac, the anti-spasmodic flavoxate, tolterodine, and doxazosin) in 108 stented patients found no effects [40]. All measures worsened following ureteric stenting, despite treatment.

3.1. Alpha-1 adrenoceptor antagonists versus other drug classes

Three trials compared tamsulosin 0.2 mg od to solifenacin monotherapy and combination therapy with controls and

Table 3. Trials on comparison and combination pharmacotherapy for stent-related symptoms

Study	Trial characteristics	Efficacy	Side effects
Norris *et al.* [65]	*n*=52 (18 on placebo; 19 on oxybutynin at 10 mg od; 15 on phenazopyridine at 200 mg od)	No statistically significant differences in urinary symptoms, pain scores, or adjunctive analgesia between treatment groups and placebo group at stent removal	
Lim *et al.* [41]	*n*=168 (48 serving as controls; 43 on tamsulosin at 0.2 mg; 45 on solifenacin at 5 mg od; 32 on tamsulosin + solifenacin)	Treatment was associated with significant improvements in IPSS, QoL, and VASP scores compared to controls after stent removal (P<0.001); combination therapy was associated with a greater magnitude of improvements, followed by solifenacin, and then tamsulosin monotherapy.	Minimal side effects; no discontinuation
Kuyumcuoglu *et al.* [40]	*n*=108 stent post-procedure (23 on diclofenac at 50 mg tds as prn; 22 on flavoxate at 200 mg tds prn; 21 on tolterodine at 4 mg od; 21 on doxazosin 4 mg od; 21 as controls)	No statistically significant differences were found between IPSS, QoL, and OABQ scores from pre-stent and at week 4 in all groups; all scores were higher (*i.e*., worse symptomatology and QoL) following ureteric stenting, despite treatment.	
Shalaby *et al.* [44]	*n*=338 stent post-procedure (84 as controls; 85 on tamsulosin at 0.4 mg od; 84 on solifenacin at10 mg od; 85 receiving tamsulosin + solifenacin)	Significant improvements were found in IPSS, QoL, and OABQ scores with treatment compared to placebo at week 2 (P<0.005); combination therapy was superior to tamsulosin and solifenacin monotherapy (P<0.001); solifenacin achieved better symptom control and tamsulosin better QoL	Treatment was well tolerated; no discontinuations
Tehranchi *et al.* [49]	*n*=104 (26 on placebo; 26 on terazosin at 2 mg bd; 26 on tolterodine at 2 mg od; 26 receiving terazosin + tolterodine)	Significant improvements were observed in IPSS across all treatment groups compared to placebo on stent removal; greater improvement was seen in the combination group, followed by terazosin and tolterodine (P=0.002); terazosin monotherapy was inferior to tolterodine monotherapy or combination therapy in terms of pain control; treatment was also associated with improved QoL (i.e., better QoL with combination therapy)	Postural hypotension (13.8%); headache and dry mouth across all groups; no side effect-related discontinuation
Aggarwal *et al.* [59]	*n*=161 (54 on tadalafil 5 mg od for 3 weeks; 53 on tamsulosin at 0.4 mg od; 54 taking placebo)	Treatment was associated with improvements in USSQ scores versus placebo; especially tadalafil yielded improvement in urinary symptoms, body pain, and sexual health domains, and reduced adjunctive analgesia versus tamsulosin.	No side effects resulting in discontinuation
Park *et al.* [43]	*n*=112 (28 as controls; 28 on tamsulosin at 0.2 mg for 2 weeks; 28 on solifenacin at 5 mg od; 28 given tamsulosin + solifenacin)	No statistically significant differences were seen in USSQ and QoL scores, and use of adjunctive analgesics use between treatment and control groups.	Discontinuation due to side effects in the tamsulosin and solifenacin groups (*n*=2), in the combination therapy group (*n*=1), and none in the control group
El-Nahas *et al.* [45]	*n*=149 (50 taking placebo; 50 on tamsulosin at 0.4 mg od for 2 weeks; 49 administered solifenacin at 5 mg od)	Significant improvement was observed in total USSQ scores with treatment versus placebo; solifenacin had better scores versus tamsulosin (P=0.001).	Discontinuation with tamsulosin (*n*=1), placebo (*n*=2), and none in the solifenacin group
Gangkak *et al.* [60]	*n*=240 (60 on placebo; 60 on diclofenac at 50 mg od; 60 on silodosin at 8 mg od; 60 on diclofenac + silodosin)	Significant reduction in VASP scores with treatment versus placebo (P<0.001); combination treatment superior over other groups, similar to diclofenac monotherapy, with silodosin inferior to both groups	
Hekal [36]	*n*=200 (40 on solifenacin 5 mg od for 2 weeks; 40 on trospium at 20 mg bd; 40 on hyoscine butylbromide at 10 mg od; 40 on alfuzosin 10 mg od; 40 on placebo)	Significant reduction in USSQ urinary symptoms domain; trospium superior to other groups in both frequency and urgency (both P<0.01), followed by solifenacin, hyoscine, and tamsulosin	Constipation (46.7% with solifenacin, 33.3% with trospium) versus other groups (P=0.048); dry mouth (33.3% with solifenacin, 20.0% with trospium)
Liu *et al.* [42]	*n*=100 (28 as controls; 26 receiving solifenacin 5 mg od for 2 weeks; 22 tamsulosin 0.2 mg od; 24 on combination use)	Treatment statistically significantly superior versus placebo, but non-inferior to each other by week 2 as measured by USSQ; effects more apparent in early stages of treatment with combination therapy	Dry mouth with solifenacin; dizziness with tamsulosin, both in combination; no discontinuation

(*Cont'd*...,)

Table 3. (*Continued*)

Study	Trial characteristics	Efficacy	Side effects
Maldonado-Avila *et al.* [47]	*n*=51 (17 on tamsulosin 0.4 mg od for 3 weeks; 17 on oxybutynin 5 mg od; 17 taking tamsulosin + oxybutynin)	Significant differences found between urinary symptoms ($P<0.001$) and sexual health with treatment ($P<0.036$), but not pain scores; combination therapy superior to oxybutynin, tamsulosin monotherapy in terms of urinary symptoms and sexual health	No side effects reported
Sivalingam *et al.* [48]	*n*=80 (44 on tamsulosin 0.4 mg od+tolterodine 4 mg od; 36 on tamsulosin + placebo)	Combination therapy did not yield significant improvements in urinary symptoms or pain compared to tamsulosin monotherapy, but tamsulosin was associated with better sexual health scores ($P=0.01$)	
Dellis *et al.* [46]	*n*=260 (80 on tamsulosin 0.4 mg od for 4 weeks; 80 receiving solifenacin 5 mg od; 20 on combination treatment; 80 on placebo)	Treatment superior to placebo in reducing USSQ scores ($P<0.001$); non-inferiority between treatment groups	Well-tolerated; no discontinuation
Moradi *et al.* [15]	*n*=125 (42 on placebo; 40 on tamsulosin at 0.4 mg for 4 weeks; 40 on tolterodine at 2 mg bd)	Improved urinary symptoms with treatment (both $P<0.001$); pain scores were better with tolterodine than with placebo ($P=0.027$), but not tamsulosin versus placebo nor tolterodine versus tamsulosin; no QoL improvements with either tolterodine or tamsulosin treatment	Discontinuation with tamsulosin due to side effects (asthenia; *n*=3)
Ragab *et al.* [67]	*n*=500 (125 administered solifenacin 5 mg od; 125 on pregabalin 75 mg bd; 125 receiving solifenacin + pregabalin; 125 as controls)	Treatment was associated with favorable changes in USSQ scores compared to placebo at day 15 (all $P<0.05$); combination therapy was superior in score reduction compared to solifenacin and pregabalin monotherapy ($P<0.05$); combination treatment had better outcomes with urinary symptoms compared to pregabalin and with bodily pain compared to solifenacin (all $P<0.05$).	Higher frequency of side effects in the combination group (dry mouth, flushing, somnolence, headache, drowsiness, and body pain) versus monotherapy and placebo groups
Bhattar *et al.* [37]	*n*=335 (43 on silodosin 8 mg od for 2 weeks; 43 on solifenacin 10 mg od; 42 on tadalafil 5 mg od; 40 on silodosin + solifenacin + tadalafil; 42 on silodosin + solifenacin; 41 on silodosin + tadalafil; 42 on solifenacin + tadalafil; 42 on placebo)	All treatment groups were associated with statistically significant reductions in USSQ domains, QoL, and analgesic requirements versus placebo; urinary symptom scores superior with silodosin + solifenacin, followed by triple therapy, silodosin, solifenacin, solifenacin + tadalafil, silodosin + tadalafil, and tadalafil; pain better controlled with silodosin + solifenacin, and subsequently silodosin, solifenacin, triple therapy, solifenacin + tadalafil, silodosin + tadalafil, and tadalafil; lower analgesic requirement with silodosin + solifenacin, superiority with triple therapy, solifenacin, silodosin + tadalafil, solifenacin + tadalafil, solifenacin, and tadalafil; sexual health better improved with triple therapy, tadalafil, silodosin + solifenacin, silodosin + tadalafil, solifenacin + tadalafil, silodosin, and solifenacin; QoL better with silodosin + solifenacin, followed by triple therapy, solifenacin, silodosin, silodosin + tadalafil, solifenacin+tadalafil, and tadalafil (all $P<0.001$)	
Hadibrata *et al.* [61]	*n*=80 (20 on placebo; 20 on diclofenac on 50 mg bd; 20 on tamsulosin 0.2 mg od; 20 on combination use)	Significant reduction in VASP scores at days 1 and 2 with treatment versus placebo ($P<0.05$); combination therapy superior to diclofenac, which in turn was superior to tamsulosin	
Falahatkar *et al.* [68]	*n*=256 (64 on pregabalin 75 mg bd for 4 weeks; 64 on solifenacin 5 mg od; 64 on pregabalin + solifenacin; 64 as controls)	Combination therapy associated with improvement in all USSQ domains ($P<0.0001$)	Tolerable side effects; no discontinuation
Jaworski *et al.* [63]	*n*=40 (21 on oxybutynin 5 mg od; 19 on mirabegron 50 mg od)	No statistically significant differences in USSQ domains between groups on days 3, 6, and 15	
Yavuz *et al.* [57]	*n*=161 (56 taking placebo; 55 on tamsulosin 0.4 mg od; 50 on mirabegron 50 mg od)	Treatment associated with urinary symptom domain scores than placebo at 4 weeks, with tamsulosin more so than mirabegron ($P=0.01$); less adjunctive analgesic requirement with treatment compared to controls, with mirabegron being slightly more superior than tamsulosin ($P<0.001$)	Discontinuation in the tamsulosin group, with hypotension and ejaculation disorders (*n*=2), and mirabegron group, with hypertension and flushing (*n*=2)
Chandna *et al.* [38]	*n*=150 (50 on mirabegron 50 mg od; 50 on solifenacin 5 mg od; 50 on tamsulosin 0.4 mg od)	No statistically significant intra-group differences were found in the USSQ urinary symptom domain at 4 weeks; solifenacin was associated with less bodily pain versus mirabegron and tamsulosin.	
Zhang *et al.* [58]	*n*=102 (51 on mirabegron 50 mg od; 51 on mirabegron + tamsulosin 0.4 mg od)	No difference in USSQ domains between mirabegron monotherapy and combination therapy with tamsulosin	
Narang *et al.* [69]	*n*=90 (45 on cannabidiol oil 20 mg od for 3 days; 45 serving as controls)	No difference in USSQ domains between cannabidiol oil and control groups	

bd: Twice daily; IPSS: International prostate symptom score; OABQ: Overactive bladder questionnaire; Od: Once daily; prn: *Pro re nata* (as required); QoL: Quality of life; tds: *Ter die sumendus* (three times a day); USSQ: Ureteral stent symptom questionnaire; VASP: Visual analog scale for pain.

Table 4. Meta-analyses on comparison and combination pharmacotherapy for stent-related symptoms

Study	Trial characteristics	Efficacy	Side effects
Zhou *et al.* [50]	1408 patients from 13 trials on alpha-blockers (tamsulosin, alfuzosin, doxazosin, terazosin), antimuscarinics, and in combination	Both alpha-blockers and antimuscarinics were associated with improvements in USSQ, IPSS, VASP, and QoL scores compared to placebo; combination therapy was superior to alpha-blocker monotherapy.	Well-tolerated treatments
Wang *et al.* [64]	1786 patients from 10 trials evaluating solifenacin alone or in combination with tamsulosin	Solifenacin monotherapy improved all USSQ urinary, pain, sexual, and hematuria symptoms, as well as general health domains; combination with tamsulosin did not have any beneficial effects compared to monotherapy.	Dry mouth associated with solifenacin treatment versus controls (P=0.02)
Yan *et al.* [51]	710 patients from seven trials on antimuscarinics alone (solifenacin 5–10 mg od; tolterodine 2 mg od) or in combination with alpha-blockers (tamsulosin 0.2–0.4 mg od; terazosin 2 mg od)	Improvements in IPSS and USSQ urinary symptoms scores were associated with combination therapy versus anti-muscarinic monotherapy (all P<0.01); anti-muscarinic monotherapy still elicited favorable changes in IPSS and USSQ domains versus controls (all P<0.01), but the magnitude was higher with combination therapy.	
Zhang *et al.* [52]	545 patients from seven trials on the combination of alpha-blockers (tamsulosin, terazosin) and antimuscarinics (tolterodine, solifenacin)	Combination therapy was superior to monotherapy with either in improving urinary symptoms as measured by the IPSS, but not USSQ or VASP.	
Chen *et al.* [54]	1087 patients from eight trials on tamsulosin 0.4 mg od monotherapy and in combination with antimuscarinics	Tamsulosin monotherapy was associated with mitigated urinary symptoms (P=0.0001) and bodily pain (P=0.0002), and improved sexual health compared to placebo (P=0.01); no significant differences were seen in symptoms compared to anti-muscarinic monotherapy or combination therapy.	
Deliveliotis *et al.* [55]	8 trials on alpha-blocker monotherapy (tamsulosin 0.4 mg od, alfuzosin 10 mg od, silodosin 8 mg od) and combination with antimuscarinics and PDE5 inhibitors	Statistically significant improvements in USSQ urinary symptom, bodily pain, and general and sexual health domain scores versus placebo with alpha-blockers; magnitude of improvements higher in early post-stenting period	Well-tolerated with no discontinuations
Gao *et al.* [56]	654 patients from nine trials on alpha-blocker and anti-muscarinic monotherapy	Alpha-blockers and antimuscarinics were non-inferior to each other in their ability to improve USSQ scores.	
Jian *et al.* [53]	2036 patients from 19 trials on alpha-blockers (tamsulosin, alfuzosin) and solifenacin	Tamsulosin and solifenacin combination therapy was superior in reducing USSQ scores versus solifenacin, followed by tamsulosin, alfuzosin, and controls	Tolerable side effects
Sharma *et al.*[66]	280 patients from three trials on PDE5 inhibitors (tadalafil, sildenafil), alpha-blockers, and antimuscarinics	PDE5 inhibitors were superior to placebo in USSQ score improvements; compared to both alpha-blockers and antimuscarinics, tadalafil was non-inferior in urinary symptoms and body pain effects, but superior in sexual health parameters	Well-tolerated
Pecoraro *et al.*[39]	2842 patients from 14 trials on alpha-blockers, antimuscarinics, and PDE inhibitors	All treatments were associated with improvements in symptoms and QoL versus placebo; combination of alpha-blockers and antimuscarinic therapy was superior to monotherapy of either; antimuscarinics were superior to alpha-blockers; PDE inhibitors were associated with sexual health domain improvements, and non-inferior in terms of the other symptom domains and QoL.	

IPSS: International prostate symptom score; Od: Once daily; PDE: Phosphodiesterase; QoL: Quality of life; USSQ: Ureteral stent symptom questionnaire; VASP: Visual analog scale for pain.

results were conflicting. Treatment was associated with statistically significant improvements in symptoms and QoL compared to controls [41,42]. Furthermore, Lim *et al.* [41] indicated that combination therapy was associated with a greater magnitude of improvements, followed by solifenacin and tamsulosin monotherapies; whereas Liu *et al.* [42] concluded its non-inferiority within the treatment groups. However, another trial found no differences in USSQ and QoL scores between treatment and control groups [43]. Trials looking at combination with a higher dose of tamsulosin (0.4 mg) were more positive, with combination therapy being associated with statistically significant improvements in outcome measures versus placebo [44-46]. Only one trial showed tamsulosin-solifenacin combination therapy was superior to monotherapy [44], with the others identifying non-inferiority. Mono- and combination therapy were

well tolerated, but one tamsulosin-related trial reported discontinuation [45]. An uncontrolled study observed improvements in urinary symptoms ($P < 0.001$) and sexual health ($P < 0.036$) but not in pain scores with tamsulosin and oxybutynin combination therapy compared with monotherapy of either drug [47]. One trial compared tamsulosin monotherapy with tolterodine combination therapy [48]. No statistically significant differences were revealed in outcome measures between the two groups, suggesting no added benefit with combination therapy. A comparison of terazosin 2 mg twice daily (bd) and tolterodine 2 mg od with combination therapy and placebo in 104 patients also identified statistically significant improvements in symptom and QoL measures with treatment, with a greater magnitude observed in the combination group ($P = 0.002$) [49]. Meta-analyses were equally conflicting with regard to conclusions on whether alpha-blockers are inferior to combination therapies. Several meta-analyses have concluded that alpha-blocker and anti-muscarinic combination therapy was superior to monotherapy in eliciting SRS and QoL benefits [50-53], but other meta-analyses found no difference [54,55]. However, all analyses agreed they are well-tolerated treatments. One meta-analysis of 654 patients found that alpha-blocker and anti-muscarinic monotherapy were non-inferior to each other in efficacy [56].

A head-to-head comparison of tamsulosin and mirabegron with placebo in 161 patients found lower symptom scores with treatment than with placebo, with tamsulosin reportedly superior to mirabegron ($P = 0.01$). In addition, mirabegron was associated with less adjunctive analgesic use compared to controls ($P < 0.001$) [57]. A similar study involving 102 patients found no difference in USSQ domains between mirabegron monotherapy and combination therapy with tamsulosin [58]. Comparing tamsulosin and tadalafil treatment revealed favorable outcomes in terms of USSQ scores versus placebo, but tamsulosin was inferior to tadalafil in reducing urinary symptoms, body pain, and sexual health scores [59]. Tadalafil was also associated with reduced analgesic requirement compared to tamsulosin. A comparison of silodosin and diclofenac monotherapy with combination therapy and placebo found that the treatments provided better pain control than placebo [60]. Diclofenac mono- and combination therapy had equivalent benefits, with silodosin inferior to both groups. A placebo-controlled trial observed similar findings when comparing diclofenac and tamsulosin with combination therapy [61].

3.2. Muscarinic receptor antagonists versus other drug classes

A randomized single-blinded study comparing mirabegron, solifenacin, and hydration (control group) in 97 patients found that mirabegron and solifenacin were associated with favorable changes in outcome measures with equivalent efficacy [62]. Patients were randomized to oxybutynin and mirabegron to receive treatments for SRS, but no statistically significant differences were found in USSQ scores, which improved over time regardless of treatment [63]. A meta-analysis of 10 trials evaluating solifenacin or combination with tamsulosin reported that solifenacin monotherapy attained improvements in all USSQ domains [64]. Combination with tamsulosin did confer additional benefits but was non-inferior to solifenacin monotherapy. Dry mouth was associated with solifenacin treatment compared to controls ($P = 0.02$). One trial compared oxybutynin with phenazopyridine, which has a local analgesic effect after being excreted into the urine [65]. No significant differences in outcomes were observed between groups.

3.3. Other drug classes

A meta-analysis of 280 patients aggregated from three RCTs evaluating PDE5 inhibitors on stent symptoms compared placebo, alpha-blockers, and antimuscarinics and found that they were superior to placebo in improving USSQ scores [66]. They were well tolerated, with tadalafil displaying superiority in sexual health and non-inferiority in other symptom domains.

Pregabalin is derived from the inhibitory neurotransmitter gamma-aminobutyric acid, which acts on certain calcium channels. It has been compared with solifenacin single and combined therapy in two trials [67,68]. Treatment was associated with statistically significant improvements in USSQ scores compared to placebo. Combination therapy was superior to monotherapy. A novel treatment, cannabidiol oil, has been investigated, but no benefits were observed compared to controls [69].

3. DISCUSSION

SRSs are associated with significant impairments of QoL. Thus, whilst different variations in stent makeup, including material, have been of clinical utility, as well as intravesical treatments and injections, pharmacotherapy remains the mainstay of SRS treatment (Table 5). The available trials consistently demonstrate the superiority of pharmacotherapy over placebo and controls for SRS. There are clear benefits in terms of urinary symptoms, pain, QoL, and even sexual function. However, the literature is less clear on which drug classes and individual drugs are superior. Mounting individual trials and meta-analyses have been conducted comparing alpha-blockers and anti-muscarinic monotherapy with combination therapy. More studies reported that the effects of combination therapy [39,41,44,50-53] were superior to those of the non-inferiority of monotherapy [46,54,56]. Indeed, some mechanisms have been suggested for the enhanced

Table 5. Action mechanisms of available pharmacotherapies for stent-related symptoms

Drugs	Dose	Mechanism
Alpha-1 adrenoceptor antagonists		
Tamsulosin	0.2–0.4 mg od	Alpha-1 adrenoceptor blockade that reduces smooth muscle tone in the urinary tract
Alfuzosin	10 mg od	
Terazosin	2–4 mg od	
Doxazosin	4 mg od	
Naftopidil	75 mg od	
Silodosin	8 mg od	
Beta-3 adrenoceptor agonist		
Mirabegron	50 mg od	Mediation of smooth muscle relaxation in the lower urinary tract
Muscarinic receptor antagonists		
Oxybutynin	5 mg od	Cholinergic blockade at M2 and M3 receptor subtypes promotes bladder relaxation and reduction of overactivity.
Solifenacin	5–10 mg od	
Tolterodine	2–4 mg od	
Trospium	40–60 mg od	
Hyoscine butylbromide	10 mg od	Anti-spasmodic action via muscarinic receptor blockade
Flavoxate	200 mg prn tds	
Phosphodiesterase-type 5 inhibitors		
Sildenafil		They increase intracellular cyclic mononucleotide by reducing breakdown by phosphodiesterase; promote urinary tract smooth muscle relaxation
Tadalafil		
Other drugs		
Pregabalin	75 mg bd	A gamma-aminobutyric acid derivative that acts on certain calcium channels
Phenazopyridine	200 mg od	It is excreted into the urine to exert a local analgesic effect.
Diclofenac	50 mg prn tds	Non-steroidal anti-inflammatory action
Cannabidiol oil	20 mg od	Anti-inflammatory and analgesic effects

bd: Twice daily; Od: Once daily; prn: *Pro re nata* (as required); tds: *Ter die sumendus* (three times a day).

effects of combination therapy. For instance, PDE5 inhibitor therapy may potentiate the effects of alpha-1 adrenoceptor blockade, further reducing smooth muscle contraction in the bladder and urethra [34]. A graded approach could involve initial monotherapy, with the option for combination therapy if clinical outcomes are suboptimal, guided by patient choice.

Trials comparing different treatments also point to the superiority of certain drugs and their combination use with regard to specific symptom domains. Bhattar *et al.* [37] compared different treatments and found that silodosin and solifenacin dual therapy controlled urinary symptoms and pain better than monotherapy with either drug, tadalafil monotherapy, triple therapy, and placebo. Two meta-analyses comparing PDE5 inhibitors with alpha-blockers and antimuscarinics demonstrated that sexual health outcomes were better with PDE5 inhibitor treatments and were non-inferior to other drugs used for urinary symptoms and pain [39,66]. This is especially important for sexually active patients, particularly those with longer-staying stents or who require long-term treatments.

Overall, treatments have been well-tolerated. A small number of trials reported statistically significant differences in SEs when treatment was compared to placebo. Constipation was quite common with the antimuscarinics solifenacin (46.7%) and trospium (33.3%, $P = 0.048$), with dry mouth appearing in 33.3% and 20.0% of patients, respectively ($P = 0.005$) [36]. Yavuz *et al.* [57] reported discontinuation in the tamsulosin group due to hypotension ($n = 2$), with other SEs including ejaculation disorders, as well as in the mirabegron group due to hypertension and flushing ($n = 2$). Whilst well-tolerated, some of these minor SEs arguably should not occur, especially given that some reports suggested that combination therapy may not provide additional clinical benefits [48,64].

A significant variability in the published trials and meta-analyses that aggregate them was the treatment and follow-up periods, with differences in the order of days to weeks and the lack of evidence from well-designed studies evaluating long-term treatments. This is important because trials with serial outcome measurements throughout the stented period and even after stent removal display differences in the magnitude of clinical effects, indicating greater improvement in the early stented period [41,55]. Thus, clinical effects may be missed with longer follow-up or overstated with early follow-up.

4. CONCLUSION

Ureteric stenting is a ubiquitous procedure in urology, but SRS can impact patient QoL and require treatment. There is consistent evidence that adrenergic receptor modulators (alpha-blockers, beta-3 agonists), antimuscarinics, PDE5 inhibitors, and some novel treatments improve SRS and QoL compared to placebo, with more evidence from trials on alpha-blockers and antimuscarinics. Furthermore, increasing evidence supports that combination therapy with these drugs is more beneficial compared to monotherapy, and certain

drug classes are more beneficial for different SRS domains. PDE5 inhibitors have positive effects on sexual health without compromising favorable outcomes related to urinary symptoms and pain domains. These treatments are also well tolerated. However, treatment decisions should be shared with the patient, balanced against the severity of symptoms, the duration of stent placement *in situ*, and potential SEs.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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