R E V I E W

# Evolving Role of Silodosin for the Treatment of Urological Disorders – A Narrative Review

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**Abstract:** Use of α-androgenic receptor blockers remains a mainstay therapeutic approach for the treatment of urological diseases. Silodosin is recommended over other α-blockers for the treatment of lower urinary tract symptoms (LUTS) and benign prostate hyperplasia (BPH), due to its high $\alpha_{1A}$ uroselectivity. Current research data suggest that silodosin is efficacious in the management of various urological diseases. Thus, we herein review the current evidence of silodosin related to its efficacy and tolerability and appraise the available literature that might ultimately aid in management of various urological conditions at routine clinical practice. Literature reveals that silodosin is beneficial in improving nocturia events related to LUTS/BPH. Silodosin exerts effect on relaxing muscles involved in detrusor obstruction, therefore prolonging the need for patients undergoing invasive surgery. Silodosin treatment, either as a monotherapy or combination, significantly improves International Prostate Symptom Score (IPSS) including both storage and voiding symptoms in patients with BPH/LUTS. Patients on other treatment therapies such as phosphodiesterase 5 inhibitors or other α-blockers are well managed with this drug. Steadily, silodosin has proved beneficial in the treatment of other urological disorders such as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), overactive bladder/acute urinary retention (AUR), premature ejaculation (PE), and prostate cancer post brachytherapy-induced progression. In patients with distal ureteral stones, silodosin treatment is beneficial in decreasing stone expulsion time without affecting stone expulsion rate or analgesic need. Moreover, there were significant improvements in intravaginal ejaculation latency time, quality of life scores, and decrease in PE profile among patients with PE. Silodosin has also demonstrated promising results in increasing the likelihood of successful trial without catheter in patients with AUR and those taking antihypertensive drugs. Reports from Phase II studies have shown promising role of silodosin in the treatment of CP/CPPS as well as facilitating ureteral stone passage. From the robust data in this review, further silodosin treatment strategies in the management of different urological conditions need to be focused on.

**Keywords:** efficacy, benign prostate hyperplasia, ureteral calculi, prostatitis, silodosin, urological

## Introduction

The field of urology encompasses disorders of the urinary tract and the genital system, both benign and malignant.[1] Most men and women with urological disorders hugely suffer from a decreased quality of life (QoL) ultimately leading to economic burden.[2,3] Urological disorders include urinary tract infections (UTIs), kidney stones, problems with bladder control and prostate, among others.[4] While a few urological conditions prevail for a shorter period, others are long-lasting.[4] With age, men in particular, experience urinary changes, which may be caused by inflammation or enlargement of the prostate gland.[5]

A typical bacterial infection acquired in the community and hospital settings is a UTI.[6] Lower urinary tract symptoms (LUTS) are accompanied along with many other disorders such as acute urinary retention (AUR), bladder outlet obstruction (BOO), benign prostatic hyperplasia (BPH), ureteral calculi, chronic pelvic pain syndrome (CPPS), overactive bladder (OAB). The pathologies of each urological disorder are different, and there is still much progress to be made in available therapeutic options in order to minimize adverse events (AEs) and provide effective care.[1] The conservative approach to

treatment remains watchful waiting (WW), behavioral and dietary modifications till date. When conservative treatment fails to cure the disease, medical therapy with either $\alpha_1$-adrenoceptor antagonists ($\alpha_1$-blockers), 5α-reductase inhibitors, muscarinic receptor antagonists, phosphodiesterase 5 (PDE5) inhibitors, phytotherapy or β-3 agonist in monotherapy or in combination is preferred. In an era of an increasing array of treatment options, it has become of utmost clinical importance to refine therapeutic strategies in order to optimize efficacy while limiting systemic toxicity.[1] Urological treatment often carries a high rate of undesirable AEs leading to greater rates of patient noncompliance.[1]

The American Urological Association (AUA) and European Association of Urology (EAU) guidelines state that, $\alpha_1$-blockers are the preferred treatment modality for patients with moderate/severe LUTS, BPH/LUTS, ureteral calculi, CPPS, OAB, and so on. α1-androgenic receptors (ARs) are highly concentrated along the urinary tract, bladder, and prostate.[7] Typically, the $\alpha_{1B}$-receptors are found in vascular tissue, where they mediate arterial contraction, whereas $\alpha_{1A}$ and $\alpha_{1D}$ are more specific in the lower urinary tract. In general, $\alpha_1$-blockers focus on reducing the smooth muscle tone in the prostate and bladder neck by inhibiting the action of endogenously released noradrenaline on smooth muscle cells in the prostate.[8] The smooth muscle tension within the prostate and bladder neck was found to be relieved, after 2 weeks of administration of $\alpha_1$-blockers.[8] Previously published studies have established that $\alpha_1$-blockers reduce the International Prostate Symptom Score (IPSS) by 30–40% and increase maximum urinary flow rate ($Q_{max}$) by 20–25%.[9] The most common AEs include dizziness, orthostatic hypotension, ejaculatory dysfunction (EjD), and asthenia. Treatment with doxazosin and terazosin increases vasodilating effects which are less pronounced with tamsulosin and alfuzosin. Similarly, it seemed that EjD was more frequent with tamsulosin or silodosin whereas it was less with doxazosin and terazosin. Based on such promising results, EAU has suggested the use of $\alpha_1$-blockers as the first-line treatment for LUTS since these agents do not prevent urinary retention or need for surgery.[9]

The first selective α-blocker, prazosin, was useful in lowering blood pressure.[10] The efficacy and tolerability of prazosin have been proved by several trials.[11,12] But, prazosin required multiple daily dosing and was associated with orthostatic hypotension. Terazosin was the first long-acting $\alpha_1$-AR blocker, which had an elimination half-life two to three times that of prazosin.[13] Early clinical studies confirmed significant improvements in IPSS symptoms and flow rate in patients with LUTS.[14–16] Doxazosin was first approved by the US Food and Drug Administration (FDA) for the treatment of symptomatic BPH based on 2 clinical trials[17,18] and later, was approved for the treatment of BPH, due to its selectivity for subtype of $\alpha_1$-antagonist.[19,20] Tamsulosin is known to achieve a therapeutic effect without dose titration and with minimal effects on blood pressure; however, EjD was a common side effect observed. Thus, alfuzosin was developed as a fourth-generation $\alpha_1$-blocker and approved by FDA based on 2 randomized clinical trials (RCTs).[21,22] Alfuzosin 10 mg has proven to be clinically significant in LUTS without dose titration and showed comparable efficacy to tamsulosin without causing EjD.[23] It has been a goal to create a therapeutic drug that suppresses the urethral contractions while reducing hypotension, including postural hypotension, in patients with BPH-related LUTS. The use of drugs that selectively antagonize the $\alpha_{1A}$-adrenergic receptor can reduce this effect. During the 1990s, Shibata et al[24] discovered that the investigational drug silodosin had approximately 10-fold higher affinity at the cloned human alpha $\alpha_1$-AR than at the cloned rat alpha $\alpha_1$-AR. Subsequently, silodosin was developed in the treatment of BPH/LUTS. In this review, we aim to summarize the current evidence of silodosin, to appraise the available literature with respect to the efficacy and tolerability due to its uroselectivity, which may ultimately aid in the management of different urological conditions at routine clinical practices.

## Methods

We performed a literature search on PubMed and Embase for articles published preferably in English as well as from other languages and were extrapolated if relevant from inception till June 2021, focusing on articles related to efficacy, safety, and tolerability of silodosin either in monotherapy or in combination with other therapies for urological disorders. We included the Medical Subject Headings (MeSH) terms "silodosin", "alpha-blockers", "alpha-adrenoreceptor antagonists", "lower urinary tract symptoms", "LUTS", "Benign prostate hyperplasia", "chronic pelvic pain syndrome", "chronic prostatitis", "ureteral calculi", "ureteral stone/s", "prostate cancer", "urinary incontinence", "premature ejaculation", "pathophysiology", "symptoms", "overactive bladder". We excluded publications if no clinical comparative information about efficacy/safety/tolerability of silodosin were reported.

## Evolution of Silodosin for Treatment of Urological Disorders

Silodosin, is the most selective antagonist of the $\alpha_{1A}$-adrenoreceptors (ARs) family. Silodosin was approved first in Japan in 2006, and later received approval in the USA[25] and Europe.[26,27] Receptor-binding studies were conducted to study the effect of silodosin and other $\alpha_1$-AR antagonists on the increase in intraurethral pressure (IUP) induced by phenylephrine, as well as blood pressure (BP), in anesthetized rats.[28] In this study, all drugs inhibited the increase in IUP and decreased BP, but silodosin, in particular, demonstrated higher uroselectivity followed by tamsulosin, naftopidil in both intravenous and intraduodenal administration. These findings suggested that silodosin, an $\alpha_{1A}$-AR selective antagonist might be useful in the LUTS without causing hypotension.[28] An early randomized, placebo-controlled trial in Japan showed a greater reduction in IPSS with silodosin after 12 weeks of treatment compared to both tamsulosin and placebo. This clinical benefit in IPSS was observed from the first week of therapy. Compared with tamsulosin, silodosin selectivity was 38 times higher toward $\alpha_{1A}$-receptor blockade.[29] Multiple in vivo studies and those using cloned human subtypes have underscored varying degrees of uroselectivity of silodosin for $\alpha_{1A}$-ARs compared with both $\alpha_{1B}$ or $\alpha_{1D}$ ARs. In humans, $\alpha_{1A}$-ARs are located in the prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra and mediate smooth muscle contraction in these tissues.[30] Thus, blocking $\alpha_{1A}$-ARs is the first line of action in the treatment of LUTS and other associated urological disorders.

## Pharmacokinetic-Pharmacodynamic Features

Silodosin exerts its effect by blocking $\alpha_{1A}$-ARs, which prevents the binding of the neurotransmitter epinephrine, thus relaxing bladder and prostate smooth muscle, alleviating urinary flow.[31] Silodosin has low affinity for $\alpha1B$-ARs. An in vitro receptor binding study showed that the affinity of silodosin for human prostate tissue was ≈200-fold higher than for the mesenteric human aorta tissue and 100-fold higher for human mesenteric artery tissue.[32] Preclinical studies have investigated the effect of silodosin on bladder and prostate function. Goi et al observed that after 8 weeks of treatment, silodosin was able to suppress the chronic bladder ischemia decrease in empty bladder, reduced signs of bladder overactivity in spontaneously hypertensive male rats.[33] Similarly in a male rat model for BOO, silodosin-treated rats had small numbers of non-voiding contractions and a lower single unit afferent activities compared with control group rats.[34] A competition-binding assay on human embryonic kidney showed that silodosin and tamsulosin had higher affinity for $\alpha_{1A}$-AR, but had Ki ratios of 25.3 and 50.2 for the $\alpha_{1D}$ and $\alpha_{1B}$-AR, respectively, compared with 2.92 and 5.1 for tamsulosin.[35]

The absolute bioavailability of silodosin is ≈32% and follows linear pharmacokinetics over a dose range 0.1 to 24 mg/day. The drug has a volume distribution of 49.5 L and is ≈97% protein bound. It is extensively metabolized by UDP-glucoronosyltransferase-2B7 (UGT2B7), alcohol and aldehyde dehydrogenase, and cytochrome P450 3A4. It is excreted primarily in urine (≈34%) and feces (≈55%), with a half-life ($t_{1/2}$) of approximately 13 hours.[26,36] Administration of silodosin with food decreased maximum concentration ($C_{max}$) by 18–43% and area under curve (AUC) by 4–49%.[36] The pharmacokinetic profile of silodosin and its metabolites were similar in geriatric populations. In addition, unbound exposure to total silodosin resulted in a 1.6-fold increase of $C_{max}$ and 1.7-fold AUC relative to normal renal controls.[26] These changes were greater on exposure of total (unbound + bound) silodosin with AUC, $C_{max}$, and elimination $t_{1/2}$, which were 3.2-, 3.1-, and 2-fold higher compared with patients with normal renal function.[36] In case of severe renal impaired function, unbound silodosin $C_{max}$, and AUC values were 2.2 and 3.7-fold higher than normal renal function patients.[26] No dose adjustment is required for patients with mild renal impairment whereas an initial dose of 4 mg/day is advised for patients with moderate renal impairment.[26,36]

Silodosin has been associated with low rate of serum aminotransferase elevations (<2%); however, these effects are transient and do not require dose modification.[37] The instances of acute symptomatic liver injury due to silodosin has been rarely reported in literature.[38] In addition, the cause of hepatotoxicity remains to be elucidated. It is speculated that partial metabolism of silodosin by the cytochrome P450 enzymes of the liver (predominantly CYP 3A4) results in generation of a mildly toxic intermediate.[37]

## Mechanism of Action

The $\alpha_{1A}$-ARs belongs to the family of G protein-coupled receptors. Phospholipase C is activated by the binding of norepinephrine and epinephrine, which results in the production of second messengers such as inositol triphosphate and diacylglycerol. Finally, they cause smooth muscle contraction and intracellular calcium level rises.[39] Blocking $\alpha_{1A}$-ARs causes prostatic and urethral smooth muscle to relax, which may alleviate voiding symptoms. Silodosin, however, also acts on symptoms of bladder overactivity and storage by targeting afferent nerves in the bladder.[40]

## Potential Drug Interactions

Numerous studies have been conducted to understand putative interactions of silodosin with other drugs. Co-administration of silodosin with a diltiazem, a CYP3A4 inhibitor, increases AUC of silodosin by ~30%, without any dose adjustment and without affecting $C_{max}$ and $t_{1/2}$.[26] The use of silodosin is discouraged in patients taking cyclosporine, as it increases the concentration of drug. Co-administration of digoxin with silodosin is safe and no dose adjustment is required.[26,36] Similarly, the administration of antihypertensive drugs with silodosin causes no clinically significant orthostatic effects and is considered safe. Higher but insignificant orthostatic hypotension was observed on concomitant administration of tadalafil with silodosin in healthy men. The co-administration of sildenafil or both tadalafil and silodosin may be an appropriate treatment for patients who experience EjD. Therefore, its concomitant treatment with PDE5 inhibitors needs to be closely monitored, particular in patients with symptomatic hypotension.[41]

## Benign Prostate Hyperplasia/Lower Urinary Tract Symptoms

Lower urinary tract symptoms (LUTS) are very common disorders affecting both the sexes, especially in aged population and adversely affecting the QoL of affected individuals. LUTS have been historically linked to BPH and its symptoms include storage, voiding, and post-micturition.[42] Several large epidemiological studies have been conducted to evaluate the prevalence and inconvenience of LUTS in population-based analysis,[43,44] with over 60% of men and women affected by LUTS. The probability of developing moderate-to-severe LUTS were higher post 50 years of age with 3.5 times more frequent in men with a prostate volume ≥50 mL and 2.4 times more in those with prostate volume <50 mL.[45] LUTS are associated with OAB syndrome as well as AUR. The prevalence of BPH is strongly related to age, present in about 50% of men between 51 and 60 years old, and it reaches 90% over 80 years.[4] Furthermore, LUTS are linked to greater problems such as AUR, with 6.8 episodes per 1000 patients per year in the general population, and 34.7 episodes in patients aged more than 70 years.[45]

### Silodosin Monotherapy

A pooled analysis of 2 RCTs (n = 923) revealed significant and rapid recovery in patients treated with silodosin in terms of IPSS score (−4.2 ± 5.3 vs −2.3 ± 4.4; $P<0.0001$) and $Q_{max}$ (2.8 ± 3.4 vs 1.5 ± 3.8) compared with placebo. Within 3 to 4 days of commencing treatment, patients receiving silodosin achieved significant improvement in total IPSS score (difference −1.9, $P<0.0001$), as well as irritative (−0.5, $P = 0.0002$) and obstructive (−1.4, $P<0.0001$) sub scores. Significant improvement in urinary flow rate occurred at 2–6 hours. The proportion of orthostatic hypotension was similar in both groups (2.6% vs 1.5%).[46] An extended follow-up study (n = 661) in the same patient population for 40 weeks reconfirmed the efficacy of the drug and also suggested that the risk of orthostatic hypotension is unlikely to increase with increasing duration of therapy.[47] Yamanishi et al reported mean improvement in total IPSS, voiding IPSS sub score, storage IPSS sub score, and QoL sub score of 7.9, 3.8, 2.0, and 1.1 points, respectively, over a year on treatment with silodosin in at least 44% of patients with LUTS. Also, the BOO index and detrusor opening (DO) pressure significantly reduced within 3 months after receiving treatment. This highlights that silodosin has a significant effect on DO and obstruction grades, making them less likely to undergo invasive surgery and manage the condition safely for at least 1 year.[48] These results were in agreement with another study conducted in Japan.[49] Similarly, in this study the silodosin mean detrusor pressure at maximum flow was decreased from 72.5 mm to 51.4 mm and BOO index reduced significantly from 60.6 to 33.8 in patients with benign prostatic obstruction (BPO). Thus the mean improvements in total IPSS, voiding IPSS sub score, storage IPSS sub score, and QoL sub score were 6.2, 3.6, 2.6, and 1.6 points, respectively.[49] However, Fusco et al reported 10.7, 4.0, 6.7, and 3.0 points of mean improvements in total IPSS, voiding

IPSS sub score, storage IPSS sub score, and QoL sub scores, respectively with silodosin at 8 weeks of treatment. The authors speculated that these lower rates might be due to differences in the baseline characteristics of patients. It is hypothesized that the subjects with a moderate-to-high compromised baseline level might have a greater margin of improvement compared with subjects that are less compromised at baseline, however, further studies are needed.[50] Chapple et al provided evidence that silodosin can be used for the treatment of both storage and voiding LUTS associated with BPH. Here the change from baseline in the IPSS total score with silodosin (difference, −2.3, 95% confidence interval [CI], −3.2, −1.4) and tamsulosin (difference, −2.0; 95% CI: −2.9, −1.1) was significantly superior to that with placebo (P < 0.001); number of responders with total IPSS were significantly higher (P < 0.001) with silodosin (66.8%) and tamsulosin (65.4%) than with placebo (50.8%) after 12 weeks of treatment. In addition, only silodosin significantly reduced nocturia versus placebo along with improved $Q_{max}$ and QoL. The authors particularly emphasized that silodosin might be more helpful in elderly patients where there is a high risk for drug-drug interactions and greater risk of cardiovascular (CV) side effects.[51] The SiRe study, a Phase IV trial in elderly population, investigated the benefit-risk balance of silodosin in the real-world setting. About 77.1% had ≥25% decrease in IPSS score, and nocturia decreased from 85.7% to 52.4% after 24 weeks of treatment. Overall, 74.2% patients were satisfied with silodosin.[52] In a post hoc analysis of 2 Phase III trials, patients were treated with 8-mg silodosin once daily or placebo. Those treated with silodosin were stratified into two groups, namely, by absence or presence of retrograde ejaculation (RE). Irrespective of ejaculatory status, patients receiving silodosin experienced significant improvement in IPSS (*P*<0.0001), $Q_{max}$ (*P*<0.02), and QoL (*P*<0.0001). RE (+) patients experienced numerically greater improvement in voiding symptoms compared with RE (−) patients, though not statistically significant (*P*>0.05). Further interesting observation was noticed in this study. Patients with RE (+) receiving silodosin achieved more improvement of at least 30% in IPSS points and $Q_{max}$ than in placebo and RE (−) with silodosin-treated groups (27.5% vs 9.2% vs 20.9%). Similarly, total IPSS improved by ≥3 points and $Q_{max}$ by ≥3 mL/sec in RE (+) and with silodosin-treated groups (34.4% vs 12.9% vs 23.0%). The odds of achieving improvement of ≥3 points in IPSS and ≥3 mL/sec in $Q_{max}$ over 12 weeks were 1.75 times than those for RE (−) patients (P = 0.0127). These observations suggest that the absence of seminal emission in silodosin-treated patients may predict greater treatment efficacy. Having said that, the biological basis for differences in treatment response among individual patients remains to be elucidated.[53] Table 1 describes the summary of the included studies.

## Silodosin Combination Therapy

The co-administration of silodosin with sildenafil or tadalafil was clinically significant in the treatment of BPH in healthy men with no history of symptomatic hypertension. The number of post-dose positive orthostatic tests was similar for all treatments (sildenafil with silodosin: 57/154; tadalafil with silodosin: 59/154; placebo: 53/154). In comparison with placebo, sildenafil or tadalafil was able to reduce the blood pressure significantly in smaller levels, however, there were no significant orthostatic changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), or heart rate (HR; *P* > 0.05).[41] A recent study showed that patients treated with silodosin and dutasteride combination demonstrated similar efficacy to those who switched from silodosin to dutasteride monotherapy after 12 months of therapy. Both the groups showed significant improvements in the subjective and objective symptoms of urodynamics. However, 38.3% patients who continued with dutasteride after silodosin withdrawal reported worsening of IPSS, as well as BOO index and storage function especially in those with higher body mass index (BMI). The mechanism behind this phenomenon remains unknown. However, it has been postulated earlier that patients with higher BMI achieved greater clinical efficacy with $\alpha_1$-blocker, and the withdrawal of the same resulted in more adverse effects. These indicate that caution needs to be exerted while deciding switch in medical treatment course for patients with LUTS/BPH.[54] A total of 103 patients with LUTS/BPH and IPSS >8 after ≥4 weeks of silodosin treatment were further treated with silodosin 4 mg twice daily (BID) or silodosin 4 mg BID plus tadalafil 5 mg once daily (QD). After 8 weeks of treatment, the analysis revealed that the IPSS, OAB symptom score (OABSS), and $Q_{max}$ scores showed a greater improvement in the silodosin plus tadalafil combination therapy than monotherapy group (−3.92 vs −1.24, −1.18 vs 0.10, and 1.09 vs −1.04, respectively; all *P*<0.05). Further subgroup analysis in patients with overactive bladder (n = 55) also showed significantly greater improvements in the IPSS storage symptom sub score, IPSS urgency sub score, and OABSS urgency sub score in the combination therapy than monotherapy group (−2.23 vs 0.17, −0.88 vs 0.28, and −1.5 vs −0.48, respectively; all *P*<0.05).[55]

**Table 1** Summary of Included Studies for Patients with LUTS/BPH/Voiding Symptom/Nocturia

| Study Name | Sample Size | Study Period | Intervention | Comparator | Significant Outcomes |
|---|---|---|---|---|---|
| Patient with BPH/LUTS | | | | | |
| Marks et al 2009[46] | 923 | 12 weeks | • Silodosin 8 mg QID (n = 466) | • Placebo (n = 457) | • Mean total IPSS: −4.2 ± 5.3 vs −2.3 ± 4.4; $P$ <0.0001<br>• Mean peak urinary flow rate: 2.8 ± 3.4 vs 1.5 ± 3.8; $P$<0.0001 |
| Marks et al 2009[47] | 661 | 40 weeks | • De novo silodosin (n = 347) | • Silodosin (n = 314) | • Mean total IPSS: −4.5 ± 6.7 vs −1.6 ± 6.0<br>• Mean IPSS irritative sub score: −1.7 ± 3.2 vs −0.6 ± 2.8<br>• Mean IPSS obstructive sub score: −2.8 ± 4.2 ± −1.0 ± 3.9 |
| Yamanishi et al 2010[48] | 36 | 12 months | • Silodosin (n = 36) | - | • Mean total IPSS: 13.7 ± 7.7; $P$<0.05<br>• Mean total storage sub score: 5.3 ± 3.6<br>• Mean total voiding sub score: 7.0 ± 4.1<br>• Mean QoL score: 3.5 ± 1.2; $P$<0.05<br>• Mean post-micturition score: 1.5 ± 1.6; $P$<0.05<br>• Mean maximal flow rate: 10.5 ± 5.4; $P$<0.001<br>• Mean post-void volume: 64.0 ± 47.8; $P$<0.01 |
| Matsukawa et al 2013[49] | 57 | 4 weeks | • Silodosin 8 mg QID (n = 57) | - | • Mean total IPSS: 12.0 ± 6.1 vs 18.2 ± 6.4; $P$<0.0001<br>• Mean total IPSS QoL: 3.3 ± 0.8 vs 4.8 ± 0.8; $P$<0.0001<br>• Mean $Q_{max}$: 11.5 ± 4.7 vs 8.4 ± 3.8; $P$ = 0.0007<br>• Mean BOOI: 33.8 ± 20.4 vs 60.6 ± 28.9; $P$<0.0001<br>(Results are 4 weeks vs baseline) |
| Fusco et al 2018[50] | 34 | 8 weeks | • Silodosin 8 mg QID (N = 34) | - | • Mean DO: 2 ± 6.7 vs 4 ± 13.3; $P$ = 0.3173<br>• Mean $P_{det}$ $Q_{max}$: 58.2 ± 17.3 vs 86.1 ± 19.7; $P$<0.0001<br>• Mean $Q_{max}$: 9.5 ± 3.8 vs 7.8 ± 3.1; $P$ = 0.015<br>• Mean BOOI: 39.2 ± 18.3 vs 70.6 ± 18.9; $P$<0.0001<br>• Mean PVR volume: 52.5 ± 23.2 vs 71.1 ± 33.1; $P$<0.0001<br>(Results are 8 weeks vs baseline) |
| Chapple et al 2011[51] | 932 | 12 weeks | • Silodosin 8 mg daily (n = 371)<br>• Tamsulosin 0.4 mg (n = 376) | • Placebo (n = 185) | • Mean difference in total IPSS from baseline: −7.0 vs −6.7 vs −4.7<br>• Baseline change in the IPSS total score: silodosin (−2.3; 95% CI: −3.2, −1.4) and tamsulosin (−2.0; 95% CI: −2.9, −1.1)<br>• Baseline change in nocturia: −0.9, −0.8, and −0.7 for silodosin, tamsulosin, and placebo, respectively (silodosin vs placebo; $P$ = 0.013; tamsulosin vs placebo; $P$ = 0.314 for).<br>• Baseline change in $Q_{max}$: 3.77 P>, 3.53 P>, 2.93 P> (silodosin vs placebo: $P$ = 0.089; tamsulosin vs placebo: $P$ = 0.221) |

| Montorsi et al 2016[52] | 994 | 24 weeks | • Silodosin 8 mg QID | - | • Mean total IPSS: 12.4 ± 5.7 vs 18.9 ± 4.9<br>• Mean IPSS storage score: 5.6 (2.7) vs 8.1 ± 2.7<br>• Mean IPSS voiding score: 6.8 (3.8) vs 10.8 (3.6)<br>• Mean QoL score: 2.8 (1.3) vs 4.0 (1.2)<br>(Results are 4 weeks vs baseline) |
|---|---|---|---|---|---|
| MacDiarmid et al 2010[41] | 22 | 21 days | • Silodosin 8 mg plus sildenafil 100 mg<br>• Silodosin plus tadalafil 20 mg | • Placebo | • Number of positive 1-minute orthostatic test: 34/154 vs 35/154 vs 34/154 for sildenafil, tadalafil, and placebo<br>• Number of positive 3-minute orthostatic test: 23/154 vs 24/154 vs 19/154 for sildenafil, tadalafil, and placebo |
| Matsukawa et al 2017[54] | 132 | 24 months | • Silodosin with dutasteride (n = 57) | • Dutasteride (n = 60) | • Mean change in IPSS: 177 ± 64 vs 173 ± 61; $P<0.001$<br>• $Q_{max}$: 10.0 ± 3.2 vs 9.9 ± 3.8; $P = 0.02$<br>• $P_{det}Q_{max}$: 61.8 ± 16.2 vs 59.7 ± 18.4; $P<0.001$<br>• BOOI: 41.8 ± 20.4 vs 39.9 ± 21.4; $P<0.001$<br>• Disappearing rate of DO: 46.4% vs 39.4%; $P = 0.01$ |
| Yoshida et al 2017[55] | 101 | 8 weeks | • Silodosin 4 mg BID with tadalafil 5 mg QID (n = 50) | • Silodosin 4 mg BID (n = 51) | • Mean IPSS voiding symptom sub score: 7.64 ± 5.13 vs 7.63 ± 4.69; $P = 0.231$<br>• Mean IPSS storage symptom sub score: 5.30 ± 3.33 vs 6.47 ± 3.18<br>• Mean change in total IPSS: −3.92 vs −1.24; $P = 0.028$<br>• Mean change in OABSS: −1.18 vs 0.10; $P = 0.027$<br>• Mean change in $Q_{max}$: 1.09 vs −1.04; $P = 0.026$ |
| Matsukawa et al 2017[56] | 104 | 12 months | • Silodosin 8 mg QID with propiverine 20 mg QID (n =53) | • Silodosin 8 mg QID (n = 51) | • Mean total IPSS: 13.3 ± 8.1 vs 11.0 ± 5.1; $P = 0.09$<br>• Mean OABSS: 5.2 ± 2.6 vs 4.2 ± 2.2L; $P = 0.04$<br>• Mean OABSS urgency: 1.8 ± 2.2 vs 1.2 ± 1.0; $P = 0.006$<br>• Mean $Q_{max}$: 10.1 ± 3.8 vs 9.6 ± 4.4; $P = 0.27$<br>• Mean BOOI: 38.7 ± 19.8 vs 38.6 ± 20.4; $P <0.001$<br>• Disappearing rate of DO: 34.2% vs 54.5%; $P = 0.07$ |
| Shirakawa et al 2013[57] | 121 | 8 weeks | • Tamsulosin to silodosin (n = 22) | • Tamsulosin to naftopidil (n = 24) | • Mean total IPSS: −4.2 ± 3.5 vs −4.7 ± 6.9; $P = 0.519$<br>• Mean subtotal storage symptoms: −1.4 ± 2.1 vs −1.8 ± 3.3; $P = 0.460$<br>• Mean subtotal voiding symptoms: −2.1 ± 2.4 vs −2.3 ± 3.4; $P = 0.292$<br>• Mean residual urine volume (mL): 4.4 ± 56.7 vs −6.6 ± 35.3; $P = 0.441$<br>• Mean post-micturition symptoms: −0.7 ± 1.0 vs −0.6 ± 1.8; $P = 0.427$<br>• Mean $Q_{max}$ (mL/sec): 1.5 ± 3.8 vs 1.3 ± 7.0; $P = 0.839$ |
| Osman et al 2015[58] | 500 | 9 months | • Silodosin 8 mg (n = 197)<br>• Tamsulosin 0.4 mg (n = 204) | • Placebo (n = 99) | • Mean IPSS score: −1.0 ± 4.4 vs −0.6 ± 5.0 vs −3.0 ± 4.4<br>(Results are silodosin vs tamsulosin vs placebo) |

(*Continued*)

**Table 1** (Continued).

| Study Name | Sample Size | Study Period | Intervention | Comparator | Significant Outcomes |
|---|---|---|---|---|---|
| Takahashi et al 2019[59] | 3355 | 12 weeks | • Silodosin | - | • Mean total IPSS score: 16.6 ± 6.7 vs 12.5 ± 6.4; $P<0.0001$ <br> • Mean QoL score: 4.2 ± 0.9 vs 3.0 ± 1.3; $P<0.0001$ <br> • Mean total OABSS: 5.7 ± 2.9 vs 4.5 ± 2.7; $P<0.0001$ <br> • Mean residual urine volume (mL): 55.0 ± 68.6 vs 37.8 ± 49.7; $P<0.0001$ <br> (Results are before and after silodosin administration) |
| Patients with voiding dysfunction in BPH/LUTS | | | | | |
| Watanabe et al 2010[63] | 37 | 12 weeks | • Silodosin 4 mg QID | - | • Mean total IPSS: 13.0 ± 7.6; $P<0.0001$ <br> • Mean QoL score: 3.4 ± 1.4; $P = 0.0008$ <br> • $Q_{max}$: 8.9 ± 3.3; $P = 0.0102$ |
| Kawabe et al 2006[62] | 456 | 12 weeks | • Silodosin 4 mg BID (n = 175) | • Tamsulosin 0.2 mg QID (n = 192) <br> • Placebo (n = 89) | • Baseline change in the total IPSS was −8.3, −6.8, and −5.3 for silodosin, tamsulosin, and placebo, respectively <br> • Baseline change in QoL was −1.7, −1.4, and −1.1 |
| Moon et al 2014[64] | 98 | 12 weeks | • Silodosin 8 mg QID (n =98) | - | • Mean total IPSS: 9.47 ± 6.22; $P = 0.0214$ <br> • Mean QoL score: 1.40±1.22; $P<0.0001$ <br> • Mean $Q_{max}$: 3.54 ± 6.60; $P<0.0001$ <br> • Mean PVR: 0.33 ± 42.25; $P = 0.9404$ |
| Patients with Nocturia | | | | | |
| Cho et al 2018[65] | 112 | 12 weeks | • Silodosin 8 mg QID | - | • Mean nocturia events reduction: −1.12 ± 1.05 events; $P<0.0001$ <br> • Mean IPSS total score: −7.93 ± 6.75; $P<0.0001$ <br> • Mean voiding score: −3.41 ± 3.64; $P<0.0001$ <br> • Mean postvoid volume: −1.29 ± 1.51; $P<0.0001$ <br> • Mean storage sub score: −3.22 ± 3.22; $P<0.0001$ <br> • Mean OABSS: −2.34 ± 2.76; $P<0.0001$ <br> • Mean IPSS QoL score: −1.26 ± 1.29; $P<0.0001$ <br> • Mean ICIQ-N score: −3.59 ± 3.04; $P<0.0001$ |
| Choi et al 2017[66] | 32 | 12 weeks | • Silodosin 4 mg or 8 mg OD | - | • Mean IPSS score: 12.5 ± 6.4 vs 18.4 ± 7.0; $P< 0.001$ <br> • Maximal flow rate (mL/sec) 14.0 ± 4.5 vs 10.7 ± 6.0; $P<0.001$ <br> • Postvoid residual urine volume: 25.0 ± 26.3 vs 47.5 ± 51.6; $P<0.001$ <br> • Night-time frequency (score 0–3): 2.0 ± 0.8 1.6 ± 0.8 0.007 <br> • Daytime frequency score (0–2): 0.6 ± 0.6 vs 0.7 ± 0.6; $P = 1.000$ |

| Eisenhardt et al 2014[67] | 1266 | 12 weeks | • Silodosin 8 mg QID (n = 714) | • Placebo (n = 552) | • Nocturia improvement rate: 53.4 vs 42.8%; *P*<0.0001<br>• Nocturia worsening rate: 9.0 vs 14.3%; *P*<0.0001<br>• ≥1 nocturnal voids: 61% and 49%; *P* = 0.0003<br>• <2 nocturia episodes: 29.3 vs 19.0%; *P* = 0.0002 |
|---|---|---|---|---|---|
| Seki et al 2014[68] | 108 | 12 weeks | • Silodosin 4 mg QID (n = 93) | • Silodosin 8 mg BID (n =95) | • Mean total IPSS: 13.2 ± 6.2 vs 11.7 ± 6.4; *P* = 0.218<br>• Mean QoL score: 3.7 ± 1.2 vs 3.2 ± 1.5; *P* = 0.020<br>• Mean OABSS: 5.6 ± 2.5 vs 4.7 ± 2.5; *P* = 0.022<br>• $Q_{max}$: 10.8 ± 6.4 vs 12.6 ± 5.4; *P* = 0.439<br>• PVR: 37.8 ± 57.0 vs 27.5 ± 37.4; *P* = 0.721 |
| Choo et al[69] | 424 | 12 weeks | • Silodosin 8 mg QID (n = 215) | • Silodosin 4 mg BID (n = 209) | • Change in mean total IPSS: −6.70 and −6.94; 95% CI: −0.88, 1.36.<br>• Percentages of patients with ≥25% improvement in total IPSS: 63.41% vs 67.82%; *P* =0.349<br>• Percentages of patients with ≥4-point improvement in total IPSS: 65.85% vs 69.31%; *P* = 0.457<br>• Percentages of patients with maximum urinary flow rate improvement ≥30%: 47.32% vs 40.59%, respectively; *P* = 0.172<br>• Mean maximum urinary flow rate: 3.55 ± 5.93 vs 3.74 ± 6.79; *P* = 0.768 |

**Abbreviations**: BID, twice a day; BOOI, bladder outlet obstruction index; BPH, benign prostate hyperplasia; DO, detrusor overactivity; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract syndrome; OABSS, overactive bladder symptom score; PVR, postvoid residual volume; $P_{det.}Q_{max}$, voiding detrusor pressure at $Q_{max}$; QID, once a day; $Q_{max}$, maximum urinary flow rate; QoL, quality of life; UUI, urinary urge incontinence.

A randomized prospective study of silodosin monotherapy (n = 53) and silodosin 8 mg/day in combination with propiverine 20 mg/day (n = 51) was conducted by Matsukawa et al. The mean IPSS and OABSS significantly improved in both groups, however, the combination group showed statistically significant improvement in OABSS (−3.4 vs −2.4, $P$ = 0.04), IPSS-QOL (−1.9 vs −1.2, $P$ = 0.01), and OAB-urgency score (−1.8 vs −1.2, $P$<0.01). Further there was a greater improvement in the disappearance rate of DO (54.5% vs 34.2%, $P$ = 0.07) and bladder capacity (+61 mL vs +33 mL, $P$ = 0.02) compared with the monotherapy group. A decrease in the residual urine volume from baseline by 20 mL (range −9 to +64 mL) with silodosin monotherapy was observed, whereas, an increased urine volume (range −51 to +140 mL) was observed on treatment with combination therapy after 1 year. At 1 year, the disappearance rate of DO in the combination group tended to be superior with that in the monotherapy group (54.5% vs 34.2%; $P$ = 0.07). This observation signifies that silodosin in combination therapy is also a suitable treatment option in patients with LUTS/BPH.[56]

## Switching Therapy

A study exhibited improved total IPSS and QoL scores in patients with LUTS/BPH when treated with silodosin compared with those treated with naftopidil at 4 or 8 weeks ($P$<0.05). It was observed that patients treated with silodosin took shorter time (at 4 weeks) to obtain subtotal IPSS storage and voiding symptoms scores while improvement with naftopidil was obtained at 8 weeks. Switching of patients from tamsulosin therapy to either silodosin or naftopidil showed significant improvements in total IPSS and QoL scores with both the drugs, with no significant differences. As for $Q_{max}$, residual urine volume and safety events, there was no significant change in all the treatment groups. The present study reported the clinical usefulness of silodosin in treating storage and voiding symptoms in BPH-associated LUTS. However, the study was limited due to the sample size necessitating a larger study population.[57] A long-term study among European patients with LUTS demonstrated a marked reduction in IPSS in patients having de novo silodosin compared with previously treated silodosin and tamsulosin therapy; QoL also improved among these patients. In patients with arterial hypertension, the drug was well tolerated and no event of orthostatic hypotension was observed.[58] A large prospective observational study in 3355 patients with BPH was conducted who switched from another α-blocker to silodosin due to therapy failure. This post-marketing surveillance study showed that mean total IPSS improved from 16.6 ± 6.7 to 12.5 ± 6.4 after silodosin treatment ($P$ < 0.0001). OABSS, residual urine volume, and QoL score showed significant improvement after switching from other α-blockers. There was no increase in the incidence of AEs with the use of any type of concomitant drug for LUTS treatment.[59] In a crossover study, 40 patients with LUTS/BPH were assigned to 2 treatment groups: (a) silodosin 4 mg 4 weeks, followed by tamsulosin 0.2 mg 4 weeks and (b) tamsulosin at 0.2 mg, 4 weeks, followed by silodosin at 4 mg 4 weeks. Though there was significant improvement in IPSS and QoL, an interesting observation was that $Q_{max}$ decreased after switching to tamsulosin in group a, while in group b, $Q_{max}$ continued to rise after switching to silodosin. This signifies that continued use of silodosin could significantly improve the $Q_{max}$.[60]

# Voiding Dysfunction in BPH/LUTS

In patients with LUTS aged ≥45 years and suggestive of BPH, early and timely diagnosis of BPH with silodosin showed signs of improvement in voiding symptoms and QoL scores from day 1 of administration. Moreover, silodosin also improved the storage and post-micturition symptoms.[61] These observations were similar to those reported by Kawabe et al who observed improvement after 1 month of therapy.[62] Watanabe et al[63] also reported similar findings. The study reported that daytime frequency in those who voided over 8 times/day declined significantly ($P$ = 0.0391) after 1 month, and nocturnal frequency in those who voided over 2 times tended to decrease ($P$ = 0.0833) after 3 months, using a frequency/volume chart (FVC). After 1 and 3 months, mean voided volume in those who at the beginning voided <250 mL increased significantly ($P$ = 0.0446 and $P$ = 0.0138, respectively), while maximum voided volume in those who initially voided <300 mL tended to rise ($P$ = 0.0833) after 1 month. AEs were mostly mild in nature (5%), where the dose reduction to 2 mg in a patient due to dizziness also showed symptom improvement as evidenced by his low IPSS and $Q_{max}$ at 1 and 3 months of treatment. These rates of AEs were quite low when compared with a Phase III study by Kawabe et al.[62] The reason for this difference in AEs may be that in this study the patient was satisfied with the therapy despite AE.[63] Continuous administration of silodosin monotherapy in patients with severe LUTS/BPH (IPSS ≥20) in

Korea showed statistically significant improvements in total IPSS and QoL scores after 12 weeks of therapy. There was no difference in postvoid residual volume (PVR) and the presence of CV AEs was low (3%). None of them discontinued treatment due to improved health. Thus, silodosin proved to be effective and safe.[64]

## Nocturia in BPH/LUTS

Among patients with BPH, approximately 85% experience two or more episodes per night. Several studies have shown the efficacy of silodosin in reducing nocturia. Silodosin reduced the incidence of nocturia in patients with BPH after 12 weeks of treatment ($-1.12 \pm 1.05$, $P<0.0001$). There were also improvements in the IPSS total score, voiding, postvoid and storage sub scores as well as the OABSS ($P<0.0001$). Both the IPSS QoL score ($-1.26 \pm 1.29$, $P<0.0001$) and the International Consultation on Incontinence Questionnaire-Nocturia (ICIQ-N) score measures ($-3.59 \pm 3.04$, $P<0.0001$) improved significantly. The subjects with $\geq25\%$ decrease in rate of nocturia and the IPSS were 65.18% (n = 73) and 63.39% (n = 71), respectively.[65] Intake of silodosin among elderly patients with LUTS/BPH and hypertension also resulted in beneficial effects. Patients on antihypertensive medications showed decrease in total IPSS, voiding score sum, storage score sum, and QoL score after receiving silodosin. Though the frequency of nocturia and urgency scores on the OABSS questionnaire improved, the daytime frequency or urge incontinence scores did not improve. There was also an objective rise in the $Q_{max}$ and a decrease in PVR. After treatment, only 2.5% of patients had orthostatic hypotension. A notable finding in this study was that adding silodosin to treatment in individuals who already had orthostatic hypotension did not worsen the condition, but rather showed improvement in 2 patients.[66]

A pooled analysis of 3 Phase III studies (n = 1479), reported that 8-mg silodosin improved the frequency of nocturia (53.4% vs 42.8%; $P<0.0001$) and prevented worsening events (9.0% vs 14.3%; $P<0.0001$) compared with placebo. Silodosin 8 mg QD reduced nocturia from $\geq1$ episode to $<2$ episodes/night at the end of the study.[67] In a study involving 268 Japanese men with BPH, comparing QD vs BID of 4 mg of silodosin, Seki et al[68] reported a significant reduction in IPSS voiding and storage subtotal scores, total IPSS, QoL index, PVR, and increase in $Q_{max}$ in both groups. However, only QoL gained more significance from 8 mg/day dosage of silodosin. Although the rates of AEs were lower in the 4 mg QD group, it did not reach statistical significance. The SILVER study compared whether silodosin 8 mg QD is as effective as 4 mg BID in patients with BPH. The results showed that 8 mg QD administration of silodosin was not inferior to 4 mg BID in terms of efficacy and safety.[69] Another study by Gul et al[70] outlined that both 4-mg silodosin was as effective as 8-mg silodosin QD in patients with moderate LUTS but not with severe LUTS. A meta-analysis evaluating the efficacy and safety of silodosin in patients with non-neurogenic male LUTS/benign prostate enlargement (BPE), found that 8-mg silodosin was significantly more effective than placebo and tamsulosin 0.2 mg in improving void symptoms and was noninferior to tamsulosin 0.4 mg.[71] Novara et al conducted a systematic literature review to evaluate the effect of silodosin in various patient subgroups with LUTS/BPH. They found that silodosin was more effective than placebo in improving total IPSS, all IPSS-related parameters, and $Q_{max}$ (all $P<0.0414$) in both patients aged $<65$ years and $\geq65$ years old. Silodosin proved to be more effective than placebo in reducing all IPSS-related parameters regardless of baseline IPSS and $Q_{max}$ ($P\leq0.0011$ and $P\leq0.0197$).[72]

## Newer Indications for Silodosin Treatment
### Overactive Bladder and Acute Urinary Retention in LUTS/BPH Patients

Sometimes, LUTS/BPH syndrome is accompanied by OAB. Despite management of such patients with $\alpha_1$-blockers, storage problems still persist. In such cases, guidelines recommend the addition of an anticholinergic agent or a $\beta3$-AR agonist.[9,73,74] Add-on treatment with fesoterodine in patients with persistent OAB symptoms and taking silodosin monotherapy for 12 weeks showed greater significant improvements in storage functions, detrusor overactivity alleviation rate and PVR urine flow compared with mirabegron group.[75] Silodosin exhibited greater improvement in total OABSS ($P = 0.03$), OABSS urgency score ($P < 0.001$), and IPSS-QOL score ($P = 0.005$) at 12 weeks compared with the naftopidil group. In voiding function, the $Q_{max}$ in the silodosin group (+3.6 mL/sec) at 12 weeks was significantly greater as compared with that in the naftopidil group (+2.1 mL/sec). Therefore, silodosin is the first choice of treatment for patients with BPE/OAB.[76] In patients with AUR in BPH, success rate of trial without catheter (TWOC) was 76.7% in the silodosin group compared with 36.7% in placebo group. Multivariate analysis revealed lesser odds of having failure with

silodosin than placebo group ($P = 0.008$). No AEs were observed with this treatment, facilitating the double effect of silodosin in management of AUR.[77] Similarly, in patients with a first episode of AUR (n = 80), the success rate of TWOC was 88.8% with 8 mg silodosin and 0.5 mg dutasteride therapy. Void volume and $Q_{max}$ were significantly higher, while IPSS and IPSS-QOL were significantly lower at 2, 4, 8, and 12 weeks. However, a control group was lacking in this study to determine the superiority of this treatment.[78] The SNIPER study evaluated the efficacy of silodosin and naftopidil in LUTS patients complicated with OAB (n = 350). There was a greater and significant improvement in the silodosin group than in the naftopidil group in total OABSS ($P = 0.03$), IPSS-QoL score ($P = 0.005$), and OABSS urgency score ($P < 0.001$) at 12 weeks. The $Q_{max}$ significantly improved in both groups, but the change was greater in the silodosin group (+3.6 mL/sec) at 12 weeks compared with the naftopidil group (+2.1 mL/sec). These findings suggest silodosin is clinically meaningful in improving storage symptoms. The difference in the selectivity for $\alpha_1$-AR subtypes play a significant role in achieving storage and OAB symptoms. The suppression of $\alpha_{1A}$ AR subtype is more important in voiding and storage function compared with $\alpha_{1D}$-AR subtype.[76] A summary of included studies is summarized in Table 2.

## Chronic Prostatitis/Chronic Pelvic Pain Syndrome

About 35–50% of men have symptoms suggesting prostatitis during their life time,[79] reflecting an approximate prevalence of 8.2% (range: 2.2% to 9.7%).[80] The different types of symptomatic and chronic forms of prostatitis are chronic bacterial prostatitis (category II), chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS; category III) and asymptomatic inflammatory prostatitis (AIP; category IV).[81] CP/CPPS is known to worsen the QoL and has presented diagnostic and therapeutic challenges for physicians. Despite these limitations, this syndrome has been less investigated as compared with other urological conditions.[82] This can be attributed to the unknown etiology of CP/CPPS. Though limited, treatment with $\alpha_1$-blockers have shown significant efficacy in reducing CP/CPPS-specific symptoms in several randomized, double-blind, placebo-controlled trials.[83–88] $\alpha_1$-blockers have the ability to block mediated signaling in the peripheral or central nervous system (CNS) thus ameliorating CP/CPPS-associated LUTS and pain by reducing voiding pressures and void flow patterns.[85,89] The EAU guidelines recommend the use of α-blockers for patients with a duration of prostate pain syndrome (PPS) <1 year.[90] A Phase II study was conducted to evaluate the response rate on treatment with silodosin 4 mg (n = 52) or 8 mg (n = 45) in patients with CP/CPPS based on total change in National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score from baseline to 12 weeks. There was significant decrease in NIH-CPSI score compared with placebo (mean ± SD change, $-12.1 \pm 9.3$ vs $- 8.5 \pm 7.2$, $P = 0.0224$), with improved urinary scores ($-2.2 \pm 2.7$ vs $-1.3 \pm 3.0$, $P = 0.0102$) and QoL ($-4.1 \pm 3.1$ vs $-2.7 \pm 2.5$, $P = 0.0099$), and SF-12 physical component scores ($4.2 \pm 8.1$ vs $1.7 \pm 9.0$, $P = 0.0492$). Nearly twice as many patients achieved marked improvement in global response assessment (GRA) (56% vs 29%) with the 4-mg silodosin ($P = 0.0069$). The increase in dose from 4 mg to 8 mg showed no additional treatment effects.[91] RE was common in patients with 4-mg silodosin compared with those treated with placebo (26.9% vs 1.9%). The proportion of drug-related AEs was greater in the 8-mg silodosin group than in the 4-mg silodosin group. The remaining AEs were similar to that in the placebo group.[91] These results indicate that treatment with silodosin is more beneficial in comparison to other $\alpha_1$-blockers as observed in other clinical studies.[92,93] A summary of included studies is summarized in Table 2.

## Premature Ejaculation

Premature ejaculation (PE) is the most common sexual disorder in men and affects 30% of men, though it is not fatal. It is assumed that contractile dysfunction of seminal vesicle and spermatic duct is the major cause of onset of ejaculation by $\alpha_1$-blockers.[94,95] A comparison of 5 $\alpha_1$-blockers in patients with PE demonstrated that the success rate of treatment was 85.7% with silodosin, 69.6% with tamsulosin, 45.5% with alfuzosin, 52.4% with terazosin, and 66.7% with doxazosin. Additionally, there were statistical improvements in intravaginal ejaculation latency time (IELT), QoL scores and decrease in premature ejaculation profile (PEP) in patients treated with silodosin compared with other groups.[96] A preliminary study among 8 patients with PE in Japan showed that off-label silodosin significantly prolonged IELT from 3.4 to 10.1 minutes ($P = 0.003$). Based on these findings, the authors carried out further investigations in 26 patients with PE. Here also, 4-mg silodosin produced greater improvements in these patients by prolonging IELT and PEP scores compared with naftopidil ($P < 0.001$). Though 2 (25%), 3 (37.5%), and 7 (87.5%) patients experienced an ejaculation,

**Table 2** Summary of Included Studies for Overactive Bladder and Acute Urinary Retention in Patients with LUTS/BPH, Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP-CPPS), and Premature Ejaculation

| Study Name | Sample Size | Study Period | Intervention | Comparator | Significant Outcomes |
|---|---|---|---|---|---|
| Patients with overactive bladder and acute urinary retention and LUTS/BPH | | | | | |
| Matsukawa et al 2019[75] | 102 | 12 weeks | • Silodosin with fesoterodine 4 mg QID (n = 50) | • Silodosin with mirabegron 50 mg QID (n = 52) | • Mean total IPSS: 12.5 ± 6.2 vs 13.0 ± 4.2; $P$ = 0.84<br>• Mean IPSS QoL: 3.3 ± 1.2 vs 3.8 ± 1.3; $P$ = 0.04<br>• Mean OABSS: 5.8 ± 3.0 vs 6.7 ± 2.7; $P$ = 0.004<br>• Mean OABSS urgency sub score: 1.8 ± 1.4 vs 2.4 ± 1.3; $P$ = 0.008<br>• Mean OABSS UUI sub score: 0.9 ± 1.2 vs 1.3 ± 1.2; $P$ = 0.02 |
| Matsukawa et al 2017[76] | 314 | 12 weeks | • Silodosin (n = 157) | • Naftopidil (n = 157) | • Mean total IPSS: 11.3 ± 6.6 vs 12.7 ± 6.7; $P$ = 0.08<br>• Mean OABSS: 4.8 ± 2.8 vs 5.5 ± 3.0; $P$ = 0.03<br>• Mean OABSS urgency score: 1.3 ± 1.2 vs 1.9 ± 1.2; $P<0.001$<br>• Mean $Q_{max}$: 11.8 ± 4.1 vs 10.5 ± 4.6; $P<0.01$<br>• Mean void volume: 175 ± 92 vs 154 ± 85; $P$ = 0.05<br>• PVR: 24 ± 25 vs 31 ± 29; $P$ = 0.05 |
| Kumar et al 2013[77] | 34 | 2 weeks | • Silodosin 8 mg QID (n = 23) | • Placebo (n = 11) | • $Q_{max}$:<br>  At TWOC: 12.4 ± 5.6 vs 8.6 ± 5.8; $P$ = 0.002<br>  At 2 weeks: 14.8 ± 5.7 vs 10.5 ± 5.6; $P$ = 0.016<br>• PVR:<br>  At TWOC: 80 ± 36 vs 110 ± 25; $P$ = 0.001<br>  At 2 weeks: 60 ± 27 vs 67 ± 26; $P$ = 0.517<br>• IPSS:<br>  At TWOC: 25.7 ± 2.5 vs 24.9 ± 1.8; $P$ = 0.02<br>  At 2 weeks: 23.0 ± 1.7 vs 21.9 ± 0.9; $P$ = 0 0.044 |
| Hagiwara et al 2016[78] | 80 | 12 weeks | • Silodosin 8 mg with dutasteride 5 mg QID (n = 80) | - | • Void volume and $Q_{max}$ were significantly higher at 2, 4, 8, and 12 weeks compared with baseline ($P<0.001$).<br>• IPSS and IPSS-QOL were significantly lower at 2, 4, 8, and 12 weeks compared with the baseline ($P<0.001$). |
| Patients with chronic prostatitis/chronic pelvic pain syndrome | | | | | |
| Nickel et al 2011[91] | 151 | 12 weeks | • Silodosin 4 mg BD (n = 52)<br>• Silodosin 8 mg QID (n = 45) | • Placebo (n =54) | • Total NIH-CPSI score: (mean change ± SD: 12.1 ± 9.3 vs −8.5 ± 7.2) $P$ = 0.0224<br>• SF-12 physical component score: 4.2 ± 8.1 vs 1.7 ± 9.0; $P$ = 0.0492<br>• NIH-CPSI urinary symptoms score: −2.2 ± 2.7 vs −1.3 ± 3.0; $P$ = 0.0102 |

(Continued)

**Table 2** (Continued).

| Study Name | Sample Size | Study Period | Intervention | Comparator | Significant Outcomes |
|---|---|---|---|---|---|
| Patients with premature ejaculation | | | | | |
| Akin et al 2015[96] | 108 | 6 months | • Silodosin 4 mg BID (n = 21) | • Tamsulosin hydrochloride 0.4 mg (n = 23) Alfuzosin 10 mg (n = 22) <br> • Terazosin 5 mg (n = 21) <br> • Doxazosin mesylate 4 mg (n = 21) | • IPSS score: 18.8 ± 12.93 vs 151 ± 53.9 <br> • QoL score: 23 ± 12.8 89.7 ± 31.4 |
| Sato et al 2012[97] | 8 | 2 months | • Silodosin 4 mg (n = 8) | – | • Mean average IELT: 3.4 min to 10.1 min; $P = 0.003$ |
| Sato et al 2016[98] | 52 | – | • Silodosin 4 mg (n = 26) | • Naftopidil (n =26) | • CGIC score: 92.3% vs 46.1%; $P = 0.0002$ <br> • Median IELT score: 7.6 ± 5.1 (1–20) vs 4.1 ± 2.8 (1–12); $P<0.0001$ |
| Bhat et al 2016[99] | 143 | 1 year 5 months | • Silodosin 4 mg (n = 33) | • Placebo (n = 31) | • CGIC score: 1.82 ± 0.85 vs 3.8 ±0.63 <br> • IELT, PEP scores were improved with silodosin than placebo ($P<0.005$) |

**Abbreviations**: BOOI, bladder outlet obstruction index; CGIC score, clinical global impressions scale; DO, detrusor overactivity; IELT, Intravaginal ejaculation latency time; IPSS, International Prostate Symptom Score; NIH CPSI score, National Institutes of Health Chronic Prostatitis Symptom Index; PVR, postvoid residual volume; OABSS, overactive bladder symptom score; $P_{det}Q_{max}$, voiding detrusor pressure at $Q_{max}$; $Q_{max}$, maximum urinary flow rate; QoL, quality of life; UUI, urinary urge incontinence; TWOC, trial without catheter.

reduced semen volume and discomfort during orgasm, these problems were reported to be insignificant to the study participants.[97] Due to clinical global impression change (CGIC), 24 patients (92.3%) and 12 patients (46.1%) reported that their own PE problems improved with silodosin and naftopidil administration, respectively. However, the authors noticed that 50% of patients had reduced semen volume with silodosin. This issue was resolved on limiting the dose to half its actual volume. Furthermore, 42% of patients with EjD were managed by PDE5 inhibitors before enrollment to the study. This shows that demographics of patients treated for PE are varied and frequently suffered from PE combined with EjD.[98] Dapoxetine 30 mg is widely used for the treatment of PE; however, the patient adherence is low due to its adverse effects or inefficacy.[99] In such conditions, about 123 patients dissatisfied with dapoxetine treatment were administered with 4-mg silodosin and were evaluated for its effects on PE. On treatment with silodosin, patients showed improvement in the IELT, PEP score, and CGIC for PE whereas only 4 patients reported uncomfortably delayed ejaculation.[99] A summary of included studies is summarized in Table 2.

## Ureteral Calculi

Ureteroscopy and shockwave lithotripsy (SWL) remain the most effective treatment modalities for DUS,[100–102] however, these treatments are expensive and accompanied by adverse events. Medical expulsion therapy (MET) with $\alpha_1$-blockers is recommended for the treatment of ureteral stones >5 mm as per the latest EAU guidelines.[102] With time it has been observed that the site of stone formation has migrated from the lower to the upper urinary tract.[103] A previous study reported that SER of ureteric stones after WW was 25% to 54% with a mean expulsion time >10 days, associated with high analgesic requirement for stones >5 mm. Thus to improve the expulsion rate and requirement for analgesics, MET is the preferred treatment for ureteral stones.[104,105] Itoh was the first researcher to perform a prospective randomized study with silodosin in patients with proximal, mid, or DUS. They found that silodosin did not affect SER (66.3% vs 50%), expulsion duration (10.27 ± 8.35 days vs 15.19 ± 7.14 days; $P = 0.0058$), or analgesic need when compared with those not receiving any treatment. However, silodosin decreased stone expulsion time (SET) without affecting SER or analgesic need in patients with DUS. A subgroup analysis of patients with ureteral stones 6 mm to 9 mm in diameter reported that silodosin increased SER and decreased stone expulsion duration but did not affect analgesic need. However, the findings should be interpreted with caution because the study included only men.[106] Another study demonstrated that a higher proportion of patients achieved stone expulsion with silodosin (82% vs 58%; $P = 0.008$) and a shorter duration of expulsion (12.5 ± 3.5 vs 19.5 ± 7.5 days, $P = 0.01$) than tamsulosin.[103] These findings are consistent with the silodosin's greater selectivity for the $\alpha_{1A}$-receptor compared with tamsulosin. Kumar et al[107] demonstrated that patients treated with silodosin had significantly higher SER compared with tamsulosin (83.3% vs 64.4%; $P = 0.006$) and tadalafil (83.3% vs 66.67%; $P = 0.016$) treated groups. The mean SET was significantly less in silodosin-treated groups (14.8 ± 3.3 days vs 16.5 ± 4.6 days, $P = 0.005$; 14.8 ± 3.3 days vs 16.2 ± 4.2 days, $P = 0.013$). Compared with tamsulosin (1.70 ±1.2) and tadalafil (1.60 ± 0.8), there was a decrease in the average episodes of colicky pain with silodosin (0.8 ± 0.9; $P<0.001$). The analgesic requirements were also significantly less with silodosin than other drugs. Thus, the authors concluded that the use of silodosin increases ureteric stone significantly along with better control of pain and lesser analgesic requirement. Probably, $\alpha_1$-blockers decrease analgesic requirement by two ways ie, expulsion of stones and blockade of C fibers; however, it is difficult to know the primary responsible factor.[107] However, Imperatore et al[108] observed that there was no significant difference in the stone clearance rates and expulsion time between silodosin and tamsulosin groups. Here the incidence of side effects related to peripheral vasodilation (dizziness, postural hypotension, headache, nasal congestion) were significantly higher in the tamsulosin arm.[108] A multicenter study on silodosin was found to be beneficial and well tolerated in facilitating passage of DUS 4 mm to 10 mm compared with placebo. Commonly observed AEs were RE, nausea, dizziness, headache, and nasal congestion.[109] A prospective randomized study in 115 patients with DUS ≤10 mm was randomized to either 8-mg silodosin or 0.4-mg tamsulosin QD. After 1 month of treatment, the SER was significantly different between the groups, at 83% with silodosin and 57% with tamsulosin ($P = 0.007$). The SET was also significantly shorter in silodosin-treated patients than with tamsulosin (mean ± SD: 13.3 ± 4.1 vs 16.7 ± 5.4 days; $P < 0.001$). Silodosin-treated patients exhibited fewer ureteric colic episodes and lower incidences of orthostatic hypotension (3.8% vs 7.8%). Abnormal ejaculation was recorded more in silodosin-treated patients than tamsulosin; however, this result was non-significant ($P = 0.18$).[110] Similar findings were obtained where silodosin reported higher efficacy and safety against tamsulosin in reducing SET (82.4% vs 61.5%; $P = 0.007$) in patients having a single unilateral stone ≤10 mm.[111] A summary of included studies is summarized in Table 3.

**Table 3** Summary of Included Studies for Ureteral Stones

| Study Name | Sample Size | Study Period | Intervention | Comparator | Significant Outcomes |
|---|---|---|---|---|---|
| Itoh et al 2011[106] | 187 | 8 weeks | • Silodosin 8 mg (n = 95) | • Placebo (n = 92) | • Stone expulsion rate: 92 (50%) vs 89 (66.3%)<br>• Mean expulsion time: 15.19 ± 7.14 vs 10.27 ± 8.35 days; $P = 0.0058$ |
| Gupta et al 2013[103] | 100 | 4 weeks | • Silodosin 8 mg (n = 50) | • Tamsulosin 0.4 mg (n = 50) | • Stone expulsion rate: 29 (58%) vs 41 (82%); $P = 0.008$<br>• Mean expulsion time: 19.5± 7.5 vs 12.5 ± 3.5; $P = 0.01$ |
| Imperatore et al 2014[108] | 100 | 12 months | • Silodosin 8 mg (n = 50) | • Tamsulosin 0.4 mg (n = 50) | • Stone expulsion rate: 41 (82%) vs 44 (88%); $P$ = not significant<br>• Stone expulsion time: 6.5 (3–9) vs 6.7 (3–9); $P$ = not significant<br>• Side effects related to peripheral vasodilation: 13 (26%) vs 4 (8%); $P<0.05$ |
| Kumar et al 2015[107] | 180 | 4 weeks | • Silodosin 8 mg = 90 | • Tadalafil 10 mg (n = 90)<br>• Tamsulosin 0.4 mg = 90 | • Stone expulsion rate: 64.4% vs 83.3% vs 66.67% ($P$ = 0.006, 0.016)<br>• Mean stone expulsion time: 16.5 ± 4.6 days vs 14.8 ± 3.3 days vs 16.2 ± 4.2 days ($P$ = 0.005, $P$ = 0.013)<br>(Results are tamsulosin vs silodosin vs tadalafil) |
| Sur et al 2015[109] | 232 | 4 weeks | • Silodosin (n = 115) | • Placebo (n = 117) | • Stone expulsion rate: 60 (52%) vs 117 (44%); $P = 0.2$<br>• Stone expulsion rate (distal): 36 (69%) vs 27 (46%); $P = 0.01$<br>• Stone expulsion rate (mid): 8 (40%) vs 10 (48%); $P = 0.73$<br>• Stone expulsion rate (proximal): 16 (37%) vs 15 (41%); $P = 0.87$ |
| Elgalaly et al 2016 | 115 | 6 weeks | • Silodosin (n = 52) | • Tamsulosin (n = 51) | • Stone expulsion rate: 43 (83%) vs 29 (57%); $P = 0.007$<br>• Mean stone expulsion time: 13.3 ± 4.1 days vs 16.7 ± 5.4 days; $P<0.001$ |
| Gharib et al 2018[111] | 150 | 4 weeks | • Silodosin 8 mg (n = 75) | • Tamsulosin 0.4 mg (n = 75) | • Stone expulsion rate: 56 (82.4%) vs 40 (61.5%); $P = 0.007$<br>• Stone expulsion time: 9.4 ± 3.8 vs 12.7 ± 5.1 days; $P = 0.001$<br>• Analgesic requirements: 193 ± 83.3 and 204.2 ± 95.1<br>• Dizziness: 4.4% vs 6.2%<br>• Postural hypotension: 1.47% vs 3.1%<br>• Headache: 1.47% vs 1.51%<br>• Retrograde ejaculation: 23.3% vs 12.2% |

## Prostate Cancer Post Brachytherapy-Induced Progression

Prostate cancer is one the main causes of death in men with a 5.6% death rate annually. Urinary frequency and urgency are the frequently observed adverse events.[112,113] A comparison of 2 $\alpha_1$-ARs in patients who underwent low-dose-rate (LDR) brachytherapy for prostate cancer showed no significant difference between the naftopidil and silodosin groups ($P = 0.728$). For the first 12 months after seed implantation, the FVC indicated a similar increase in urine frequency and a decrease in total urinated volume and mean voided volume. Patients with a urethral dose (UD30) <200 Gy had a better IPSS recovery rate at 12 months after seed implantation.[114] In contrast, Tsumura et al found greater efficacy for silodosin compared with tamsulosin and naftopidil in improving total IPSS at 1 month after prostate implantation (+7.5, +10.3, and +8.9, respectively). A significant decrease was observed with silodosin than naftopidil in the straining on urination score at 6 months (0.4 vs 1.1, $P = 0.02$). Thus silodosin better resolves the urinary symptoms of voiding, emptying, and nocturia after prostate implantation than naftopidil and tamsulosin.[115] Oyama et al also made a similar observation in patients with LUTS who received $\alpha_1$-blockers after 1 year of brachytherapy. The patients administered with tamsulosin and naftopidil reported a worsening of health condition than those receiving silodosin. These findings suggest that silodosin may have an added advantage in management of LUTS after[125] I prostate brachytherapy compared with other $\alpha_1$-blockers.[116] A pressure flow study to check the urodynamics of silodosin treatment revealed a significantly enlarged bladder capacity when first non-voiding contraction was seen at 3 and 12 months (3M: 127.1 ± 74.8 vs 118.2 ± 83.9 mL, $P = 0.001$; 12M: 123.7 ± 79.3 vs 100.3 ± 73.4 mL, $P = 0.01$).[117] A summary of included studies is summarized in Table 4.

## Limitations, Future Implications for Research and Clinical Practice

We reviewed the various α-blockers in the available literature and found that silodosin, due to its high uroselectivity, has advantages over other α-blockers in improving the voiding symptoms, urinary flow, and improved QoL in patients dissatisfied with other therapeutic options as well as those newly diagnosed with any urologic disease. Though certain adverse events such as orthostatic hypotension, dizziness, diarrhea are observed occasionally, patients prefer to continue their treatment due to its superior and well-improved efficacy.

Fusco et al in a meta-analysis of 23 RCTs for various medical therapy reported that BOO index, $P_{det}Q_{max}$, and $Q_{max}$ were significantly improved in patients receiving α-blockers and 5-alpha reductase inhibitors while PDE5 inhibitors and phytotherapy compounds had no significant effects on urodynamic parameters in LUTS related to BPH.[118] Another meta-analysis of 22 RCTs comprising >9000 patients with LUTS/BPH established that silodosin and tadalafil were more effective than placebo in improving LUTS but these drugs had more AEs. The authors stated that the evidence gathered was insufficient to assess long-term efficacy, need for surgical intervention, prevention of symptom progression, or long-term AEs. To assess the effect of these therapies on response rates using established minimal detectable difference thresholds, disease progression, and harms, long-term studies were suggested to gather enough evidence.[119] Creta et al performed a post hoc analysis of Phase III and IV trials containing 8-mg silodosin as the main therapeutic regimen in patients with severe LUTS/BPO. Here, when compared with placebo, patients receiving silodosin experienced significantly higher mean improvements in total IPSS (8.1 vs 4.7), storage (3.1 vs 2.0), voiding (5.0 vs 2.7), and QoL (1.3 vs 0.7) (all $P<0.0001$), including for patients with severe LUTS.[120] A systematic review and subsequent meta-analysis has proven that $\alpha_1$-AR blockers are superior to placebo in achieving successful voiding in patients with AUR. They reported that a suprapubic catheter (SPC) might provide superior advantages over urethral catheterization. Catheterization for <3 days is a safe option in avoiding catheterization-related complications.[121]

In terms of ureteral calculi, a study showed that silodosin achieved significantly higher expulsion rates (pooled risk difference [RD]: 0.13, 95% CI: 0.09, 0.18) and SET (pooled mean difference [MD]: −2.55 days, 95% CI: −4.06, −1.04) than tamsulosin. A subgroup analyses demonstrated a significantly higher expulsion rate on stone sizes of 5–10 mm with silodosin compared with tamsulosin (pooled RD: 0.14, 95% CI: 0.06, 0.22). With stone sizes <5 mm, the superior effect was not observed. After adjusting for age and gender, multivariate regression analysis revealed that the RD was negatively linked with the control expulsion rate (coefficient −0.658, $P = 0.01$). Also, these patients had fewer incidences of pain episodes (pooled MD: −0.3, 95% CI: −0.51, −0.09) compared with those receiving tamsulosin.[122] Ozsoy et al[123] compared the efficacy of silodosin with tamsulosin in a pooled data of 409 patients. The meta-analysis results favored

**Table 4** Summary of Included Studies for Prostate Cancer Post Brachytherapy-Induced Progression

| Study Name | Sample Size | Study Period | Intervention | Comparator | Significant Outcomes |
|---|---|---|---|---|---|
| Tsumura et al 2011[115] | 212 | 12 months | • Silodosin (n = 71) | • Naftopidil (n =71)<br>• Tamsulosin (n = 70) | • The mean change in the IPSS QoL index score at 3 months in the naftopidil, tamsulosin, and silodosin groups was +1.3, +1.4, and +0.9, respectively<br>• Silodosin also resulted in a significantly lower mean difference in the nocturia score at 3 months than either naftopidil ($P$ = 0.032) or tamsulosin ($P$ = 0.028).<br>• The change in the nocturia score at 3 months from baseline was +1.0, +1.0, and +0.6 in the naftopidil, tamsulosin, and silodosin groups, respectively<br>• The mean change in the total IPSS at 1 month after PI in the naftopidil, tamsulosin, and silodosin groups was +10.3, +8.9, and +7.5, respectively<br>• There were significantly greater decreases with silodosin than with naftopidil at 1 month in the total IPSS ($P$ = 0.039). |
| Tanaka et al 2014[114] | 141 | 12 months | • Silodosin (n =71) | • Naftopidil (n =70) | • Mean total IPSS: 9.8 ± 7.2 vs 9.8 ± 7.1; $P<0.01$<br>• Mean OABSS: 4.0 ± 3.0 vs 4.5 ± 3.0; $P<0.01$ |
| Oyama et al 2014[116] | 116 | 6 months | • Silodosin (n = 32) | • Tamsulosin (n = 49)<br>• Naftopidil (n = 35) | • Mean total IPSS: 19.2 ± 9.8 vs 16.5 ± 7.2 vs 20.4 ± 8.8 for tamsulosin, silodosin, and naftopidil group<br>• PVR peaked at 1 month in tamsulosin (38.8 ± 9.5 mL) and at 6 months in naftopidil groups, (41.1 ± 9.5 mL) and at 3 months in silodosin group (30.3 ± 5.2 mL) |
| Shimizu et al 2014[117] | 105 | 12 months | • Silodosin (n = 53) | • Silodosin (n = 52) | • Mean prostate volume: 28.3 ± 11.1 vs 26.1 ± 9.7<br>• Prostate specific antigen level: 7.1 ± 3.6 vs 8.1 ± 4.3<br>• IPSS sub score: 123.7 ± 79.3 vs 100.3 ± 73.4 mL; $P$ = 0.01 |

**Abbreviations**: DO, detrusor overactivity; IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score; PVR, postvoid residual volume; $P_{det.}$ $Q_{max}$, voiding detrusor pressure at $Q_{max}$; $Q_{max}$, maximum urinary flow rate; UUI, urinary urge incontinence; QoL, quality of life.

silodosin in terms of SER with an RR of 1.33 (95% CI: 1.17, 1.50). Similarly, faster SET were observed with silodosin when compared with tamsulosin (−2.49; 95% CI: −3.40, 1.58). Recently, Sharma et al reviewed the three most commonly used α-blockers (tamsulosin, alfuzosin, and silodosin) as MET for ureteral calculi. They observed that all the treatment groups were more effective for both SER and SET compared with placebo. However, silodosin had the highest surface under the cumulative ranking area curves (94.8 and 90.4) values followed by alfuzosin (58.8 and 64.9) and tamsulosin (46.2 and 44.5) in terms of SER and SET. The incidence of postural hypotension was similar with all the drugs, whereas silodosin emerged as the most efficacious drug as MET for lower ureter stones.[124] The same researchers reported that a tadalafil plus silodosin combination and silodosin as an individual drug are the best for treating lower ureter stones considering the SET and SER.[125] A meta-analysis carried out by Liu et al reported similar findings stating that tadalafil plus silodosin has the highest probability of reducing SET, and treating ureteral stones ≤10 mm.[126]

Considering that α-blockers show improved efficacy in various urological disorders, these findings could serve as an evidence-based practice and can be considered by physicians and researchers to develop clinical-based guidelines. The overall efficacy and tolerability of treatment has been confirmed by the various Phase II and III trials as discussed above. In addition, the evidence from the recent meta-analysis also confirms these findings. Though the short-term effects of silodosin reported in the above literature is promising, the long-term benefit of silodosin in a larger sample size and scientifically sound study needs to be observed. The small amount of published meta-analysis available at present has limitations of small sample sizes, poor quality of included trials, and no proper conduct of study. Given these limitations, further research needs to assess the findings of this review to obtain a more efficient performance of high-quality, long-term RCTs to verify and explore the efficacy and safety of silodosin.

Nonselective drugs, such as doxazosin and terazosin, are associated with a higher incidence of cardiovascular AEs. In contrast, silodosin has shown to be effective and safe for management of LUTS in elderly patients taking antihypertensive medications.[66] It is speculated that due to the high uroselectivity for $\alpha_{1\beta}$ adrenergic receptors is mainly responsible for controlling BP enabling silodosin to have minimum effects on CV system. Silodosin has demonstrated promising results in increasing the probability of successful TWOC in patients with AUR and those taking antihypertensive drugs. The use of silodosin should be explored in the treatment of brachytherapy-induced progression of urinary function in patients with prostate cancer. Another advantage of silodosin is that the dose does not need to be adjusted according to age, concurrent medication with antihypertensives, and PDE5 inhibitors.[127] Future consideration of research areas might also include further studies that analyze silodosin as a MET for distal ureteral stones >5 mm, and the combination of silodosin and oral chemolysis for distal ureteral stones >8 mm. More often, the influence of factors such as age, gender, ethnicity, previous history is overlooked or not reported in the RCTs, thus these factors need to be considered in the research to understand the subgroup population who will benefit the most from silodosin. Considering the robust data available from this review, further treatment strategies where silodosin may play a role in the management of different urological conditions needs to be focused. Finally, it was reported that LUTS/BPH patients had decreased storage function and deteriorated LUTS after withdrawal of silodosin from 12-month combination therapy with 5α-reductase inhibitors, dutasteride.[54] The combination of silodosin and β-3 agonists/PDE5 inhibitors for BPE patients with OAB showed safety and significantly greater improvement on IPSS and OABSS over silodosin monotherapy.[55,56] This approach warrants further investigation in combination of silodosin with β-3 agonists, or with 5α-reductase inhibitors and beta-3-agonists on improving symptoms of patients with LUTS/BPH so as to reduce the risk of progression of the disease as well as to avoid the need for invasive therapy in long-term.

# Conclusion

In light of the advancement of treatment approaches for urological disease, therapies that offer high satisfaction rates for patients and compliance need to be focused on. From our review, it is evident that silodosin, a selective $\alpha_{1A}$-blocker, is versatile in the treatment of various urological diseases. Silodosin demonstrated high efficacy and well generalized tolerability in treatment of LUTS/BPH. Despite mild AEs, silodosin demonstrates significant clinical improvement with a good CV profile. Silodosin is also beneficial in improving nocturia events. Silodosin has proven to be beneficial in decreasing SET without affecting SER or analgesic need in patients with DUS. Patients on other treatment therapies such

as PDE5 inhibitors or another α-blocker are well managed with this drug. Phase II results have reported significant evidence of silodosin in the treatment of CP/CPPS and facilitating ureteral stone passage, as well.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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