REVIEW ARTICLE

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Silodosin in the management of lower urinary tract symptoms as a result of benign prostatic hyperplasia: who are the best candidates

U. Capitanio, A. Salonia, A. Briganti, F. Montorsi

Department of Urology, Vita Salute San Raffaele University, Milan, Italy

Correspondence to:
Francesco Montorsi
University Vita-Salute San Raffaele, via Olgettina 60, 20132, Milan, Italy
Tel.: +39 2 2643 7286
Fax: +39 2 2643 7298
Email: montorsi.francesco@hsr.it

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SUMMARY

Background: As the clinical effects of the available α1-adrenoceptors (ARs) blockers are usually considered comparable for treatment in patients suffering from lower urinary tract symptoms (LUTS) secondary to prostatic enlargement, officially recognised guidelines do not make specific recommendations regarding the choice of which agent should be considered according to the patient's characteristics. **Aim:** To analyse data supporting the use of silodosin, a highly selective once-daily dosing α1-ARs blocker, in different daily clinical practice scenarios. **Materials and methods:** A structured literature review was performed using data retrieved from articles assessing the role of silodosin in the management of LUTS secondary to benign prostatic hyperplasia (BPH). A literature search of English language publications was performed using MEDLINE® and Web of Science from 2000 to 2012 using the terms LUTS; BPH; silodosin; α1-ARs blockers. The papers with the highest level of evidence were identified and represent the basis of the present review. **Results:** Available data coming from basic research analyses, randomised trials and prospective studies showed that silodosin is efficacious for the initial management of patients with LUTS. Clinical developmental safety data from patients receiving silodosin with concomitant antihypertensive therapy do not indicate an increase in risk of orthostatic hypotension. In this context, a recent study demonstrated that silodosin can be safely administered to patients who are consensually assuming phosphodiesterase type 5 inhibitors. A recent randomised crossover study comparing the efficacy of silodosin and tamsulosin in patients with LUTS showed that further significant improvement was observed after switching to silodosin treatment, while worsening or little improvement was observed after switching to tamsulosin treatment. Preliminary results seem to demonstrate a potential role of silodosin in the treatment of chronic prostatitis/chronic pelvic pain syndrome and to facilitate ureteral stone passage, as well. **Discussion:** When considering the above cited pharmacological and clinical characteristics of the drug, silodosin can be considered in the following clinical scenario: patients suffering from moderate–severe nocturia, patients with low normal blood pressure levels and patients concomitantly treated with antihypertensive medications, patients concomitantly treated with phosphodiesterase type 5 inhibitors, patients not satisfied (for efficacy or tolerability) with previous treatment with other α1-ARs blockers. **Conclusion:** Silodosin is efficacious for the initial management of patients with LUTS. Silodosin has a good cardiovascular safety profile and can be considered an option in patients with cardiovascular co-morbidities. It seems to be especially beneficial in patients with nocturia alone or presenting with the symptomatic trial nocturia-frequency-incomplete emptying. Patients on phosphodiesterase type 5 inhibitors treatment can be safely managed with silodosin.

Review criteria
A structured literature review was performed using data retrieved from articles assessing the role of silodosin in the management of LUTS secondary to BPH. A literature search of English language publications was performed using MEDLINE® and Web of Science from 2000 to 2012 using the terms LUTS; BPH; silodosin; α1-ARs blockers. The papers with the highest level of evidence were identified and represent the basis of the present review.

Message for the clinic
Silodosin is efficacious for the initial management of patients with LUTS. Silodosin has a good cardiovascular safety profile and can be considered an option in BPH/LUTS patients with cardiovascular comorbidities. Patients on PDE5-Is treatment can be safely managed with silodosin.

Introduction

After coronary artery disease, hypertension and type 2 diabetes, lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) represent the fourth most diagnosed condition in men aged $\geq$ 50 years (1–4). The incidence of BPH is reported to over 80% in men aged 70 years or older and LUTS in men increase from 56% in men aged 50–79 years to 70% of men 80 years of age (5).

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Whereas surgery does represent a crucial step in moderate-to-severe BPH-related medical conditions, medical therapy does remain the main pillar in the management of uncomplicated cases.

Although LUTS secondary to BPH is not commonly life threatening, the influence on quality of life (QoL) can be significant (6) and the primary treatment goal remains to alleviate bothersome symptoms (7). The European Association of Urology and the American Urological Association guidelines recognise α1-adrenoceptors (α1-ARs) blockers as the first-line medical treatment of patients with LUTS as a result of BPH (2,3).

In this context, silodosin has been gaining popularity for its uro-selectivity, limited effect on cardiovascular system and virtually no interaction with other drugs (8–11). For these reasons, silodosin can be considered for the initial management in patients suffering from LUTS as a result of BPH, especially in those men who are on treatment with other medical therapies in general or are affected by concomitant comorbidities.

As the clinical effects of the available α1-ARs blockers are usually considered comparable within their class, officially recognised guidelines do not make specific recommendations regarding the choice of which agent should be considered according to the patient's characteristics. From the economic point of view, a systematic assessment of all direct and indirect costs of the use of the different medications is needed to provide a complete comparison analyses among the different alpha-blockers available. Moreover, costs comparison should require evaluation regarding the balance between efficacy, individual satisfaction and clinical outcomes. All those considerations required additional data, which cannot be provided in this manuscript, as not available and above the aims of the report. In this review, we provided basic research and clinical data supporting the use of silodosin in different daily practice scenarios.

Evidences acquisition

A structured, comprehensive literature review was performed using data retrieved from recent review articles and original articles assessing the role of silodosin in the management of LUTS secondary to BPH. A literature search of English language publications was performed using MEDLINE® and Web of Science from 2000 to 2012 using the terms lower urinary tract symptoms; LUTS, benign prostatic hyperplasia; BPH; silodosin; α1-ARs blockers. Keywords included Links to related papers and cross-reading of citations in related articles were surveyed. The papers with the highest level of evidence were identified and represent the basis of this review.

What is silodosin

Silodosin is a highly selective once-daily dosing α1-ARs blocker. Precisely, α1-ARs belong to the superfamily of G-protein-coupled receptors and mediate the actions of the endogenous catecholamines, noradrenalin and adrenalin. As a result, α1-ARs are involved in the regulation of many physiological processes, including smooth muscle contraction, cardiac chronotropy and hepatic glucose metabolism. With regard to the human prostate, α1-ARs are able to control normal and hyperplastic smooth muscles of prostate and urethra (12–15). Consequently, α1-ARs blockers reduce outflow resistance and improve voiding (12–14).

Three α1-AR subtypes (α1A, α1B, α1D) have been demonstrated in normal and BPH stromal tissue (16). The α1A subtype is the predominant subtype, representing about 65–75% of the α1-AR population (16,17). To date, silodosin has the best uro-selectivity among all the available α1-ARs blockers (e.g. alfuzosin, doxazosin, prazosin, tamsulosin, terazosin) (18–22). Specifically, silodosin holds a 56-fold selectivity for α1A vs. α1D and a 583-fold selectivity for α1A vs. α1B subtypes (23). Such relatively low selectivity for the α1B-AR, which is mainly involved in the regulation of blood pressure, allows silodosin to have limited effects on cardiovascular system (17,23,24).

Urological tissue-selectivity from a clinical point of view

Main effects on prostate and bladder

The uro-selectivity demonstrated by silodosin in basic research and preclinical studies is clearly reflected in clinical practice. Matsukawa et al. investigated the effect of silodosin on pressure flow parameters in 60 patients treated for 4 weeks for LUTS secondary to BPH (25). In the voiding phase, mean detrusor pressure at maximum flow significantly decreased from 72.5 to 51.4 cmH_2O during treatment with silodosin. Similarly, the mean bladder outlet obstruction index decreased significantly from 60.6 to 33.8. Obstruction grade assessed by the Schaefer nomogram improved in 98.3% of the patients (25). Total symptom and quality-of-life (QoL) scores, maximum flow rate and postvoid residual urine volume on free uroflowmetry significantly improved (25).

Chronic silodosin treatment significantly improves hypertension-related detrusor overactivity and significantly increases blood flow in the bladder (20). Yamanishi et al. demonstrated improved bladder urodynamic parameters at 3 months after silodosin treatment (26). Silodosin significantly decreases

Table 1 Total IPSS, Q max and IPSS subscores change in patients treated with silodosin among phase III clinical trials

Study	Group	n	Total IPSS, mean	IPSS (voiding symptoms), mean	IPSS (storage symptoms), mean	Qmax, mean, ml/s
Chapple et al. (8)	Silodosin (8 mg/day)	381	−7.0	−4.5*	−2.5*	3.77
	Tamsulosin (0.4 mg/day)	384	−6.7	−4.2*	−2.4*	3.53
	Placebo	190	−4.7	−4.7	−1.4	2.93
Marks et al. (9)	Silodosin (8 mg/day)	466	−6.4*	−4.0*	−2.3*	2.6*
	Placebo	457	−3.5	−2.1	−1.4	1.5
Kawabe et al. (10)	Silodosin (8 mg/day)	175	−8.3*	−5.8*	−2.5*	1.7
	Tamsulosin (0.2 mg/day)	192	−6.8	−4.8	−2.1	2.6
	Placebo	89	−5.3	−3.8	−1.5	0.3
Yu et al. (11)	Silodosin (8 mg/day)	87	−10.6	−7.1	−3.5	0.9
	Tamsulosin (0.2 mg/day)	83	−10.0	−6.7	−3.3	1.4

*Statistically significantly different vs. placebo.

urinary frequency without effect on bladder contraction pressure or residual volume (26).

Main effects on symptoms

With regard to prospective randomised studies, two placebo-controlled phase III studies and two non-inferiority study of silodosin vs. tamsulosin and of superiority vs. placebo (8–11) and one randomised, double-blind vs. tamsulosin for the treatment of LUTS/BPH were carried out in Europe (8), USA (9), Japan (10) and Taiwan (11) (Table 1). Those studies, all testing the dosage regimen of 8 mg, have shown that silodosin is significantly more effective than placebo and at least as effective as tamsulosin in improving the International Prostate Symptom Score (IPSS) total score, storage subscore and voiding subscore (Table 1).

The European trial included 1228 men in a multicentre double-blind, placebo and active-controlled parallel group study. Men $\geq$ 50 years of age with an IPSS $\geq$ 13 and a urine maximum flow rate (Qmax) ranging from 4 to 15 ml/s were selected at 72 sites in 11 European countries (8). Patients were entered into a 2-week wash-out and a 4-week placebo run-in period. A total of 955 patients were randomised (2 : 2 : 1) to silodosin 8 mg (n = 381), tamsulosin 0.4 mg (n = 384) or placebo (n = 190) once daily for 12 weeks (8). Treatment responders were defined as 25% decrease in IPSS and 30% increase in Qmax from baseline. In the primary end-points, superiority of silodosin and tamsulosin treatments vs. placebo was observed with highly statistically significant differences at all weeks (difference from placebo −2.3 and −2.0, respectively, $p < 0.001$). In all the three treatment groups, the percentage of IPSS responders progressively increased from baseline to week 12. At study end, 66.8% and 65.4% of the patients receiving silodosin or tamsulosin were responders, respectively, compared with 50.8% in the placebo group. The differences vs. placebo were highly statistically significant ($p < 0.001$) for both active compounds, whereas the comparison between silodosin and tamsulosin did not show a statistically significant difference (8).

Two USA clinical studies evaluated the efficacy and tolerability of silodosin 8 mg once daily in men with BPH (9). Specifically, men 50 years or older with an IPSS of 13 or greater and peak urinary flow rate of 4–15 ml/s received placebo or 8 mg silodosin daily for 12 weeks (9). The primary end-point was IPSS change from baseline to last observation. Change in peak urinary flow rate was a secondary end-point. After 3–4 days of treatment, patients receiving silodosin vs. placebo achieved significant improvement in total IPSS (difference −1.9, $p = 0.0001$) as well as irritative (−0.5, $p = 0.0002$) and obstructive (−1.4, $p = 0.0001$) subscores. The mean change from baseline in total IPSS was −4.2 for silodosin vs. −2.3 for placebo. Mean change from baseline in peak urinary flow rate after initial dose was greater ($p = 0.0001$) with silodosin (+2.8 ml/s) than placebo (+1.5 ml/s).

In the Japanese study (10), 457 patients were randomised to receive silodosin 4 mg twice daily, tamsulosin 0.2 mg once daily or placebo, for 12 weeks. Inclusion criteria were age $\geq$ 50 years, total IPSS $\geq$ 8, QoL score $\geq$ 3, Qmax < 15 ml/s, prostate volume $\geq$ 20 ml and postvoid residual urine volume < 100 ml (10). The primary end-point was the change in IPSS from baseline. The change in the total IPSS in the silodosin, tamsulosin and placebo groups was −8.3, −6.8 and −5.3 respectively (10). The change in QoL from baseline was −1.7, −1.4 and −1.1 in the silodosin, tamsulosin and placebo groups respectively (10).

In Taiwan, a 12-week, randomised, double-blind, multicentre study was carried out (11). Overall, 170 men aged $\geq$ 40 years, with an IPSS $\geq$ 13, QoL score $\geq$ 3, prostate volume $\geq$ 20 ml, Qmax $<$ 15 ml/s and voided volume $\geq$ 100 ml were enrolled. The primary efficacy measure was the mean IPSS change from baseline. Secondary efficacy measures included change in Qmax and QoL score. The mean difference (silodosin minus tamsulosin) in IPSS change from baseline was −0.60 (95% confidence interval: −2.15–0.95), inferring the non-inferiority of silodosin to tamsulosin. The mean changes in the Qmax and QoL score from baseline were comparable between the groups (both, $p < 0.05$).

Side effects of silodosin relative to other α1-ARs blockers

Cardiovascular safety

Silodosin exhibits cardiovascular safety in efficacy trials with events rate similar to placebo (8–11). In the European trial, no patient treated in the silodosin group recorded clinically meaningful changes for any of the laboratory parameters, vital signs or ECGs observed during the study (8). With regard to the potential effect on blood pressure and/or heart rate, no clinically relevant or statistically significant differences vs. placebo were observed with silodosin (8). In the US trial, the percentage of patients suffering from orthostatic hypotension was similar in the placebo (1.5%) and in the silodosin group (2.6%) (9). In the Taiwan trial, tamsulosin treatment resulted in a significant reduction in mean systolic blood pressure (−4.2 mmHg, within-group $p < 0.004$) relative to a negligible change in silodosin (−0.1 mmHg, within-group $p = 0.9$).

Similar to these phase III trials, a randomised, double-blind, placebo and moxifloxacin-controlled study tested the effects of silodosin on ECG parameters in 186 healthy men. Specifically, therapeutic and supra-therapeutic doses (8 and 24 mg) of silodosin were analysed. No clinically effects on heart rate, PR segment, QRS complex or morphological ECG data were recorded during treatment with silodosin (27).

Retrograde ejaculation

Overall, retrograde ejaculation (RE) is largely reported during treatment with α1-ARs blockers and it is thus considered a class effect (28–30). Moreover, in selective α1-ARs antagonists, RE prevalence is increased by the fact that α1-AR has been demonstrated to be implicated in the normal contractility of the vas deferens (28,31). Moreover, RE during α1-ARs blockers administration may be related to a central effect, as well, as tamsulosin shows a strong affinity for 5HT1A- and D2-like receptors, both of which are involved in the central control of ejaculation (32). Finally, the mechanism of ejaculatory dysfunction is intricately related to insufficient rhythmic contraction of the muscles of the pelvic floor, as well (33). Therefore, the term 'RE', although widely used, should be theoretically considered misinforming, based on the above-cited mechanisms.

Clinically, patients treated with α1-ARs antagonists who develop RE experienced greater LUTS-related symptoms improvements. A recent *post hoc* analysis of phase III studies of silodosin for treatment of BPH symptoms was performed to examine the relationship between treatment efficacy and occurrence of abnormal ejaculation (34). Silodosin-treated patients were stratified by the absence or presence of RE. Silodosin-treated patients with and without RE showed significant improvement in IPSS, Qmax and QoL vs. placebo. RE patients experienced numerically greater improvement relative to patients without RE. For RE patients, the odds of achieving improvement of $\geq$ 3 points in IPSS and $\geq$ 3 ml/s in Qmax were 1.75 times than those for patients without RE ($p = 0.01$) (34).

A second post hoc analysis was performed relying on the Japanese clinical trial and confirmed that ejaculation disorder caused by selective α1-AR antagonists may be associated with very large improvements in LUTS (35). Specifically, the patient who experienced RE is more likely to achieve a combination of symptom improvement (IPSS total) by at least three points and Qmax improvement by at least 3 ml/s (35). In the US studies, the most common adverse event was mild RE (silodosin vs. placebo 28.1% vs. 0.9% respectively). However, only few patients treated with silodosin (2.8%) discontinued because of RE (9).

It is clear that in the younger and sexually active men, the problem of ejaculation might be very bothersome and thus the potential onset of ejaculatory changes and its positive clinical implication should be discussed with the patients (24).

How to get the most out of silodosin: from the critical analysis of the literature to personal clinical experience

Beside the above-cited basic research and clinical findings, some specific recommendations regarding the use of silodosin can be done according to specific patient's characteristics.

Silodosin is rapidly absorbed after oral ingestion and it is advisable to take it after breakfast in the morning. By doing this, the drug reaches a peak serum concentration, which is less if ingested with an

empty stomach: although this concentration is clearly within the therapeutic range, it does not reach the high levels, which are typically associated with adverse events, particularly postural hypotension. As it is well known that sudden hypotension may be dangerous in patients with known cardiovascular disorders and already on treatment with one or more cardiovascular drugs, it is safer not to administer silodosin or any other α1-ARs blockers at bedtime as hypotensive episodes are more common during sleep.

Once treatment with silodosin is started, patients report a symptomatic improvement with silodosin very rapidly. Silodosin has been demonstrated to be efficacious within 2–4 h after administration (concentration peak: T_{max} 2.5 h, $T_{half\ life}$ 11–15 h) (36) with a sustained efficacy during long-term treatment (8–10). Thus, in patients who are bothered by LUTS, silodosin is a very favourable drug as it is able to relieve symptoms very rapidly, which is the first request of the patients.

Besides those clinical practice recommendations, who are the best candidates for silodosin? When considering the pharmacological and clinical characteristics of the drug, silodosin can be considered in the following clinical scenario:

Patients suffering from moderate–severe nocturia

Nocturia is associated with increased prevalence of depressive symptoms (37), sleep loss which causes daytime fatigue (38), potential cardiovascular events, modification in carbohydrate and endocrine function, significantly increased risk of falls and hip fractures in elderly people (39) and, finally, increased mortality (40).

The general management of nocturia would require pre-emptive voiding, nocturnal dehydration, dietary and fluid restrictions, adequate diuretic timing, evening leg elevation to mobilise fluids and, finally, correct potential sleep disturbances.

Although the absolute numbers showed small differences between the three groups in the European trial, only silodosin significantly reduced nocturia vs. placebo (the change from baseline was −0.9, −0.8 and −0.7 for silodosin, tamsulosin and placebo, respectively; $p = 0.013$ for silodosin vs. placebo) (8). In the pooled dataset of all the randomised studies, the mean number of nocturia episodes diminished significantly by −0.2 episodes per night (95% CI; −0.3, −0.1; $p < 0.001$). Moreover, the percentage of patients with simultaneous improvement in three bothersome symptoms (incomplete emptying, frequency and nocturia) was significantly higher in the silodosin group than in the placebo group, both in the ITT population (30.5% vs. 20.2%; $p < 0.0001$) and in the subgroup of patients who reported two or more episodes of nocturia at baseline (34.9% vs. 23.2%; $p < 0.0001$) (41). In addition, in the European study, the improvement in the percentage of these patients was significantly higher with silodosin than with both tamsulosin ($p = 0.03$) and placebo ($p = 0.02$) (41).

Finally, Michel and colleagues explored the effects of silodosin on nocturia by analysing the results of the three above-cited placebo-controlled studies (42). The Authors demonstrated that silodosin consistently induced a significantly greater reduction in nocturia. Specifically, 35% of patients on silodosin had a reduction of $\geq$ 1 episode of nocturia from baseline, as compared to 23% in the placebo group ($p < 0.0001$) (42).

Patients with low normal blood pressure levels and patients concomitantly treated with antihypertensive medications

A significant, age-independent association exists between BPH symptoms and hypertension with increased sympathetic stimulation as a proposed pathophysiological factor for both disease states (43,44). Approximately, 25–30% of all men 60 years of age have concomitant BPH and hypertension. Increased prostate gland volume has been positively correlated with increased diastolic blood pressure and treated hypertension. Thus, the presence of hypertension should be considered in all patients complaining of LUTS (43,44).

According to The European Medicines Agency's Committee for Medicinal Products for Human Use, clinical developmental safety data from patients receiving silodosin with concomitant antihypertensive therapy do not indicate an increase in risk of orthostatic hypotension (45). Specifically, a large number of patients received concomitant treatment with antihypertensive agents during the phase III trials (8–11). In particular, 24% of the patients were administered drugs acting on the renin-angiotensin system, 13% beta-blocking agents, 8.7% calcium antagonists and 7.5% diuretics (45). A comparison of the safety data from patients on concomitant antihypertensive therapy and those not receiving the antihypertensive treatment indicated no increase in the risk of orthostatic hypotension in patients taking antihypertensive agents. Dizziness was slightly more frequent in patients taking antihypertensive medication, whereas there is no increase in the number of patients complaining of vertigo, fatigue or asthenia (45).

Patients concomitantly treated with phosphodiesterase type 5 inhibitors

Erectile dysfunction is common in patients with LUTS as a result of BPH and its management in this

clinical scenario may be difficult because of potential interactions and adverse effects between medication for BPH and phosphodiesterase-5 inhibitors (PDE5I). In this context, a recent study demonstrated that silodosin can be safely administered to patients who are consensually assuming PDE5I (46). Specifically, MacDiarmid et colleagues recently published a placebo-controlled, open-label crossover study including 22 healthy men aged 45–78 years who received 8 mg silodosin for 21 days. On days 7, 14 and 21, subjects also received a single dose of sildenafil 100 mg, tadalafil 20 mg or placebo in random sequence. In comparison with placebo, sildenafil or tadalafil caused small reductions in blood pressure, but no statistically significant orthostatic changes in either blood pressure or heart rate was recorded. The number of positive orthostatic tests was similar for all treatments groups (46). No serious or severe adverse events occurred. In conclusion, the study found no evidence for clinically important pharmacodynamics interaction of silodosin with maximum therapeutic doses of sildenafil or tadalafil. Co-administration appeared not to be associated with a clinically significant risk of orthostatic hypotension or increased HR, and the study raised no safety concerns (46).

Patients not satisfied (for efficacy or tolerability) with previous treatment with other α1-ARs blockers

Silodosin can be considered as second-line drug when adverse events or insufficient clinical effects are recorded with other α1-ARs blockers. A recent randomised crossover study compared the efficacy of silodosin and tamsulosin in patients with LUTS associated BPH (Figure 1) (47). Ninety-seven patients were randomly divided into two groups: a silodosin-preceding group (4 weeks of twice-daily administration of silodosin at 4 mg, followed by 4 weeks of once-daily administration of tamsulosin at 0.2 mg) or a tamsulosin-preceding group (4 weeks administration of tamsulosin, followed by 4 weeks administration of silodosin) (47). No drug withdrawal period was provided when switching the drug. In the first treatment period, both drugs significantly improved the total IPSS score (47). However, after the crossover treatment period, further significant improvement was observed after switching to silodosin treatment, while worsening or little improvement was observed after switching to tamsulosin treatment. Moreover, intergroup comparison of changes revealed that silodosin showed significant improvement of straining and nocturia with first and crossover treatments, respectively, compared with tamsulosin. Silodosin also significantly improved QoL score in both treatment periods, whereas tamsulosin significantly improved QoL score only in the first treatment period (47).

Chronic prostatitis/chronic pelvic pain syndrome-related symptoms

Nichel et al. evaluated the efficacy and safety of silodosin vs. placebo in men with moderate-to-severe non-bacterial chronic prostatitis/chronic pelvic pain syndrome who had not been treated previously with α1-ARs blockers for chronic prostatitis/chronic pelvic pain syndrome (48). They conducted a multicentre, randomised, double-blind, phase II study in 151 patients (mean age 48 years) diagnosed with chronic prostatitis/chronic pelvic pain syndrome, a total National Institutes of Health Chronic Prostatitis Symptom Index (NIHCPSI) score of 15 or greater and a National Institutes of Health Chronic Prostatitis Symptom Index (NIHCPSIP) score of 8. They demonstrated that silodosin relieved symptoms and improved QoL in men with chronic prostatitis/chronic pelvic pain syndrome (48). Specifically, silodosin was

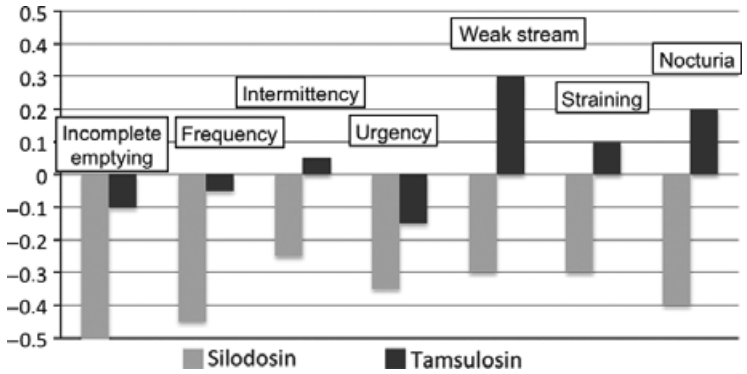

Figure 1 Change from baseline of International Prostate Symptom Score in crossover treatment period. After the crossover treatment period, further significant improvement was observed after switching to silodosin treatment, while worsening or little improvement was observed after switching to tamsulosin treatment. Adapted from Miyakita et al. (47)

associated with a significant decrease in total NIHCPSI score (mean ± SD change: −12.1 ± 9.3) vs. placebo (−8.5 ± 7.2, p = 0.02), including a decrease in urinary symptom and QoL subscores (48). During global response assessment, 56% of patients receiving silodosin vs. 29% receiving placebo reported moderate or marked improvement (p = 0.007) (48).

Patient with either ureteral stones or stone fragments following ESWL treatment

Recently, α1-ARs, especially α1A and α1D subtypes, have been detected in ureters from both animals and humans (49). Moreover, various α1-AR antagonists available in clinics, e.g. alfuzosin, doxazosin, tamsulosin and silodosin, exhibit inhibitory effects on contractions on isolated ureter of a variety of species, including humans and appear to reduce human ureteral activity *in vivo* (50,51). Kobayashi et al. compared the effects of silodosin vs. naftopidil on intraureteral pressure in anesthetised dogs (49,52). They found that silodosin dose dependently suppressed the phenylephrine-induced increase in intravesical ureteral pressure, but decreased the mean blood pressure only at higher doses. In contrast, naftopidil decreased mean blood pressure at the same doses as those that phenylephrine-induced increase in intravesical ureteral pressure (49,52). Therefore, conversely to other α1-ARs blockers, silodosin may facilitate distal ureteral stone passage without reaching potential hypotensive doses.

Moreover, two randomised clinical trials in Japanese male patients demonstrated that silodosin treatment led to significantly higher stone expulsion rates compared with naftopidil and significantly shorter stone expulsion time in the distal ureter at various stone sizes (19,53).

Brachytherapy-related symptoms

Tsumura and colleagues compared the efficacy of naftopidil, tamsulosin and silodosin in improving LUTS secondary to brachytherapy in 212 patients with prostate cancer (54). Patients were randomised to receive naftopidil, tamsulosin or silodosin for 1 year after brachytherapy. The mean changes in the total IPSS at 1 month after brachytherapy in the naftopidil, tamsulosin and silodosin groups were +10.3, +8.9 and +7.5 respectively. There were significantly greater decreases with silodosin than with naftopidil at 1 month in the total IPSS (p = 0.039). The mean change in the PVR at 6 months was +14.6, +23.7 and +5.7 ml in the naftopidil, tamsulosin and silodosin groups, respectively, and silodosin showed a significant improvement in the PVR at 6 months vs. tamsulosin (p = 0.02). Silodosin also resulted in a significantly lower mean difference in the nocturia score at 3 months than either naftopidil (p = 0.03) or tamsulosin (p = 0.02). 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. In conclusion, silodosin has a greater impact on improving brachytherapy-induced LUTS than the other available α1-ARs blockers.

Conclusions

Silodosin is efficacious for the initial management of patients with LUTS. Silodosin has a good cardiovascular safety profile and can be considered an option in BPH/LUTS patients with cardiovascular comorbidities. It seems to be especially beneficial in patients with nocturia alone or presenting with the symptomatic trial nocturia-frequency-incomplete emptying. Patients on PDE5-Is treatment can be safely managed with silodosin. Preliminary results seem to demonstrate a potential role of silodosin in the treatment of chronic prostatitis/chronic pelvic pain syndrome and to facilitate ureteral stone passage, as well.

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