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ABSTRACT

Available α1-blockers (ABs) have different profiles of receptor selectivity. Silodosin exhibits the highest selectivity for the α1A adrenergic receptor. This pharmacological feature couples with a singular urodynamic and clinical profile. The magnitude of bladder outlet obstruction improvement in patients receiving silodosin is higher if compared to other ABs. From a clinical point of view, current evidence suggests an advantage in favor of silodosin in terms of nocturia improvement and cardiovascular safety. The incidence of ejaculatory dysfunction with silodosin is higher compared to other ABs.

Keywords: Alpha-blockers; Silodosin; Urology

INTRODUCTION

For many years, surgery has been accepted as the standard therapy for relieving bladder outlet obstruction secondary to benign prostate hyperplasia (BPH). In recent years, the introduction of medical therapy has dramatically changed the landscape of BPH management, and surgery mainly in the form of transurethral resection of the prostate, laser procedures, or open adenomectomy has been pushed to the second line and offered to patients mainly when they fail medical therapy. Consequently, the total rate of all BPH procedures has progressively declined [1]. Transurethral microwave therapy and transurethral needle ablation of the prostate are characterized by higher retreatment rates with respect to conventional surgery [2]. α1-Blockers (ABs) represent the mainstay of
medical therapy for BPH. They are recommended in men with moderate-to-severe lower urinary tract symptoms related to benign prostatic enlargement (LUTS/BPE). 5-Alpha-reductase inhibitors can be offered in men who have moderate-to-severe LUTS and an enlarged prostate (>40 mL) [2]. They can prevent disease progression with regard to acute urinary retention and need for surgery [2]. ABs are often considered the first-line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events [2]. They can be prescribed in combination with 5-alpha-reductase inhibitors in men with troublesome moderate-to severe LUTS, enlarged prostate, and reduced peak urinary flow (Qmax) [2]. To date, six ABs have been approved for the treatment of LUTS/BPE: terazosin, doxazosin, tamsulosin, naftopidil, alfuzosin, and silodosin [2]. Naftopidil has been approved for the treatment of LUTS/BPE only in Japan, China, and South Korea. ABs inhibit \( \alpha_1 \)-adrenergic receptors (\( \alpha_1 \)-AR) and aim to counteract the effects of endogenously released catecholamines at the level of the lower urinary tract in order to reduce bladder outlet resistance [2]. All available ABs have been reported to significantly improve LUTS with respect to placebo [2]. Although there are no specific indications in favor of one drug over others under specific clinical situations, ABs have different profiles of uroselectivity, a feature that can be defined on the basis of pharmacologic, functional, or clinical features [3, 4]. Silodosin is the most recent AB approved by the US Food and Drug Administration for the treatment of LUTS/BPE (October 2008). The aim of the present review is to summarize the available evidence about pharmacodynamic, urodynamic, and clinical features of silodosin with respect to other ABs.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

PHARMACOLOGICAL AND FUNCTIONAL SELECTIVITY PROFILE

To date, three distinct \( \alpha_1 \)-AR subtypes have been cloned and characterized: \( \alpha_{1A} \), \( \alpha_{1B} \), and \( \alpha_{1D} \). The three receptor subtypes, although related, are structurally distinct. These proteins are proposed to traverse the membrane in seven transmembrane-spanning \( \alpha \)-helical domains linked by three intracellular and three extracellular loops. They differ in terms of amino acids composition, molecular structure of the binding pockets, and signaling pathways [5, 6]. The \( \alpha_1 \)-ARs are distributed in many tissues throughout the body. The \( \alpha_{1A} \)-AR subtype predominates in prostate tissue, where it regulates contraction of the smooth muscle. Interestingly, \( \alpha_{1A} \)-AR subtype expression is increased in BPH prostatic tissue relative to non-BPH prostatic tissue [7]. In non-BPH prostatic tissue, the proportion of \( \alpha_{1A} \) to \( \alpha_{1D} \) to \( \alpha_{1B} \) receptors was found to be 63:31:6, whereas in BPH tissue the proportion was 85:14:1 [7]. In BPH tissue, therefore, \( \alpha_1 \)-AR is by far the predominant subtype, with little expression of \( \alpha_{1D} \) and virtually no expression of \( \alpha_{1B} \) receptors. \( \alpha_{1A} \)-AR subtype also regulates contraction of the smooth muscle in the bladder base and neck, urethra, seminal vesicles, and vas deferens [8]. In BPH tissue, therefore, \( \alpha_1 \)-AR is by far the predominant subtype, with little expression of \( \alpha_{1D} \) and virtually no expression of \( \alpha_{1B} \) receptors. \( \alpha_{1B} \)-AR subtype also regulates contraction of the smooth muscle in the bladder base and neck, urethra, seminal vesicles, and vas deferens [8]. The \( \alpha_{1B} \)-AR is the predominant subtype in the peripheral vasculature of men aged 65 years or older and it regulates contraction of arterial blood vessels in response to postural
redistribution of blood volume. The $\alpha_{1D}$-AR subtype is the primary subtype in the bladder, spinal cord, and nasal passages. The exact role of $\alpha_{1D}$-ARs has not been established, but they are thought to play a role in bladder symptoms. Pharmacologic uroselectivity of ABs is defined on the basis of binding affinities for the three $\alpha_1$-AR subtypes [3]. Quinazolone first-generation ABs such as terazosin and doxazosin and alfuzosin are non-subtype-selective drugs with similar affinity for all $\alpha_1$-ARs [8, 9]. Selective ABs, in contrast, have greater and more favorable interactions with one receptor subtype versus others. Tamsulosin, naftopidil, and silodosin are considered subtype selective. Tamsulosin preferentially blocks $\alpha_{1A}$-AR and $\alpha_{1D}$-AR [8]. Tamsulosin is 15- and 3-fold more selective for the $\alpha_{1A}$-AR subtype than for the $\alpha_{1B}$-AR and $\alpha_{1D}$-AR subtypes [10, 11]. Naftopidil is a subtype-selective AB with high affinity for the $\alpha_{1D}$-AR. It has a three times greater affinity for the $\alpha_{1D}$-AR subtype than for the $\alpha_{1A}$-AR subtype. Silodosin is highly selective for $\alpha_{1A}$-AR, with a 162-fold greater affinity than for $\alpha_{1B}$-AR and about a 50-fold greater affinity than for $\alpha_{1D}$-AR [8, 11].

Functional uroselectivity has been defined using in vitro and in vivo methodologies. The in vitro methodology involves the comparison of the relative affinity of the ABs to inhibit prostate or vascular smooth muscle, whereas in vivo methodologies are based on relative potency for reducing intraurethral pressure versus lowering blood pressures [3]. Tatemichi et al. investigated the selectivity of silodosin for the three distinct $\alpha_1$-AR subtypes by means of receptor-binding and functional pharmacological studies and compared its subtype-selectivity with those of other ABs [12]. Silodosin showed higher selectivity for the $\alpha_{1A}$-AR subtype than tamsulosin or prazosin [12]. Moreover, silodosin strongly antagonized noradrenaline-induced contractions in rabbit lower urinary tract tissues (including prostate, urethra, and bladder trigone) with respect to noradrenaline-induced contractions in rat isolated spleen and rat isolated thoracic aorta [12]. Silodosin was about 280 times more selective for prostate tissue than for splenic tissue and about 50 times more selective than for thoracic aortic tissue [12]. Furthermore, the selectivity for the urethra and bladder trigone was found to be comparable with that for the prostate [12]. The selectivity of tamsulosin for the prostate was about 20 times higher than that of selectivity for spleen, but comparable with that for the thoracic aorta [12]. Prazosin was more selective for the spleen and thoracic aorta showing the selectivity for the prostate to be lower [12]. To evaluate in vivo uroselectivity (ratio of reactivities for lower urinary tract against blood pressure) several animal studies have been performed. Tatemichi et al. investigated the effects of silodosin, tamsulosin, and prazosin on the phenylephrine-induced increase in intraurethral pressure and on blood pressure in anesthetized rats [12]. The authors demonstrated that all ABs suppressed the phenylephrine-induced increase in intraurethral pressure and lowered the mean blood pressure [12]. Uroselectivity was determined as the ratio between the dose to decrease the mean blood pressure by 15% and the dose to suppress intraurethral pressure increase by 50% (ID15/ID50). The order of uroselectivity was silodosin > tamsulosin > prazosin (Table 1) [12].

CLINICAL EFFICACY AND SAFETY

Clinical uroselectivity is defined in the clinical setting by comparing outcomes to side effects [3]. According to some authors, the only
relevant selectivity in the treatment of LUTS/BPE is clinical selectivity [3]. The relevance of \(\alpha_1\)-AR subtype pharmacologic selectivity on the clinical usefulness of existing drug therapies has not been firmly established. However, it has been suggested that selective blockade of \(\alpha_1\)-AR subtypes is necessary for the optimum balance between clinical efficacy and adverse effects [4]. In fact, most serious adverse events with ABs are cardiovascular and mediated by \(\alpha_{1B}\)-AR antagonism.

### URODYNAMIC EFFICACY

Historically, it has been assumed that ABs are able to improve LUTS/BPE by reducing benign prostatic obstruction (BPO) thanks to the relaxing effect on prostatic smooth muscle. However, a correct diagnosis of BPO requires an invasive pressure/flow study (PFS) where urodynamic Qmax and detrusor pressure at Qmax (PdetQmax) are measured, and used to calculate the Bladder Outlet Obstruction Index (BOOI). BPO is defined as a high-pressure/low-flow micturitional pattern. The urodynamic efficacy of ABs has been evaluated in a limited number of studies. The exact role of \(\alpha_1\)-AR subtype selectivity in terms of urodynamic efficacy has been not adequately investigated. Two Japanese studies assessed the urodynamic effects of silodosin. Matsukawa et al. performed the first study evaluating the effects of silodosin on PFS parameters in LUTS/BPE patients [13]. Silodosin was administered at the dosage of 4 mg twice daily for 4 weeks in the context of an open, nonrandomized, nonblinded, single-center, prospective study [13]. The authors found statistically significant improvements of both free uroflowmetry and PFS variables. PdetQmax significantly decreased from 72.5 to 51.4 cmH\(_2\)O and Qmax at PFS significantly increased from 5.9 to 8.8 mL/s (\(p = 0.0001\)) [13]. BOOI decreased in all patients and mean BOOI significantly decreased from 60.6 to 30.8 (\(p < 0.0001\)) [13]. According to the Schaefer nomogram, the degree of obstruction improved by three levels in 8 patients, by two levels in 20 patients, by one level in 28 patients, and was unchanged in 1 patient [13]. A further study was published in 2010 by Yamanishi et al. [14]. Thirty-six male patients with LUTS/BPE who were candidates for surgery were included into the study protocol [14]. Patients were asked to take silodosin 4 mg twice daily for 3 months [14]. Baseline and post-treatment urodynamic data were available from 29 patients. The authors found a statistically significant decrease of both

| Table 1 | Comparison of receptor affinity, tissue and functional selectivity of silodosin, tamsulosin, and prazosin [12] |
|----------|---------------------------------------------------------|
| | Non \(\alpha_1\)-AR subtype selective | \(\alpha_1\)-AR subtype selective |
| | Prazosin | Tamsulosin | Silodosin |
| Affinity for human \(\alpha_{1A}\)-AR subtype, mean \(K_i\) value (nmol/L) | 0.12 | 0.012 | 0.039 |
| Affinity for human \(\alpha_{1B}\)-AR subtype, mean \(K_i\) value (nmol/L) | 0.028 | 0.12 | 6.5 |
| Affinity for human \(\alpha_{1D}\)-AR subtype, mean \(K_i\) value (nmol/L) | 0.078 | 0.030 | 2.2 |
| \(\alpha_1\)-AR subtype selectivity \(\alpha_{1A}/\alpha_{1B}\) ratio | 0.204 | 9.55 | 162 |
| Functional uroselectivity (ED15/ID50) | 0.196 | 2.24 | 11.7 |

*ED15* dose to decrease the mean blood pressure by 15%, *ID50* dose to suppress intraurethral pressure increase by 50%
PdetQmax (from 80.6 to 48.6 cmH_2O, \( p < 0.0001 \)) and BOOI (from 70.2 to 32.6, \( p < 0.0001 \)) [14]. According to the International Continence Society nomogram, obstruction grade improved in 56% of patients who initially had an obstruction or equivocal grade and remained unchanged in 44% of them [14]. Fusco et al. published, for the first time, a systematic review and meta-analysis of published studies in order to clarify the urodynamic outcomes of ABs on BOOI and other major PFS urodynamic parameters in patients with LUTS/BPE [15]. Overall, 17 studies with a total of 656 patients were included in the meta-analysis [15]. The overall pooled analysis of the studies included showed reduction in BOOI after therapy with ABs with respect to baseline values (mean reduction in BOOI by \(-14.19, p < 0.0001\)) [15]. The authors pooled the results of the three randomized placebo-controlled trials containing a placebo arm and found a significant improvement in BOOI in patients undergoing treatment with ABs compared to those taking placebo (mean difference \(-20.54; 95\% \text{ CI} -24.50 \text{ to } -16.58; p < 0.0001\)) [15]. The authors also performed a subgroup analysis according to the type of AB and found a reduction in BOOI for all ABs. These data support the hypothesis that the urodynamic improvement of BPO parameters may be a class effect [15]. However, the magnitude of the improvement varies depending on the single AB. Although no direct comparisons among different ABs have been published, the highest levels of BOOI improvement were reported in the subgroup of studies on silodosin [15]. Mean BOOI change observed was \(-14.88 (95\% \text{ CI} -26.68 \text{ to } -3.08; p = 0.01)\) for alfuzosin, \(-19.41 (95\% \text{ CI} -34.93 \text{ to } -3.89; p = 0.01)\) for doxazosin, \(-16.47 (95\% \text{ CI} -21.51 \text{ to } -11.43; p < 0.0001)\) for naftopidil, \(-6.69 (95\% \text{ CI} -11.35 \text{ to } -2.04; p = 0.005)\) for terazosin, \(-14.27 (95\% \text{ CI} -23.30 \text{ to } -5.23; p = 0.002)\) for tamsulosin, and \(-30.45 (95\% \text{ CI} -40.46 \text{ to } -20.45; p < 0.0001)\) for silodosin [15] (Fig. 1). Considering that 20 points in terms of BOOI are necessary to shift from obstructed to equivocal or from equivocal to unobstructed classes, we could define as clinically relevant the BOOI improvement under therapy with silodosin. These data support a hypothetical link between urodynamic efficacy and pharmacological selectivity. However, the further studies are needed to further elucidate this hypothesis.

However, the cited meta-analysis has some limitations: the few available studies are often outdated, the number of patients is small, only three randomized controlled trials of good methodological quality were available. Moreover, studies were different in terms of populations enrolled and duration of treatment. Finally, a potential limit of evidence on silodosin is that data derived from Japanese patients may not be representative of Caucasians.

![Fig. 1 Mean BOOI change observed for various ABs in urodynamic studies [15]](image)
CLINICAL EFFICACY PROFILE

Controlled studies show that ABs reduce International Prostate Symptom Score (IPSS) by approximately 30–40% [2]. Indirect comparisons and limited direct comparisons between ABs demonstrate that all ABs have a similar efficacy in appropriate doses and can reduce both storage and voiding LUTS [2] (Table 2). Moreover ABs significantly improve Quality of Life (QoL) due to urinary symptoms with respect to placebo [16]. Although studies with less than 1 year of follow-up demonstrate that the efficacy of ABs is not influenced by prostate size, studies with longer follow-up suggest an higher efficacy in patients with prostates smaller than 40 mL [2].

Djavan et al. performed a meta-analysis on the efficacy of ABs in patients with LUTS/BPH [17]. The authors compared alfuzosin, terazosin, doxazosin, and tamsulosin in terms of total symptom score and Qmax [17]. Indirect comparison of data derived from the placebo-controlled studies involving 6333 patients and the data derived from the direct comparative studies involving 507 patients demonstrated that all ABs evaluated produced comparable improvements in LUTS and urinary flow. Total symptom score improved by 30–40% and Qmax by 16–25% [17]. The clinical efficacy of silodosin at the dose of 8 mg for the treatment of LUTS/BPH has been evaluated by two placebo-controlled phase III studies, one non-inferiority study of silodosin vs tamsulosin and one of superiority vs placebo, and one randomized, double-blind study vs tamsulosin [16, 18–21]. Results from phase III studies demonstrated a mean decrease of total IPSS in patients receiving silodosin varying from −6.4 to −10.6. The mean decrease of voiding IPSS and storage IPSS vary from −4.0 to −7.1 and from −2.3 to −3.5, respectively [16, 18–21].

Chapple et al. compared silodosin with tamsulosin and placebo in a placebo-controlled active and parallel group design [16]. The authors found statistically significant improvements in total IPSS, storage, and voiding subscores for both the silodosin and the tamsulosin groups over placebo [16]. This effect was evident soon after initiation of treatment (week 1) and was maintained throughout the study [16]. The authors found a numerical, but not significant, advantage in favor of silodosin with respect to tamsulosin in terms of total IPSS, storage, and voiding subscores [16].

NOCTURIA

LUTS are different in terms of bother and QoL impairment. Nocturia is defined as “the complaint that the individual has to wake at night one or more times to void” [22]. Nocturia is the most common symptom at diagnosis in patients with LUTS/BPH and is reported in about 71–88% of patients followed by frequency (15–79%), urgency (43–68%), and weak stream (47–64%) [23]. Nocturia is a multifactorial condition with many contributing etiological factors. Nocturnal polyuria, defined as a nocturnal urinary output greater than 33%, has been suggested as the most dominant pathophysiologic mechanism causing nocturia in older adults [24]. In elderly BPH patients, nocturnal polyuria interacts with diminution in functional bladder capacity and detrusor instability [25]. It is perceived as one of the most bothersome lower urinary tract symptoms by most men and symptom bother is related to the frequency of nighttime voiding [22]. Two or more voids per night are commonly associated with bother and decreased health-related QoL [22]. The major
| Author | Study design | Treatment | Duration (weeks) | Population (n) | Mean Δ total IPSS | Mean Δ Qmax (mL/s) |
|--------|--------------|-----------|-----------------|----------------|------------------|-------------------|
| Yu et al. [18] | Multicenter, randomized, double-blind | Silodosin 4 mg bd | 12 | 105 | -10.6 | +0.9 |
| | | Tamsulosin 0.2 mg od | | 104 | -10.0 | +1.6 |
| Kawabe et al. [19] | Multicenter, randomized, double-blind, placebo controlled | Silodosin 4 mg bd | 12 | 176 | -8.3<sup>a</sup> | +1.7<sup>a</sup> |
| | | Tamsulosin 0.2 mg od | | 192 | -6.8 | +2.6 |
| | | Placebo | | 89 | -5.3 | +0.2 |
| Chapple et al. [16] | Multicenter, double-blind, placebo controlled | Silodosin 8 mg od | 12 | 381 | -7.0<sup>a</sup> | +3.77 |
| | | Tamsulosin 0.4 mg od | | 384 | -6.7<sup>a</sup> | +3.53 |
| | | Placebo od | | 190 | -4.7 | +2.93 |
| Marks et al. [21] | Pooled analysis of two multicenter, randomized, placebo-controlled studies | Silodosin 8 mg od | 12 | 466 | -6.4<sup>a</sup> | +2.6<sup>a</sup> |
| | | Placebo | | 457 | -3.5 | +1.5<sup>a</sup> |
| Roehrborn et al. [24] | Multicenter randomized, double-blind, placebo-controlled | Terazosin 1–10 mg od | 52 | 976 | -37.8<sup>a</sup> | +2.2<sup>a</sup> |
| | | Placebo | | 973 | -18.4 | +0.7 |
| Van Kerrebroeck et al. [37] | Randomized, double-blind, placebo-controlled | Alfuzosin 10 mg od | 12 | 143 | -6.9<sup>a</sup> | +2.3<sup>a</sup> |
| | | Alfuzosin 2.5 mg tid | | 150 | -6.4<sup>a</sup> | +3.2<sup>a</sup> |
| | | Placebo | | 154 | -4.9 | +1.4 |
| Kirby et al. [38] | Integrated analysis of two multicenter, randomized, double-blind, placebo-controlled studies | Doxazosin 1× 1–8 mg IR | 13 | 640 | -8.0<sup>a</sup> | +2.6<sup>a</sup> |
| | | Doxazosin 1× 4–8 mg GITS | | 651 | -7.9<sup>a</sup> | +2.8<sup>a</sup> |
| | | Placebo | | 155 | -5.8 | +1.1 |
| Griwan et al. [39] | Randomized, controlled | Naftopidil 75 mg od | 12 | 60 | -9.38 | +1.12 |
| | | Tamsulosin 0.4 mg od | | 60 | -9.8 | +1.87 |

<sup>od</sup> once daily, <sup>bd</sup> twice a day, <sup>tid</sup> three times a day, <sup>IR</sup> immediate release, <sup>GITS</sup> gastrointestinal therapeutic system, <sup>IPSS</sup> international prostate symptom score

<sup>a</sup> Statistically significant over placebo
impact of nocturia on QoL is related to the associated sleep disorder. Nocturia is associated with increased prevalence of depressive symptoms, daytime fatigue, potential cardiovascular events, modification of endocrine function, and increased risk of falls and hip fractures in elderly patients [20]. Moreover, nocturia is a strong predictor of mortality, especially in the younger population (<65 years) [22, 26]. The effects of ABs on nocturia are a matter of debate. In their study, Chapple et al. found a significant improvement of nocturia in patients receiving silodosin with respect to placebo and this finding was not evident in the tamsulosin group [16]. This finding was confirmed in a pooled post hoc analysis of data from three randomized, placebo-controlled, double-blind phase III studies with silodosin originally designed to prove superiority over placebo and non-inferiority to tamsulosin for LUTS in patients with signs or symptoms of BPH [22]. The study demonstrated that silodosin was able to significantly reduce nocturia compared to placebo in all three individual studies and also in the pooled study population [22]. In men with at least two nocturnal voids at baseline, 61% and 49% of patients treated with silodosin and placebo had a reduction of at least one void per night, respectively ($p = 0.0003$), and significantly more patients treated with silodosin had less than two nocturnal episodes at study end compared to placebo (29.3% vs 19.0%, $p = 0.0002$). The precise mechanism behind the effect of silodosin on nocturia is yet to be elucidated. Recent guidelines stress the importance of completing frequency-volume charts to identify components of nocturnal polyuria and decreased nocturnal bladder capacity in patients with nocturia [2]. Kim et al. investigated improvement in nocturia and nocturnal polyuria after silodosin administration by using a 3-day frequency-volume chart in a prospective multicenter study [6]. Interestingly, the authors found a significant reduction of nocturnal urine volume at 12 weeks compared to screening ($p = 0.001$) [6]. We can hypothesize that reduction of nocturnal polyuria combined with improved functional bladder capacity are potential mechanisms of action of ABs on nocturia and that this effect it is related to $\alpha_1$-AR subtype selectivity as none of the individual ABs without subtype selectivity has consistently shown a significant reduction in nocturnal voiding episodes [22].

### SAFETY PROFILE

Although ABs are generally safe, adverse event data in short-term clinical trials are not negligible. The most common adverse events involve the cardiovascular system and sexual function. Vascular-related adverse events take the form of postural hypotension, dizziness, headache, syncope, fatigue, and rhinitis, and these are related to peripheral vasodilatation [27, 28]. These symptoms can be life-threatening, particularly in an older patient population and may limit their use alone and in particular with other vasoactive agents such as phosphodiesterase type-5 inhibitors [27]. The incidence of vascular adverse events differs between ABs [29]. The occurrence of vasodilatory side effects among patients using ABs may be related to the specific selectivity profile for $\alpha_1$-AR subtypes of each individual agent [27]. Nickel et al. published a meta-analysis of the vascular-related safety profile and efficacy of ABs for LUTS/BPE [27]. Alfuzosin, terazosin, and doxazosin showed a statistically significant increased risk of developing vascular-related events compared...
with placebo. Tamsulosin showed a numerical increase that was not statistically significant [27]. The odds of developing a cardiovascular-related adverse event was 1.66 for alfuzosin, 3.71 for terazosin, 3.32 for doxazosin, and 1.42 for tamsulosin, as compared with placebo [27]. Concomitant antihypertensive medication increased the incidence of hypotension with some ABs [29]. Silodosin exhibits cardiovascular safety in efficacy trials with events rate similar to placebo. In a pooled analysis of the US and European trials, the incidence of orthostatic hypotension was 1.3% in silodosin recipients and 1.1% in placebo recipients [11]. Approximately 30% of patients in these trials were receiving concomitant antihypertensive medications and the risk of orthostatic hypotension did not significantly differ between silodosin and placebo recipients among patients receiving concomitant antihypertensives (1.8% vs 2.0%) or among patients not receiving concomitant antihypertensives (1.1% vs 0.7%) [30]. Montorsi et al. published a phase IV trial to assess the benefit–risk balance of silodosin in a real-life setting of BPH patients with LUTS, 45.6% of whom had concomitant cardiovascular disease and 56.0% used antihypertensive medications. Overall, hypotension was reported in 0.7% of patients [31]. In the study by Chapple et al. there were not statistically nor clinically relevant differences between silodosin and placebo in terms of blood pressure variations. In contrast, a minor but statistically significant difference versus placebo was observed with tamsulosin [16]. Although an higher percentage of subjects in the tamsulosin group reported headache compared with the silodosin group (5.5% vs 2.9%), the incidence of headache in the tamsulosin group was similar to placebo (4.7%) [16]. In a meta-analysis performed by Novara et al. adverse events other than abnormal ejaculation such as headache, dizziness, and other cardiovascular events were more common with tamsulosin 0.4 mg than with silodosin 8 mg (OR 0.71, p = 0.05) [32]. According to some authors, uroselective ABs should be considered over older, more vasoactive agents for the medical management of LUTS/BPE, particularly in patients with hypertension [33]. Ejaculatory dysfunction (EjD) is considered a class effect of treatment with ABs. It includes a broad spectrum of conditions ranging from absence of seminal emission, reduced ejaculate volume, and reduced ejaculation force [11]. Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor [2]. The impaired contraction of seminal vesicle and spermatic duct at the time of ejaculation is assumed as the major cause of the EjD induced by ABs [34]. Moreover, retrograde ejaculation and insufficient rhythmic contraction of the muscles of the pelvic floor have also been identified as potential causes [33]. This effect is typical of ABs with selectivity for \( \alpha_{1A} \)-AR subtype because this subtype is distributed throughout the organs participating in the emission phase of ejaculation [16]. In fact, \( \alpha_{1A} \)-ARs are essential for the physiologic contractions of the vas deferens and hence for sperm delivery from the testes to the urethra [16]. Gacci et al. performed a systematic review and meta-analysis of the available randomized clinical trials reporting the impact of medical treatments for LUTS/BPE on ejaculatory function [35]. EjD was significantly more common with ABs than with placebo (OR 5.88; \( p < 0.0001 \)) [35]. Doxazosin and terazosin
were associated with a risk of EjD similar to placebo [35]. The risk of EjD with tamsulosin was significantly lower with respect to silodosin (OR 8.58; \( p = 0.006 \) vs OR 32.5; \( p < 0.0001 \)) [35]. In the study by Chapple et al. the incidence of EjD was 14.2% in the silodosin group and 2.1% in the tamsulosin group [16].

EjD does not represent a safety concern because it indicates only a reduction in semen volume that is reversible within a few days upon discontinuation of treatment and is not generally perceived as particularly bothersome [16]. The risk of EjD due to ABs therapy is much lower than that from surgical intervention for BPH and it is rarely serious enough to prompt patients to withdraw from treatment [36]. Moreover, it has been suggested that patients with EjD are those with larger improvements in LUTS and Qmax as compared with those without EjD and this data may explain the very low discontinuation rate [11].

**CONCLUSIONS**

Silodosin distinguishes itself from other ABs on the market from a pharmacological, urodynamic and clinical point of view. It is characterized by the highest selectivity for the \( \alpha_{1A} \)-AR subtype with respect to \( \alpha_{1B} \)-AR and \( \alpha_{1D} \)-AR subtypes. This pharmacological feature is associated with a more pronounced efficacy in terms of BOOI reduction and with a different profile of clinical efficacy and safety with respect to other ABs. Therapy with silodosin is able to reduce the incidence of nocturia episodes and is associated with a lower incidence of vasodilatatory adverse events with respect to other ABs. Further studies are needed to better elucidate the pathophysiological link between the selectivity for the \( \alpha_{1A} \)-AR subtype, urodynamic efficacy, and clinical features.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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REFERENCES

1. Malaeb BS, Yu X, McBean AM, Elliott SP. National trends in surgical therapy for benign prostatic hyperplasia in the United States (2000–2008). Urology. 2012;79(5):1111–6.

2. Gravas S, Bach T, Bachmann A, et al. Guidelines on management of non-neurogenic male lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO). Arnheim: European Association of Urology; 2014.

3. Lepor H. Pathophysiology of benign prostatic hyperplasia: insights from medical therapy for the disease. Rev Urol. 2009;11(Suppl 1):S9–13.

4. Andersson KE, Gratzke C. Pharmacology of alpha1-adrenoceptor antagonists in the lower urinary tract and central nervous system. Nat Clin Pract Urol. 2007;4:368–78.

5. Piascik MT, Perez DM. Alpha1-adrenergic receptors: new insights and directions. J Pharmacol Exp Ther. 2001;298(2):403–10.

6. Kim YW, Park J, Chung H, et al. The effectiveness of silodosin for nocturnal polyuria in elderly men with benign prostatic hyperplasia: a multicenter study. Int Neurourol J. 2015;19(3):190–6.

7. Nasu K, Moriyama N, Kawabe K, et al. Quantification and distribution of alpha1-adrenoceptor subtype mRNAs in human prostate: comparison of benign hypertrophied tissue and nonhypertrophied tissue. Br J Pharmacol. 1996;119:797–803.

8. Rossi M, Roumeguère T. Silodosin in the treatment of benign prostatic hyperplasia. Drug Des Devel Ther. 2010;4:291–7.

9. Osman NI, Chapple CR, Cruz F, Desgrandchamps F, Llorente C, Montorsi F. Silodosin: a new subtype selective alpha-1 antagonist for the treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia. Expert Opin Pharmacother. 2012;13:2085–96.

10. Shibata K, Foglar R, Horie K, et al. KMD-3213, a novel, potent, alpha 1a-adrenoceptor-selective antagonist: characterization using recombinant human alpha 1-adrenoceptors and native tissues. Mol Pharmacol. 1995;48:250–8.

11. Novara G, Chapple CR, Montorsi F. A pooled analysis of individual patient data from registrational trials of silodosin in the treatment of non-neurogenic male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH). BJU Int. 2014;114:427–33.

12. Tatemichi S, Kobayashi K, Maezawa A, Kobayashi M, Yamazaki Y, Shibata N. Alpha1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213). Yakugaku Zasshi. 2006;126:209–16.

13. Matsukawa Y, Gotoh M, Komatsu T, Funahashi Y, Sassa N, Hattori R. Efficacy of silodosin for relieving benign prostatic obstruction: prospective pressure flow study. J Urol. 2009;182:2831–5.

14. Yamanishi T, Mizuno T, Tatsumiya K, Watanabe M, Kamai T, Yoshida K. Urodynamic effects of silodosin, a new alpha 1A-adrenoceptor selective antagonist, for the treatment of benign prostatic hyperplasia. Neurourol Urodyn. 2010;29:558–62.

15. Fusco F, Palmieri A, Ficarra V, et al. α1-blockers improve benign prostatic obstruction in men with lower urinary tract symptoms: a systematic review and meta-analysis of urodynamic studies. Eur Urol. 2016;69:1091–101.

16. Chapple CR, Montorsi F, Tammela TL, et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol. 2011;59:342–52.

17. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. Eur Urol. 1999;36(1):1–13.

18. Yu HJ, Lin AT, Yang SS, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). BJU Int. 2011;108:1843–8.

19. Kawabe K, Yoshida M, Homma Y, Silodosin Clinical Study Group. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. BJU Int. 2006;98:1019–24.

20. Capitanio U, Salonia A, Briganti A, Montorsi F. Silodosin in the management of lower urinary tract symptoms as a result of benign prostatic hyperplasia: who are the best candidates. Int J Clin Pract. 2013;67:544–51.
21. Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective alpha1A-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. J Urol. 2009;181(6):2634–40.

22. Eisenhardt A, Schneider T, Cruz F, Oelke M. Consistent and significant improvement of nighttime voiding frequency (nocturia) with silodosin in men with LUTS suggestive of BPH: pooled analysis of three randomized, placebo-controlled, double-blind phase III studies. World J Urol. 2014;32(5):1119–25.

23. Montorsi F, Mercadante D. Diagnosis of BPH and treatment of LUTS among GPs: a European survey. Int J Clin Pract. 2013;67(2):114–9.

24. Roehrborn CG, Oesterling JE, Auerbach S, et al. The Hytrin Community Assessment Trial study: a one-study of terazosin vs placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT Investigator Group. Urology. 1996;47(2):159–68.

25. Miller M. Nocturnal polyuria in older people: pathophysiology and clinical implications. J Am Geriatr Soc. 2000;48(10):1321–9.

26. Kupelian V, Wei JT, O’Leary MP, Norgaard JP, Rosen RC, McKinlay JB. Nocturia and quality of life: results from the Boston area community health survey. Eur Urol. 2012;61(1):78–84.

27. Nickel JC, Sander S, Moon TD. A meta-analysis of the vascular-related safety profile and efficacy of α1-adrenergic blockers for symptoms related to benign prostatic hyperplasia. Int J Clin Pract. 2008;62(10):1547–59.

28. Irani J. Are all alpha-blockers created the same? Eur Urol. 2006;49(3):420–2.

29. Oelke M, Gericke A, Michel MC. Cardiovascular and ocular safety of α1-adrenoceptor antagonists in the treatment of male lower urinary tract symptoms. Expert Opin Drug Saf. 2014;13(9):1187–97.

30. Novara G, Chapple CR, Montorsi F. Individual patient data from registrational trials of silodosin in the treatment of non-neurogenic male lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH): subgroup analyses of efficacy and safety data. BJU Int. 2015;115(5):802–14.

31. Montorsi F, Gandaglia G, Chapple C, Cruz F, Desgrandchamps F, Llorente C. Effectiveness and safety of silodosin in the treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia: a European phase IV clinical study (SiRE study). Int J Urol. 2016. 23(7):572–9.

32. Novara G, Tubaro A, Sanseverino R, et al. Systematic review and meta-analysis of randomized controlled trials evaluating silodosin in the treatment of non-neurogenic male lower urinary tract symptoms suggestive of benign prostatic enlargement. World J Urol. 2013;31(4):997–1008.

33. Lowe FC. Role of the newer alpha,-adrenergic-receptor antagonists in the treatment of benign prostatic hyperplasia-related lower urinary tract symptoms. Clin Ther. 2004;26(11):1701–13.

34. Sakata K, Morita T. Investigation of ejaculatory disorder by silodosin in the treatment of prostatic hyperplasia. BMC Urol. 2012;19(12):29. doi:10.1186/1471-2490-12-29.

35. Gacci M, Ficarra V, Sebastianelli A, et al. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. J Sex Med. 2014;11(6):1554–66.

36. Kaplan SA. Side effects of alpha-blocker use: retrograde ejaculation. Rev Urol. 2009;11(Suppl 1):S14–8.

37. van Kerrebroeck P, et al. Efficacy and safety of a new prolonged release formulation of alfuzosin 10 mg once daily versus alfuzosin 2.5 mg thrice daily and placebo in patients with symptomatic benign prostatic hyperplasia. ALFORTI Study Group. Eur Urol. 2000;37(3):306–13.

38. Kirby RS, Andersen M, Gratzke P, Dahlstrand C, Hoye K. A combined analysis of double-blind trials of the efficacy and tolerability of doxazosin-gastrointestinal therapeutic system, doxazosin standard and placebo in patients with benign prostatic hyperplasia. BJU Int. 2001;87(3):192–200.

39. Griwan MS, Karthikeyan YR, Kumar M, Singh BJ, Singh SK Comparative evaluation of naftopidil and tamsulosin in the treatment of patients with lower urinary tract symptoms with benign prostatic hyperplasia. Urol Ann. 2014;6(3):181–6.