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REVIEW

α1-Blockers in Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Obstruction: Is Silodosin Different?

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ABSTRACT

Available α1-blockers (ABs) have different profiles of receptor selectivity. Silodosin exhibits the highest selectivity for the α_{1A} 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.

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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 medial 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 α_1-adrenergic receptors (α_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 α_1-AR subtypes have been cloned and characterized: α_{1A}, α_{1B}, and α_{1D}. The three receptor subtypes, although related, are structurally distinct. These proteins are proposed to traverse the membrane in seven transmembrane-spanning α-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 α_1-ARs are distributed in many tissues throughout the body. The α_{1A}-AR subtype predominates in prostate tissue, where it regulates contraction of the smooth muscle. Interestingly, α_{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 α_{1A} to α_{1D} to α_{1B} receptors was found to be 63:31:6, whereas in BPH tissue the proportion was 85:14:1 [7]. In BPH tissue, therefore, α_1-AR is by far the predominant subtype, with little expression of α_{1D} and virtually no expression of α_{1B} receptors. α_{1A}-AR subtype also regulates contraction of the smooth muscle in the bladder base and neck, urethra, seminal vesicles, and vas deferens [8]. The α_{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 α_{1D}-AR subtype is the primary subtype in the bladder, spinal cord, and nasal passages. The exact role of α_{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 α_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 α_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 α_{1A}-AR and α_{1D}-AR [8]. Tamsulosin is 15- and 3-fold more selective for the α_{1A}-AR subtype than for the α_{1B}-AR and α_{1D}-AR subtypes [10, 11]. Naftopidil is a subtype-selective AB with high affinity for the α_{1D}-AR. It has a three times greater affinity for the α_{1D}-AR subtype than for the α_{1A}-AR subtype. Silodosin is highly selective for α_{1A}-AR, with a 162-fold greater affinity than for α_{1B}-AR and about a 50-fold greater affinity than for α_{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 α_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 α_{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

Table 1 Comparison of receptor affinity, tissue and functional selectivity of silodosin, tamsulosin, and prazosin [12]

	Non α_1-AR subtype selective	α_1-AR subtype selective	
	Prazosin	Tamsulosin	Silodosin
Affinity for human α_{1A}-AR subtype, mean K_i value (nmol/L)	0.12	0.012	0.039
Affinity for human α_{1B}-AR subtype, mean K_i value (nmol/L)	0.028	0.12	6.5
Affinity for human α_{1D}-AR subtype, mean K_i value (nmol/L)	0.078	0.030	2.2
α_1-AR subtype selectivity α_{1A}/α_{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%

relevant selectivity in the treatment of LUTS/BPE is clinical selectivity [3]. The relevance of α_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 α_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 α_{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 α_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_2O 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

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% CI −24.50 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% CI −26.68 to −3.08; $p = 0.01$) for alfuzosin, −19.41 (95% CI −34.93 to −3.89; $p = 0.01$) for doxazosin, −16.47 (95% CI −21.51 to −11.43; $p < 0.0001$) for naftopidil,

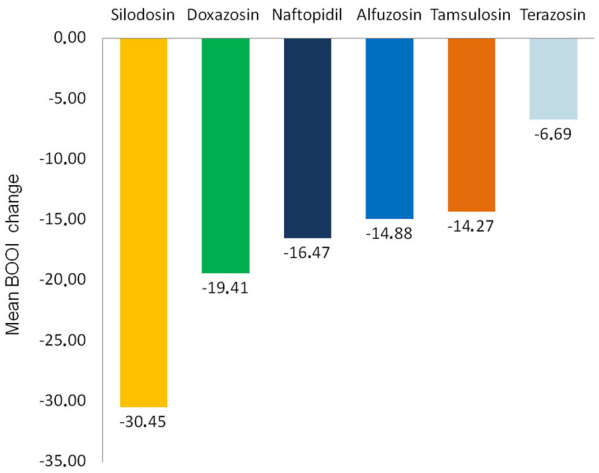

Fig. 1 Mean BOOI change observed for various ABs in urodynamic studies [15]

−6.69 (95% CI −11.35 to −2.04; $p = 0.005$) for terazosin, −14.27 (95% CI −23.30 to −5.23; $p = 0.002$) for tamsulosin, and −30.45 (95% CI −40.46 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.

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

Table 2 Trials with ABs in men with LUTS/BPE

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[a]	+1.7[a]
		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[a]	+3.77
		Tamsulosin 0.4 mg od		384	−6.7[a]	+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[a]	+2.6[a]
		Placebo		457	−3.5	+1.5[a]
Roehrborn et al. [24]	Multicenter randomized, double-blind, placebo-controlled	Terazosin 1–10 mg od	52	976	−37.8[a]	+2.2[a]
		Placebo		973	−18.4	+0.7
Van Kerrebroeck et al. [37]	Randomized, double-blind, placebo-controlled	Alfuzosin 10 mg od	12	143	−6.9[a]	+2.3[a]
		Alfuzosin 2.5 mg tid		150	−6.4[a]	+3.2[a]
		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[a]	+2.6[a]
		Doxazosin 1× 4–8 mg GITS		651	−7.9[a]	+2.8[a]
		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

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

[a] 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 α_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 α_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 α_{1A}-AR subtype because this subtype is distributed throughout the organs participating in the emission phase of ejaculation [16]. In fact, α_{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 α_{1A}-AR subtype with respect to α_{1B}-AR and α_{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 α_{1A}-AR subtype, urodynamic efficacy, and clinical features.

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