Medical therapy options for aging men with benign prostatic hyperplasia: focus on alfuzosin 10 mg once daily

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Abstract: Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) are common in aging men and can significantly affect quality of life. Men with bothersome LUTS/BPH often present with various other age-related conditions, including sexual dysfunction, heart disease, hypertension, diabetes, and the metabolic syndrome, which can complicate management decisions. Therefore, healthcare providers should be familiar with first-line treatment options for LUTS/BPH and their differing safety profiles, particularly with respect to cardiovascular and sexual function side effects. This article presents a review of first-line medical therapy options for managing aging men with LUTS/BPH and patient considerations when evaluating and selecting these therapies, with a focus on the clinical efficacy and cardiovascular and sexual function safety profiles of the uroselective α_1-adrenergic receptor antagonist alfuzosin 10 mg once daily. Alfuzosin improves LUTS, peak urinary flow rates, and disease-specific quality of life, reduces the long-term risk of overall BPH progression, and is well tolerated in aging men, with minimal vasodilatory and sexual function side effects, even in those with comorbidities. Alfuzosin is well tolerated when used in combination with antihypertensive medications and phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. The long-term clinical efficacy and good cardiovascular and sexual function safety profile of alfuzosin can contribute to an improved quality of life for aging men with LUTS/BPH.

Keywords: alfuzosin, lower urinary tract symptoms, benign prostatic hyperplasia, aging, cardiovascular system, sexual function

Introduction

Over the next 50 years, life expectancy is estimated to rise steadily to a mean of 80 years for men in more developed countries (2004a). By 2050, it is estimated that there will be more than 38 million men aged 65 years or older in the United States and more than 7 billion worldwide (US Census Bureau 2004b, 2007). With this increase in longevity comes a greater risk for age-related diseases, including benign prostatic hyperplasia (BPH). Histological BPH is found in approximately 50% of men aged 51–60 years and in approximately 90% of men aged 81–90 years (Figure 1) (Berry et al 1984). It is estimated that about half of men with histological BPH will develop moderate-to-severe lower urinary tract symptoms (LUTS), defined as a score of more than 7 points on the American Urological Association (AUA 2003) Symptom Index or International Prostate Symptom Score (IPSS), including urinary urgency, increased urinary frequency, nocturia, insufficient bladder emptying, and weak or hesitant urinary flow (AUA 2003). Interestingly, the severity of LUTS in men with BPH does not correlate with prostate size or the level of urethral obstruction (Jacobsen et al 1995).

LUTS suggestive of BPH (LUTS/BPH) have a considerable impact on the patient's quality of life. In a large, longitudinal cohort study of US health professionals, men

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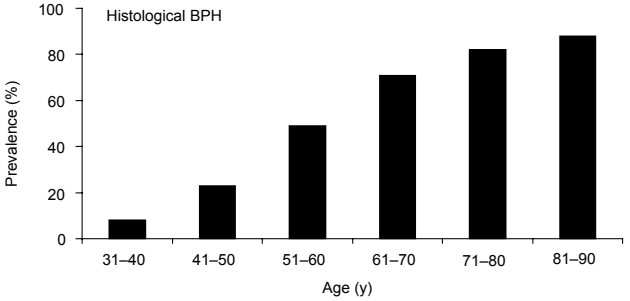

Figure 1 Prevalence of histological benign prostatic hyperplasia (BPH) as a function of age (drawn from data of Berry et al 1984).

with severe LUTS showed a greater impairment of general health status than those with gout, hypertension, angina, or diabetes (Welch et al 2002). Similarly, in the Olmsted County study, there was clear evidence that moderate-to-severe LUTS strongly impaired the daily lives of men aged 40–79 years in terms of degree of bother, interference with daily activities, degree of worry, psychological general well-being, and general health (Girman et al 1994). LUTS/BPH can be even more bothersome due to a strong association between LUTS severity and sexual dysfunction, as consistently demonstrated by various large-scale epidemiological studies (Rosen et al 2005). Sexual dysfunction, including erectile dysfunction (ED) and ejaculatory dysfunction (EjD), is strongly associated with LUTS after controlling for age, comorbidities, and lifestyle factors (Rosen et al 2003; Li et al 2005). The causality of this association is currently not known, but autonomic hyperactivity/increased sympathetic tone, alterations in the Rho/Rho kinase pathway regulating smooth muscle contraction, endothelial (nitric oxide synthase/nitric oxide) dysfunction, atherosclerosis-induced pelvic ischemia, and age-related hormone imbalances may play a role (Rosen et al 2005; McVary 2006).

BPH is often a progressive disease, predominantly characterized by a deterioration of LUTS over time, but also by the occurrence of serious outcomes, including acute urinary retention (AUR; a painful inability to pass urine that requires catheterization) and the need for BPH-related surgery (eg, transurethral resection of the prostate [TURP]) (Emberton et al 2003). Because LUTS/BPH is a common age-related disorder (Berry et al 1984), patients with LUTS/BPH often present with other conditions that increase in prevalence with increasing age, including sexual dysfunction (ED and EjD), heart disease, hypertension, diabetes, and the metabolic syndrome (ie, concurrent metabolic risk factors of abdominal fat, atherogenic dyslipidemia, hypertension, insulin resistance or hyperglycemia, a prothrombotic state, and a proinflammatory state) (Figures 2–5) (Feldman et al 1994; Ford et al 2002; Rosen et al 2003; CDC 2004a, b, c). The presence of concomitant age-related conditions in men with bothersome LUTS/BPH can pose a significant management challenge. Therefore, healthcare providers should be familiar with first-line treatment options for LUTS/BPH and their differing safety profiles, particularly with respect to cardiovascular and sexual function side effects.

The purpose of this review is to describe medical therapy options for managing aging men with LUTS/BPH and patient considerations when evaluating and selecting these therapies, with a focus on the clinical efficacy and cardiovascular and sexual function safety profiles of the uroselective α_1-adrenergic receptor antagonist alfuzosin 10 mg once daily. Relevant English-language articles on the efficacy, cardiovascular safety, or sexual function safety of alfuzosin 10 mg were identified via MEDLINE searches. Abstracts presented at recent meetings, US prescribing information for alfuzosin and other BPH medical therapies, and the current American Urological Association (AUA) BPH Guideline (AUA 2003) were also searched.

LUTS/BPH management

The primary goals of therapy for men with bothersome LUTS are to improve symptoms and improve quality of life (AUA 2003). In addition, each patient's risk for disease progression and the serious complications of BPH (eg, refractory AUR, bladder stone, recurrent urinary tract infection, hematuria, or renal insufficiency) should be considered when selecting a BPH treatment option, with the benefits and side effects of each treatment assessed and discussed with the individual patient. Risk factors for BPH progression and serious complications include increased age, severe LUTS, a high serum prostate-specific antigen (PSA) level, prostate size <30 mL, a low urinary flow rate, and a high postvoid residual urine volume (Roehrborn et al 2000, 2002; Crawford et al 2006;

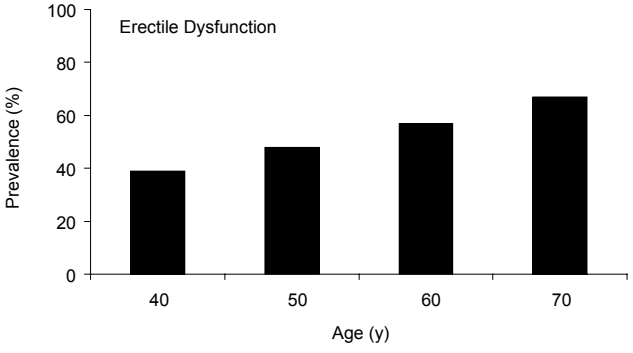

Figure 2 Prevalence of erectile dysfunction as a function of age (drawn from data Feldman et al 1994).

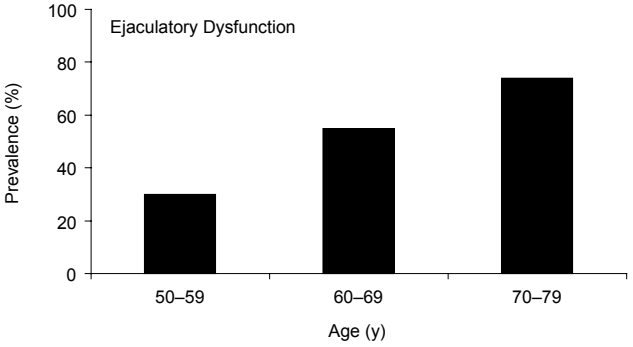

Figure 3 Prevalence of ejaculatory dysfunction as a function of age (drawn from data of Rosen et al 2003).

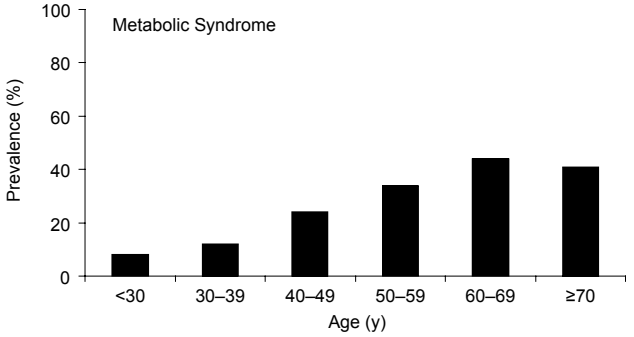

Figure 5 Prevalence of the metabolic syndrome in US men as a function of age (drawn from data of Ford et al).

Roehrborn 2006b) Other factors that need to be addressed when selecting the most appropriate BPH treatment option are the patient's comorbidities, concomitant medications, and sexual activity/sexual function. For some patients, the cost of therapy can also be an important issue (Harkaway and Issa 2006).

Irritative/storage and obstructive/voiding LUTS can be bothersome to many men with BPH. Therefore, the quantification of LUTS and their associated bother with the AUA Symptom Index (identical to the IPSS) and the IPSS bother question, respectively, are recommended by the 2003 AUA Guideline on BPH management for determining disease severity and providing a basis for discussions of BPH treatment options (AUA 2003). The 2003 AUA Guideline states that patients with mild BPH symptoms (AUA Symptom Index <7) and those with moderate-to-severe symptoms (AUA Symptom Index ≥ 8) that do not interfere with quality of life should be managed with watchful waiting (AUA 2003). Patients with bothersome moderate-to-severe BPH symptoms should be provided with information regarding the benefits and risks of recommended BPH treatment options (ie, watchful waiting, medical therapy, minimally invasive therapy, and surgical therapy) (AUA 2003). Benchmark therapy for symptomatic BPH remains TURP. Surgical management may be selected if symptoms are particularly bothersome or if serious complications of BPH have developed. Only transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA) are recommended in the 2003 AUA Guideline as minimally invasive options for the partial relief of LUTS in the standard patient (2003). In many patients with LUTS/BPH, first-line medical therapy with α_1-adrenergic antagonists (α_1-blockers), 5α-reductase inhibitors (5ARIs), or α_1-blocker plus 5ARI combination therapy can provide adequate alleviation of LUTS with fewer and less serious side effects than invasive therapies (2003).

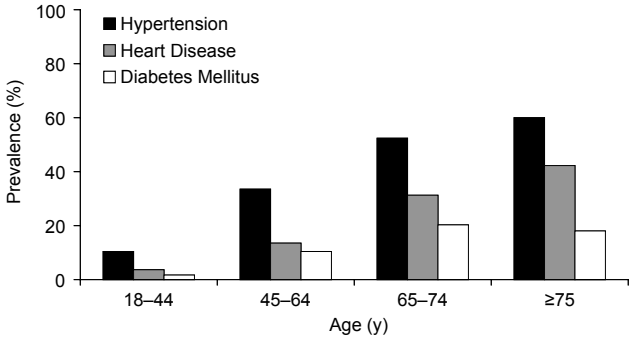

Figure 4 Prevalence of hypertension, heart disease, and diabetes in US men as a function of age (drawn from data of NHANES III (CDC 2004a, b, c).

LUTS/BPH medical therapies

α_1-Blockers

By inhibiting smooth muscle α_1-adrenergic receptors, α_1-blockers (ie, alfuzosin, doxazosin, tamsulosin, and terazosin) relax prostatic and bladder neck smooth muscle and partially relieve LUTS by improving bladder outlet obstruction. These medications have a rapid onset of action (within a few days for improving LUTS) and are considered the most effective monotherapy for the relief of LUTS, irrespective of prostate size. Alfuzosin, doxazosin, and terazosin are quinazoline derivatives, whereas tamsulosin is a sulfonamide derivative. Alfuzosin, doxazosin, tamsulosin, and terazosin have comparable clinical efficacy (ie, 4- to 6-point improvement in the AUA Symptom Index, 2- to 3-mL/s increase in the peak urinary flow rate, and 1- to 1.5-point improvement in the bother score), but differ in their side-effect profiles (AUA 2003). The main side effects associated with α_1-blockers are orthostatic hypertension, dizziness, headache, asthenia, rhinitis, and EjD. Rare instances of hypersensitivity, priapism, palpitations, and edema also have been reported. The older non-uroselective α_1-blockers,

doxazosin and terazosin, require dose titration because of first-dose vasodilatory effects. The uroselective α_1-blockers alfuzosin and tamsulosin affect the lower urinary tract to a greater extent than the cardiovascular system, require no dose titration, and allow convenient once-daily dosing. The results of 2 large randomized studies (MTOPS and ALTESS) have shown that doxazosin and alfuzosin reduce the risk of overall BPH progression, mainly by reducing the risk for LUTS deterioration (McConnell et al 2003; Roehrborn 2006a). In a study in which the cost effectiveness of watchful waiting, medical therapy (α_1-blockers, 5ARIs, or combination therapy), TURP, and TUMT in the treatment of BPH was evaluated, α_1-blockers and TURP were the most cost-effective therapies, from a US payer perspective, for patients with moderate and severe LUTS, respectively (DiSantostefano et al 2006).

5α-Reductase inhibitor (5ARI) monotherapy and combination therapy

Unlike α_1-blockers, which alleviate LUTS by relaxing smooth muscle, 5ARIs inhibit the conversion of testosterone to dihydrotestosterone, thereby inducing glandular atrophy and prostate shrinkage while preventing any further prostate growth. According to the 2003 AUA Guideline, 5ARIs (ie, dutasteride and finasteride) and combination therapy with an α_1-blocker and a 5ARI are appropriate medical therapies for men with LUTS and demonstrable prostate enlargement (AUA 2003). 5ARIs are less effective than α_1-blockers in relieving LUTS, providing a 3- to 4-point improvement in the AUA Symptom Index, a 2- to 2.5-mL/s increase in the peak urinary flow rate, and a $<$1-point improvement in the bother score and their onset of action for relieving LUTS is typically 6–12 months. In appropriate BPH patients, 5ARI therapy can reduce the risk of AUR and the need for BPH-related surgery (McConnell et al 2003). Disadvantages of 5ARI therapy include sexual function side effects (ie, hypoactive sexual desire, EjD, and ED). Although short-term studies ($\leq$1 year) have demonstrated no additional improvements in the AUA Symptom Index and the peak urinary flow rate for combination therapy over α_1-blocker monotherapy (Lepor et al 1996; Debruyne et al 1998; Kirby et al 2003), a 5-year study of combination therapy with doxazosin and finasteride demonstrated a significantly reduced risk of overall BPH progression (ie, increase in AUA Symptom Index of $\geq$4 points and increased occurrence of AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infection) when compared with doxazosin or finasteride monotherapy (McConnell et al 2003). In addition, AUR and BPH-related surgery were significantly reduced with combination therapy when compared with placebo. The benefits of combination therapy should be weighed against the combined side effects of both drugs and the cost associated with the long-term use of 2 drugs.

Mechanism of action of α1-blockers in the treatment of LUTS/BPH

α_1-Blockers are a first-line medical therapy for LUTS/BPH. Adrenergic receptors are involved in the regulation of cardiovascular, genitourinary, and central nervous system function. The second-generation (alfuzosin, doxazosin, and terazosin) and third-generation (tamsulosin) α_1-blockers used for the treatment of LUTS/BPH demonstrate greater selectivity for α_1-adrenergic receptors than α_2-adrenergic receptors (mediators of cardiovascular regulation and the central nervous system effects of α_2-adrenergic agonists). The leading hypothesis is that the blocking of α_1-adrenergic receptors causes relaxation of smooth muscle in the prostate gland and bladder neck, thereby improving urine flow and LUTS. Unlike doxazosin and terazosin, which were initially developed for the treatment of hypertension, alfuzosin and tamsulosin are considered clinically uroselective, meaning that each agent affects the prostate gland to a greater extent than the vascular system, thereby minimizing blood pressure effects.

Three known subtypes of α_1-adrenergic receptors (α_{1A}, α_{1B}, and α_{1D}) are expressed differentially in various human tissues. In the human prostate gland, approximately 70% of the α_1-adrenergic receptors are the α_{1A} subtype, with lower levels of the α_{1B} and α_{1D} subtypes (Lepor et al 1993; Testa et al 1993). Contraction of the human prostate is mediated predominantly by the α_{1A}-adrenergic receptor subtype (Michel and Vrydag 2006), whereas α_{1B}-adrenergic receptors are thought to play an increasing role in the control of blood pressure in individuals aged 65 years and older (Rudner et al 1999). α_{1D}-Adrenergic receptors predominate in the human bladder dome and spinal cord. Alfuzosin, doxazosin, and terazosin demonstrate equal affinity/selectivity for the 3 α_1-adrenergic receptor subtypes of the prostate, whereas tamsulosin exhibits selective binding to the α_{1A} and α_{1D} receptor subtypes versus the α_{1B} receptor subtype. The α_{1A}/α_{1B} selectivity ratio of tamsulosin has been estimated as 20:1 compared with 0.33–0.43:1 for alfuzosin, doxazosin, and terazosin (Fogler et al 1995). The clinical uroselectivity of tamsulosin is thought to result from its binding affinity/selectivity for α_1-adrenergic receptor subtypes (Lowe 2004). The clinical uroselectivity of alfuzosin is thought to result from its preferential distribution to the prostate gland versus blood (Martin et al 1997;

Martin et al 1998; Mottet et al 2003) and its limited ability to penetrate the blood-brain barrier (Martin 1999).

Alfuzosin pharmacology

Alfuzosin is a quinazoline derivative that differs from the other 3 α_1-blockers indicated for the treatment of LUTS/BPH by the absence of a piperidine moiety and the presence of a diaminopropyl spacer. The once-daily formulation of alfuzosin 10 mg, the Geomatrix® delivery system, is composed of 3 distinct layers, a hydrophilic matrix core of active drug and 2 inactive layers that regulate the release of active drug over time (McKeage and Plosker 2002; Data on file, Sanofi-Aventis). The tablet initially swells, with slow gastric diffusion of 30% of the alfuzosin dose, followed by constant diffusion of 40% of alfuzosin in the small intestine, and final dissolution in the colon of the remaining 30% of alfuzosin (Data on file, Sanofi-Aventis). The bioavailability of alfuzosin 10 mg tablets under fed conditions is 49%, with the extent of absorption 50% lower under fasting conditions (Uroxatral® 2006). As a result, alfuzosin should be taken after a meal.

The time to the maximum plasma concentration is reached approximately 8 hours after a single dose of alfuzosin (Uroxatral® 2006). Alfuzosin is predominantly metabolized by the liver, with only 11% of the alfuzosin dose eliminated in the urine as unchanged drug. The apparent elimination half-life of alfuzosin is 10 hours. In elderly patients with BPH, no relationship was demonstrated between peak plasma concentrations of alfuzosin and patient age. However, trough levels are 35% higher in patients aged ≥75 years (Uroxatral® 2006). Because of a reduction in plasma apparent clearance that results in higher plasma concentrations in patients with hepatic insufficiency compared with healthy subjects, alfuzosin is contraindicated in men with moderate or severe hepatic impairment. No dosage modification is required for patients with renal insufficiency, but data are limited for those with severe renal insufficiency (Uroxatral® 2006). Care should be taken when prescribing alfuzosin to men with symptomatic hypotension or with a previous hypotensive response to other medications (Uroxatral® 2006).

Alfuzosin clinical efficacy

Short-term (≤3-month) studies

The clinical efficacy of alfuzosin 10 mg once daily in the treatment of LUTS/BPH has been extensively studied in men evaluated in clinical-trial and practice-based settings, including those aged 65 years and older, those with hypertension, and those taking anti-hypertensive medications. In a randomized, placebo-controlled, crossover study of men with symptomatic BPH, a single dose of alfuzosin 10 mg caused a significant increase in the peak urinary flow rate (Q_{max}; 3.2 mL/s) compared with placebo (1.1 mL/s) as soon as 8 hours after dosing and lasting for at least 4 days (Marks et al 2003). This increase in Q_{max} occurred at the same time as the known peak plasma concentration of drug (Uroxatral® 2006). A subsequent randomized, double-blind, placebo-controlled study of men with symptomatic BPH demonstrated that 7 days of treatment with alfuzosin 10 mg results in rapid symptom relief and increases in Q_{max}, with these improvements maintained during 1 month of treatment (Resnick and Roehrborn 2007). The results of a pooled analysis of data from 3 pivotal, randomized, double-blind, placebo-controlled studies also suggested a rapid onset of action of alfuzosin 10 mg, with significant improvements in LUTS and Q_{max} at their first assessment (28 days and 14 days of treatment, respectively) (Roehrborn et al 2003). A more recent 3-month, open-label study conducted in a clinical-practice setting has also indicated a rapid onset of action of alfuzosin 10 mg in men with LUTS/BPH (Saad et al 2005). At 3 months of alfuzosin treatment, the IPSS improved 7.1 points (41%) from baseline, quality of life improved 1.5 points (38%) from baseline, and nocturia improved in 60% of men with nocturia at baseline, with these improvements predominantly occurring by the first assessment at 9 days of treatment.

In the three pivotal, randomized, double-blind, placebo-controlled studies, 3 months of treatment with alfuzosin 10 mg once daily significantly improved both irritative (frequency, urgency, and nocturia), and obstructive (incomplete voiding, interrupted urine stream, weak urine stream, and difficulty initiating urination) LUTS, Q_{max}, and disease-specific quality of life compared with placebo treatment in men with symptomatic BPH (van Kerrebroeck et al 2000; Roehrborn 2001; Nordling 2005) (Roehrborn et al 2003) (Table 1). In the pooled analysis of these 3 studies, the proportion of patients with a ≥3-point improvement in the IPSS was 76% during 3 months of treatment with alfuzosin compared with 62% for placebo ($p < 0.001$) (Roehrborn et al 2003).

In a recent randomized, double-blind, placebo-controlled study, no significant change in total prostate volume or transition zone volume was demonstrated with transurethral ultrasound measurements during 3 months of treatment with alfuzosin (combined 10-mg and 15-mg groups) compared with placebo treatment (Roehrborn 2006c). Additional investigation of prostate volume changes after long-term treatment with alfuzosin is ongoing.

Long-term (≥9-month) studies

The long-term effectiveness of alfuzosin 10 mg once daily treatment in men with LUTS/BPH has been demonstrated

Table 1 Efficacy of alfuzosin 10 mg once daily in 3-month, randomized, double-blind, placebo-controlled studies

Study	Treatment	N	IPSS[a]	p value[b]	QoL (IPSS bother)[a]	p value[b]	Q_{max} (mL/s)[a]	p value[b]
van Kerrebroeck et al (2000)	Alfuzosin	143	–7	0.002	–1.1	0.0008	2	0.03
	Placebo	154	–5		–0.6		1	
Nordling (2005)	Alfuzosin	154	–7 (5)	0.007	NR		1.5[c]	0.02[c]
	Placebo	153	–5 (6)				0.5[c]	
Roehrborn (2001)	Alfuzosin	170	–4 (5)	0.001	–0.7 (1.1)	0.002	1[c]	0.0006[c]
	Placebo	167	–2 (6)		–0.3 (1.1)		0[c]	
Pooled analysis of 3 studies (Roehrborn et al 2003)	Alfuzosin	473	–6 (5)	<0.001	–1.0 (1.1)	<0.001	2 (4)	0.001
	Placebo	482	–4 (6)		–0.7 (1.1)		1 (3)	

[a]Values represent mean (SD) change from baseline, unless noted otherwise.
[b]p value for mean change from baseline vs placebo.
[c]As assumption of normality was rejected, median change from baseline value is provided and p value represents pairwise comparison with placebo.
Abbreviations: IPSS, International Prostate Symptom Score; NR, not reported; QoL, quality of life (IPSS bother question); Q_{max}, peak urinary flow rate.

in an open-label extension phase of a 3-month pivotal study (Van Kerrebroeck et al 2002), in a 2-year clinical-practice study (ALF-ONE; (Elhilali et al 2006)), and a 2-year study of BPH clinical progression (ALTESS; (Roehrborn 2006a)). In the ALFORTI pivotal study (Van Kerrebroeck et al 2002), patients randomized to receive alfuzosin 10 mg once daily or alfuzosin 2.5 mg 3 times daily during the double-blind phase received alfuzosin 10 mg for up to 9 months in the extension phase, whereas patients randomized to receive placebo during the double-blind phase received alfuzosin 10 mg for up to 9 months in the extension phase. The improvements from baseline in LUTS, Q_{max}, and disease-specific quality of life observed during double-blind treatment with alfuzosin were maintained in the 9-month extension phase of the study. For all patients, LUTS improved 46%, Q_{max} improved 24%, and disease-specific quality of life improved 36% over baseline values at the end of the extension phase (all $p < 0.0001$; Table 2) (Van Kerrebroeck et al 2002).

In the ALF-ONE study (Elhilali et al 2006), in which the efficacy and safety of alfuzosin 10 mg once daily were evaluated in men with LUTS/BPH in a clinical-practice setting over a 2-year period, LUTS improved 39% and disease-specific quality of life improved 43% from baseline (both $p < 0.0001$; Table 2). The majority of men reported symptom relief within 2 weeks of treatment initiation that was maintained throughout the study. Overall, 77% of the men had an improvement in the IPSS of ≥3 points and 50% had a >6-point improvement during alfuzosin treatment, with both irritative and obstructive symptoms significantly improved. After 2 years of treatment with alfuzosin, the percentage of men with nocturia (ie, waking ≥3 times/night to urinate) decreased from 44% at baseline to 14% ($p < 0.001$). These results in a clinical-practice setting demonstrate the long-term efficacy of alfuzosin 10 mg and indicate that the efficacy observed in short-term clinical trials is maintained for at least 2 years.

The long-term effects of alfuzosin 10 mg once daily treatment on BPH clinical progression (ie, occurrence of first AUR episode, need for BPH-related surgery, IPSS worsening of ≥4 points, and overall BPH progression [AUR and/or surgery and/or LUTS worsening]) were evaluated in the 2-year, placebo-controlled ALTESS study (Roehrborn 2006a). In men at risk for BPH progression events, the cumulative incidence of overall BPH clinical progression was significantly reduced 26% during treatment with alfuzosin compared with that during placebo treatment (16.3% versus 22.1% for placebo; $p < 0.0001$). The percentage of men with IPSS worsening by ≥4 points was significantly reduced 30% during alfuzosin treatment compared with that during placebo treatment (11.7% versus 16.8% for placebo; $p = 0.0013$). The risk of the first occurrence of AUR was not reduced with alfuzosin (2.1% versus 1.8% for placebo; $p = 0.82$) and the risk of BPH-related surgery was reduced 22% with alfuzosin compared with placebo treatment (5.1% versus 6.5% for placebo), but this difference was not significant ($p = 0.18$). During the 2-year study, alfuzosin treatment significantly improved the IPSS, disease-specific quality of life (IPSS bother), and Q_{max} compared with placebo (Table 2). These results from the placebo-controlled ALTESS study confirm the long-term efficacy of alfuzosin treatment in the relief of LUTS and the improvement of quality of life in men with BPH observed in open-label studies. In addition, ALTESS study data indicated that high baseline levels of serum PSA (>3.9 ng/mL) predicted BPH-related surgery in both treatment groups and a high

Table 2 Long-term efficacy and safety of alfuzosin 10 mg once daily

	ALTESS study (Roehrborn 2006a)*		ALFORTI extension study (Van Kerrebroeck et al 2002)†	ALF-ONE study (Elhilali et al 2006)‡
Efficacy variable	**Alfuzosin (N = 749)**	**Placebo (N = 757)**	**Alfuzosin (N = 311)**	**Alfuzosin (N = 839)**
IPSS, Mean (SD)	19.2 (4.7) at baseline –5.9 (6.9) change from baseline at month 24 p = 0.0017[a]	19.2 (4.7) at baseline –4.7 (6.9) change from baseline at month 24	17.1 (3.6) at baseline 9.3 (5.5) at month 12 p < 0.0001[b]	16 at baseline 9 (39% improvement) at month 24 p < 0.001[b]
QoL (IPSS bother), mean (SD)	3.8 (1.1) at baseline –1.3 (1.5) change from baseline at month 24 p < 0.001[a]	3.8 (1.1) at baseline –0.9 (1.6) change from baseline at month 24	3.3 (0.9) at baseline 2.1 (1.2) at month 12 p < 0.0001[b]	3.8 at baseline 2.0 (43% improvement) at month 24 p < 0.001[b]
Q_{max} (mL/s), mean (SD)	8.9 (2.0) at baseline 2.0 (3.8) change from baseline at month 12 p = 0.001[a]	8.8 (2.0) at baseline 1.3 (3.6) change from baseline at month 12	9.1 (2.0) at baseline 11.3 (4.2) at month 12 p < 0.0001[b]	NR
Adverse event, n (%)	**(N = 754)**	**(N = 761)**	**(N = 360)**	**(N = 839)**
Vasodilation				
Dizziness	45 (6)	35 (5)	9 (3)	26 (3)
Headache	25 (3)	17 (2)	5 (1)	10 (1)
Syncope	5 (1)	2 (<1)	<1%	4 (<1)
Hypotension	9 (1)	4 (<1)	10 (3)	8 (1)
Malaise	1 (<1)	0	4 (1)	2 (<1)
Sexual function				
Impotence (erectile dysfunction)	15 (2)	14 (2)	<1%	12 (1)
Ejaculation disorder	3 (<1)	0	2 (1)	3 (<1)

*2-year, randomized, double-blind study; †3-month double-blind plus 9-month, open-label study; ‡2-year, open-label study.
[a]p value for mean change from baseline vs placebo.
[b]p value for mean (SD) change from baseline.
Abbreviations: IPSS, International Prostate Symptom Score; NR, not reported; QoL, quality of life (IPSS bother); Q_{max}, peak urinary flow rate.

baseline post-void residual urine volume (>93 mL) predicted IPSS worsening in the placebo group.

The results of a 6-month, open-label, clinical-practice study suggested that the response to treatment with alfuzosin 10 mg is the strongest predictor of AUR and BPH-related surgery in men with LUTS/BPH (Emberton et al 2006). Alfuzosin treatment was associated with a low rate of AUR (0.5%) and BPH-related surgery (1.1%). However, men with a stable or worsening IPSS at 6 months of treatment had a significantly increased risk for AUR (hazard ratio [HR] 3.75, 95% CI 1.58–8.89) and BPH-related surgery (HR 4.71, 95% CI 2.69–8.24); those with an IPSS bother score of >3 during treatment also had a significantly increased risk for BPH-related surgery (HR 7.61, 95% CI 4.16–13.93) (Emberton et al 2006). Therefore, the response to treatment with alfuzosin may help in identifying patients at risk for unfavorable BPH outcomes.

No effect of age or hypertension

When men enrolled in the 3 pivotal studies of alfuzosin 10 mg were stratified according to age <65 years and >65 years at baseline, no significant effect of age was demonstrated on the mean change in the IPSS (–5.6 for men aged <65 years; –5.4 for men aged ≥65 years) or the mean change in Q_{max} (1.9 mL/s for men aged <65 years; 1.7 mL/s for men aged ≥65 years) with alfuzosin 10 mg once daily treatment from that of the entire population (p = 0.67 and p = 0.39, respectively, for age-treatment interaction; Data on file, sanofi-aventis). In an open-label study of the effect of age on the efficacy of treatment with alfuzosin 10 mg/day, 4018 men with LUTS/BPH from general medical practices were stratified into 4 age groups: <56 years, 56 to 65 years, 66 to 75 years, and >75 years (Sanchez-Chapado et al 2000). A significant mean improvement from baseline of 11 to 12 points in the IPSS was demonstrated for all age groups after

2 months of treatment with alfuzosin, with both irritative and obstructive LUTS improving significantly when compared with baseline values. In addition, significant mean improvements in the IPSS bother score of 2–3 points were shown for all age groups after 2 months of treatment with alfuzosin when compared with baseline values (Sanchez-Chapado et al 2000). The results of this study in a clinical-practice setting are in agreement with those of clinical trials indicating that age does not affect the clinical efficacy of alfuzosin 10 mg. Thus, alfuzosin 10 mg is an effective treatment for LUTS/BPH in aging men, including the elderly. Pooled data from the 3 pivotal studies of alfuzosin 10 mg also demonstrated that the changes in IPSS and Q_{max} with alfuzosin treatment were comparable in men with hypertension (diastolic blood pressure >90 mmHg) and those without hypertension (diastolic blood pressure ≤90 mmHg; p = 0.19 and p = 0.87, respectively, for hypertensive status-treatment interaction (Data on file, sanofi-Aventis).

Role in AUR management

A 2-phase, randomized, double-blind, placebo-controlled study (ALFAUR) evaluated the effect of alfuzosin 10 mg treatment on the outcome of a trial without catheter after a first occurrence of AUR related to BPH (McNeill and Hargreave 2004; McNeill et al 2005). In phase I of the study, 360 men with a first episode of AUR secondary to BPH received alfuzosin 10 mg or placebo for 3 days before a trial without catheter (McNeill and Hargreave 2004; McNeill et al 2005). Alfuzosin treatment significantly improved the rate of a successful trial without catheter (62% for alfuzosin versus 48% for placebo; p = 0.012). In phase II of the study, all patients who successfully voided after catheter removal received either alfuzosin 10 mg or placebo for 6 months (McNeill et al 2005). Alfuzosin treatment was associated with a 61% (p = 0.04 versus placebo), 52% (p = 0.04 versus placebo), and 29% (p = 0.20 versus placebo) reduction in the risk for BPH surgery at 1, 3, and 6 months, respectively. The combined rate of successful trial without catheter during phase I and no BPH-related surgery during 6 months of treatment during phase II was 39% for men receiving alfuzosin versus 25% for those receiving placebo (p = 0.02) (McNeill et al 2005). Based on data from the ALFAUR study, alfuzosin treatment during hospitalization for the first occurrence of AUR and after a successful trial without catheter resulted in significant cost savings during the first 6 months when compared with placebo treatment and with immediate prostate surgery (both $p < 0.05$) (Annemans et al 2005). Alfuzosin is approved for the adjuvant treatment of AUR in more than 50 countries, but is not currently approved for this indication in the United States. Additional large-scale studies are needed to evaluate the role of alfuzosin in the management of BPH-related AUR.

Alfuzosin tolerability and safety

The tolerability and safety profiles of the different α_1-blockers are important considerations when selecting a medication for the long-term management of LUTS/BPH in aging men. Many of the side effects of some α_1-blockers (eg, dizziness, orthostatic hypotension, syncope) are related to the blood pressure lowering effects of these medications. These vasodilatory side effects have the potential to cause falls, broken bones, hospitalization for serious injuries, and institutionalization (Morris and Wagg 2007). A meta-analysis of placebo-controlled studies has indicated that the incidence rates of dizziness and orthostatic hypotension with alfuzosin 10 mg and tamsulosin 0.4 mg treatment are similar to or only slightly greater than those with placebo, whereas these incidence rates are generally higher with doxazosin and terazosin treatment than with placebo (Djavan and Marberger 1999). In controlled clinical trials, the incidence of myocardial infarction, angina pectoris, and death for men treated with alfuzosin 10 mg was low and typical of that of control middle-aged or older men (Data on file, Sanofi-Aventis). Sexual function also should be assessed and discussed with men before selecting a treatment option for managing bothersome LUTS/BPH and when evaluating the response to treatment. Alfuzosin 10 mg once daily, with its tolerability and good cardiovascular and sexual function safety profiles, can contribute to an improved quality of life for aging men with LUTS/BPH, including the elderly and those with other common age-related comorbidities.

Cardiovascular profile

In the three pivotal studies of alfuzosin 10 mg, no first-dose vasodilatory side effects were observed with alfuzosin treatment and the incidence of patient withdrawal was comparable in the alfuzosin (9%) and placebo groups (10%) (Roehrborn et al 2003). The incidence of vasodilation-related side effects ranged from 6% to 15% with alfuzosin compared with 2%–9% with placebo (van Kerrebroeck et al 2000; Roehrborn 2001; Nordling 2005) (Table 3). Dizziness was the most common side effect in the placebo group (3%) and the alfuzosin group (5%). The incidence of vasodilatory side effects was comparable for elderly (7%) and younger (6%) men and for hypertensive (8%) and normotensive (5%) men who received alfuzosin 10 mg. Patients with mild or moderate

Table 3 Vasodilatory and sexual function side effects of alfuzosin 10 mg once daily in randomized, double-blind, placebo-controlled studies

	van Kerrebroeck et al (2000)		Nordling (2005)		Roehrborn (2001)		Pooled analysis of 3 studies (Roehrborn et al 2003)	
	Alfuzosin (N = 143)	Placebo (N = 154)	Alfuzosin (N = 154)	Placebo (N = 153)	Alfuzosin (N = 176)	Placebo (N = 175)	Alfuzosin (N = 473)	Placebo (N = 482)
Adverse event, n (%)								
Vasodilation								
Dizziness	3 (2)	2 (1)	9 (6)	6 (4)	13 (7)	5 (3)	25 (5)	14 (3)
Headache	2 (1)	1 (<1)	3 (2)	5 (3)	9 (5)	4 (2)	14 (3)	10 (2)
Syncope	NR	NR	0	0	NR	NR	1 (<1)	0
Hypotension	1 (<1)	0	0	0	6 (3)	6 (3)	2 (<1)	0
Malaise	2 (1)	0	0	0	NR	NR	NR	NR
Sexual function								
Impotence (erectile dysfunction)	0	1 (<1)	2 (1)	0	5 (3)	2 (1)	7 (1)	3 (<1)
Ejaculation disorder	0	0	2 (1)	0	1 (<1)	0	3 (<1)	0

NR = not reported.

renal insufficiency taking alfuzosin 10 mg did not experience more vasodilatory side effects than patients taking placebo or patients with normal renal function (van Kerrebroeck et al 2000). Pooled data from the 3 pivotal studies indicated no significant change from baseline in systolic or diastolic blood pressure measurements during alfuzosin or placebo treatment (Roehrborn et al 2003). The effects of alfuzosin on blood pressure (Table 4) and heart rate in the 3 pivotal studies of alfuzosin 10 mg were small, comparable to placebo, and not considered clinically relevant (Roehrborn et al 2003). The maximum mean decrease from baseline was –2 mmHg for both men receiving alfuzosin and those receiving placebo. Changes from baseline in blood pressure measurements were comparable for elderly men and men with hypertension in the 2 treatment groups (Table 4). Importantly, the incidence of asymptomatic orthostatic hypotension (ie, a decrease in systolic blood pressure of ≥20 mmHg upon standing) was low and similar in the alfuzosin and placebo groups (Roehrborn et al 2003). Long-term treatment with alfuzosin 10 mg once daily did not alter the side effect profile or the cardiovascular safety profile of alfuzosin (Table 2) (Van Kerrebroeck et al 2002; Elhilali et al 2006; Roehrborn 2006a). Long-term treatment with alfuzosin 10 mg did not increase the incidence of orthostatic hypotension for men taking antihypertensive medications or for men with mild-to-moderate renal impairment (Van Kerrebroeck et al 2002).

Table 4 Mean (SD) blood pressure effects of alfuzosin 10 mg once daily in randomized, double-blind, placebo-controlled studies

	All patients			Elderly (≥65 y) patients			Hypertensive patients		
	Baseline	Change at 3 months	n (%)	Baseline	Change at 3 months	AOH[a], n (%)	Baseline	Change at 3 months	n (%)
SBP									
Alfuzosin	136 (17)	–2 (15)		138 (17)	–1 (15)		143 (16)	–2 (18)	
Placebo	138 (17)	–1 (15)		142 (17)	–2 (15)		147 (18)	–3 (17)	
DBP									
Alfuzosin	82 (10)	–1 (9)		81 (10)	–1 (10)		86 (10)	–2 (10)	
Placebo	83 (10)	–2 (10)		83 (9)	–0.2 (9)		88 (11)	–2 (9)	
AOH[a]									
Alfuzosin			10 (2)			5 (2)			1 (1)
Placebo			8 (2)			2 (1)			5 (4)

Adapted from Roehrborn et al (2003).

[a]Decrease in SBP of ≥20 mm Hg when changing from a supine to an upright position.

Abbreviations: AOH, asymptomatic orthostatic hypotension; DBP, diastolic blood pressure (supine); SBP, systolic blood pressure (supine).

In the clinical practice setting, large-scale studies have demonstrated that the cardiovascular safety profile of alfuzosin 10 mg is not affected by age, cardiovascular comorbidity, and anti-hypertensive comedications. In a study of 6,523 men with LUTS/BPH who were treated with alfuzosin for 6 months, the incidence of vasodilatory side effects was did not differ significantly among age quartiles (ie, <60 years, 60–64 years, 65–70 years, and >70 years), between men with and those without cardiovascular comorbidity (ie, hypertension, ischemic heart disease, or diabetes mellitus), or between men taking and those not taking antihypertensive medications (ie, diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, or calcium channel blockers) (Figure 6) (Hartung et al 2006). Furthermore, despite the increased prevalence of cardiovascular comorbidity and increased use of antihypertensive medications with age, no significant changes from baseline in blood pressure measurements and heart rate were demonstrated among the different age groups after 6 months of alfuzosin treatment. Mean changes from baseline in blood pressure measurements (decreases of <3 mmHg) and heart rate (increase of 1 beat/minute) were modest in men with and those without cardiovascular comorbidity and in men taking and those not taking antihypertensive medications (Hartung et al 2006). The good cardiovascular safety profile of alfuzosin 10 mg during long-term treatment in a clinical practice setting was confirmed in the 2-year ALF-ONE study and the 2-year ALTESS study, which demonstrated that the incidence of vasodilatory side effects and blood pressure changes from baseline were marginal and not significantly affected by age (≤65 years), hypertension, or antihypertensive comedication (Elhilali et al 2006; Roehrborn 2007).

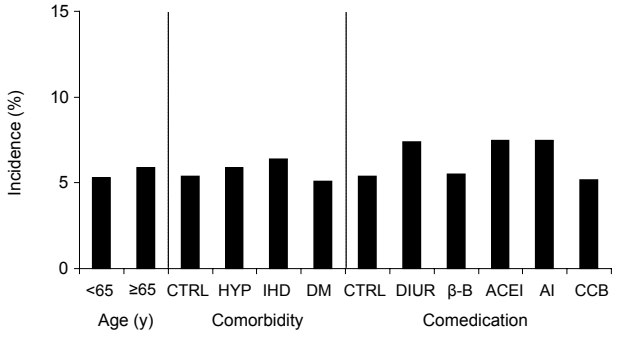

Figure 6 Incidence of vasodilatory side effects during treatment with alfuzosin 10 m g once daily according to age, comorbidities, and antihypertensive comedications (drawn from data of Hartung et al 2006).

Abbreviations: CTRL, control (no HYP, IHD, DM or no antihypertensive medication); HYP, hypertension; IHD, ischemic heart disease; DM, diabetes mellitus; DIUR, diuretic; β-B, β-blocker; ACEI, angiotensin-converting enzyme inhibitor; AI, angiotensin II inhibitor; CCB, calcium channel blocker.

Finally, in a small study in 18 healthy, middle-aged men, no hemodynamic interactions were observed between alfuzosin 10 mg once daily and the phosphodiesterase type 5 inhibitor tadalafil 20 mg (Giuliano et al 2006). In an open-label study of men with BPH who were treated with alfuzosin 10 mg once daily and tadalafil 20 mg (as needed, but no more than twice weekly), no significant change in blood pressure measurements or the side effect profile was observed over a 1-month period when compared with either monotherapy (Yassin and Diede 2003). Preliminary results of a post-marketing surveillance study of men with ED who were treated with vardenafil indicated that the type and incidence of side effects were similar in those taking and those not taking alfuzosin (Van Ahlen et al 2005). Current US labeling for sildenafil, tadalafil, and vardenafil states that these phosphodiesterase type 5 inhibitors should be started at the lowest recommended dose for patients stabilized on α-blocker therapy, whereas α-blocker therapy should be started at the lowest recommended dose for patients already taking sildenafil, tadalafil, or vardenafil (Cialis® 2005; Levitra® 2005; Viagra® 2006). Placebo-controlled studies are needed to evaluate optimal management approaches for concomitant LUTS/BPH and ED.

Sexual function profile

Sexual activity is common among older men (Diokno et al 1990; Lindau et al 2007) and is an important component of quality of life for aging men (Rosen et al 2003). The majority of men between the ages of 50 and 75 years report that they are sexually active, but many of these men are bothered by sexual problems, including sexual dysfunction. Because of BPH treatment-related sexual side effects and the known strong association between LUTS and sexual dysfunction, the effects of BPH medical therapies on sexual function are an important consideration when selecting the most appropriate BPH treatment and when monitoring men on BPH treatment. For example, tamsulosin has demonstrated a dose-related incidence of EjD (8% for tamsulosin 0.4 mg and 18% for tamsulosin 0.8 mg versus 0.2% for placebo) in US placebo-controlled studies (Flomax® 2006). Recent results of studies in healthy male volunteers have indicated that tamsulosin treatment results in decreased ejaculate volume or anejaculation (Hisasue et al 2005; Hellstrom and Sikka 2006), possibly due to peripheral effects of tamsulosin on the seminal vesicles and vas deferens and central effects of tamsulosin on serotonin and dopamine receptors that play a role in ejaculation. In each of the 3 placebo-controlled pivotal studies of alfuzosin 10 mg, the incidence of sexual function side effects during treatment with alfuzosin was

low and comparable to that with placebo treatment (Table 3) (van Kerrebroeck et al 2000; Roehrborn 2001; Nordling 2005). The pooled analysis of data from the 3 pivotal studies indicated that the incidences of ED and EjD were <1% and 0%, respectively, with alfuzosin compared with 1% and 1%, respectively, with placebo during 3 months of treatment (Roehrborn et al 2003). Alfuzosin 10 mg also has been shown to have minimal effects on sexual function during long-term treatment (Table 2) (Van Kerrebroeck et al 2002; Elhilali et al 2006; Roehrborn 2006a). Interestingly, data from a preliminary open-label study of 3076 men with LUTS/BPH demonstrated that alfuzosin 10 mg treatment for 1 year led to significant improvements from baseline in both ED and EjD (each $p < 0.001$) (van Moorselaar et al 2005). The mean improvements from baseline in ED and EjD were greater in men with severe LUTS than in those with mild or moderate LUTS at baseline. Direct comparator studies are needed to further evaluate differences in the sexual function safety profiles of the different α_1-blockers used in the treatment of LUTS/BPH.

Many aging men with symptomatic BPH are managing concomitant ED with oral phosphodiesterase type 5 inhibitors (ie, sildenafil, tadalafil, vardenafil). Moreover, the adrenergic nervous system appears to play a role in the pathophysiology of both ED and BPH. The results of studies of combination treatment with alfuzosin 10 mg once daily and phosphodiesterase type 5 inhibitors in men with ED and BPH have suggested a synergistic beneficial effect of these medications on ED, EjD, and LUTS. In a 12-week pilot study of the efficacy and safety of combination therapy with alfuzosin 10 mg and sildenafil 25 mg once daily in men with previously untreated LUTS/BPH and ED, the improvement in LUTS from baseline was greater with combination treatment (24%) than with either medication alone (alfuzosin 16%; sildenafil 17%) (Kaplan et al 2007). The frequency of urination, nocturia, and Q_{max} significantly improved with alfuzosin and combination therapy, whereas no significant improvement in these parameters was demonstrated with sildenafil monotherapy. Erectile function improved with both sildenafil (50%) and alfuzosin (17%) monotherapy, but the greatest improvement was demonstrated with combination therapy (59%) (Kaplan et al 2007). There was no evidence of hypotension or syncope during 12 weeks of treatment with alfuzosin plus sildenafil combination therapy. The possibility of a synergistic effect of alfuzosin 10 mg once daily and tadalafil 20 mg (on demand 20–60 minutes before sexual activity) in the treatment of LUTS and ED was also suggested by the results of an open-label study of 42 men with LUTS/BPH and ED who were previously unresponsive to tadalafil monotherapy (Yassin and Diede 2003). During 6 months of combination therapy, LUTS and ED improved, with 71% of the men reporting improved erectile function. The side-effect profile associated with alfuzosin plus tadalafil combination therapy was comparable to that with each monotherapy. Additional studies are needed to evaluate the beneficial effects of alfuzosin on sexual function in men with LUTS/BPH.

The 25-item Male Sexual Health Questionnaire (MSHQ) (Rosen et al 2004) and a 4-item short form of the MSHQ (MSHQ-EjD Short Form) (Rosen et al 2007a) have been validated as self-administered instruments for assessing sexual function in aging men. The MSHQ, which includes a 7-item ejaculatory function domain, provides an in-depth assessment of ejaculatory function and differentiates between men with LUTS and EjD and healthy men (Rosen et al 2004). The MSHQ-EjD Short Form, with 3 ejaculatory function items and 1 ejaculation bother item, differentiates between men with none/mild LUTS and those with moderate/severe LUTS and is useful for assessing EjD in clinical practice and research settings (Rosen et al 2007a). Both the MSHQ and the MSHQ-EjD Short Form have demonstrated sensitivity for detecting treatment-related effects in men with LUTS/BPH enrolled in the BPH Registry and Patient Survey (Rosen et al 2007b).

Intraoperative floppy iris syndrome (IFIS)

Cataract is an age-related condition that affects more than 20 million adults aged 40 years or older in the US, including nearly 8 million men (National Eye Institute 2002). The occurrence of intraoperative floppy iris syndrome (IFIS) during cataract surgery has been reported in men with BPH who were treated with tamsulosin, but not in those treated with α_1-blockers without α_1-adrenergic receptor subtype selectivity (Chang and Campbell 2005; Oshika et al 2007). It was suggested that tamsulosin-induced IFIS may be due to inhibition of the predominant α_{1A}-adrenergic receptor in the iris that regulates dilator smooth muscle tone (Chang and Campbell 2005). In a recent retrospective comparative study of 35 men who reported exclusive use of either tamsulosin or alfuzosin at their initial evaluation visit for cataract surgery, men who used tamsulosin had a significantly higher risk for IFIS relative to those who used alfuzosin (adjusted odds ratio = 32.25, 95% CI 2.74–377.11) after adjusting for duration of α_1-blocker use, diabetes mellitus, and hypertension (Blouin et al 2007). Results from in vivo studies in rabbits demonstrated that alfuzosin, doxazosin, tamsulosin, and

terazosin inhibit phenylephrine-induced mydriasis at doses similar to those required to inhibit phenylephrine-induced increases in intraurethral pressure, whereas higher doses are needed to inhibit pupil contraction in the absence of phenylephrine (Michel et al 2006). Based on these results, the authors concluded that the ocular risk of tamsulosin is comparable to other α_1-blockers. Although additional studies are needed to determine the safety of α_1-blockers with respect to the development of IFIS during cataract surgery, treatment with an α_1-blocker should be stopped at least 1 week before cataract surgery and phenylephrine should not be used to induce mydriasis.

Alfuzosin clinical utility in aging men

α_1-Blockers, including alfuzosin, are a first-line medical therapy for LUTS/BPH. Alfuzosin 10 mg once daily requires no dose titration and has a rapid onset of action, making it convenient and easy to use by elderly men, especially after a missed dose. Alfuzosin 10 mg tablets, with the Geomatrix® delivery system, break down and release drug at a constant rate over time. Alfuzosin, doxazosin, tamsulosin, and terazosin have similar efficacy profiles with respect to improvements in LUTS and Q_{max}, but their safety profiles, especially relating to their cardiovascular tolerability and sexual function side effects, are different. These safety profile differences may be related to pharmacologic differences among the 4 α_1-blockers, particularly their blood-brain barrier penetration and α_1-adrenergic receptor subtype selectivity. The efficacy of alfuzosin in relieving symptomatic BPH is not affected by age, cardiovascular comorbidity, or antihypertensive comedications, so it is an effective treatment option for the long-term management of LUTS/BPH in elderly men. Alfuzosin has a favorable safety profile, with minimal cardiovascular and sexual function side effects. The cardiovascular safety profile of alfuzosin in elderly men is comparable to that in younger men. As sexual activity is common and an important component of quality of life in many aging men, healthcare providers should consider the effects of the different medical therapies for LUTS/BPH on sexual function, both erectile function and ejaculatory function. Alfuzosin effectively relieves the irritative and obstructive urinary symptoms of BPH without any negative effects on sexual function, whereas other drugs in this class can be associated with sexual function side effects. Long-term alfuzosin treatment reduces overall LUTS progression compared with placebo and may help to select patients at risk for serious BPH outcomes. Importantly, alfuzosin and the other α_1-blockers that demonstrate equal affinity/selectivity for the 3 α_1-adrenergic receptor subtypes appear to be associated with a very low incidence of IFIS during cataract surgery relative to that observed with tamsulosin, further suggesting that α_1-adrenergic receptor subtype selectivity may be responsible for various treatment-related side effects during tamsulosin therapy.

Conclusions

Aging men with LUTS/BPH are at increased risk for the development of several other age-related diseases, including sexual dysfunction, heart disease, diabetes, and the metabolic syndrome. All of these conditions, which can negatively affect quality of life, need to be considered when evaluating and selecting BPH treatment options. The currently available α_1-blockers, alfuzosin, doxazosin, tamsulosin, and terazosin, demonstrate equal clinical effectiveness in relieving LUTS suggestive of BPH (a 4–6 point improvement in IPSS; a 2–3 mL/s increase in Q_{max}; and a 1–1.5 point improvement in the IPSS bother score), but differ with respect to their cardiovascular and sexual function safety profiles. Alfuzosin 10 mg once daily is effective in improving LUTS, Q_{max}, and disease-specific quality of life, reduces the long-term risk of LUTS progression, and is well tolerated in aging men with BPH, with minimal vasodilatory side effects, even in those with hypertension, heart disease, and diabetes and those taking antihypertensive medications. Alfuzosin also has no deleterious effect on sexual function and is well tolerated when used in combination with low doses of phosphodiesterase type 5 inhibitors for the treatment of ED. Studies suggest that alfuzosin and phosphodiesterase type 5 inhibitors may act synergistically to improve both LUTS and sexual function, but the tolerability of higher doses of phosphodiesterase type 5 inhibitors is not known. The efficacy and tolerability of alfuzosin 10 mg once daily are similar in elderly and younger patients. The long-term clinical efficacy and the cardiovascular and sexual function safety profiles of alfuzosin 10 mg once daily can contribute to an improved quality of life for aging men with LUTS/BPH.

Disclosures

CGR has been an investigator for and a consultant to Sanofi Aventis.

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