Efficacy of α-Adrenergic Receptor Blockers in the Treatment of Male Lower Urinary Tract Symptoms

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Male lower urinary tract symptoms (LUTS) are one of the most common causes for a consultation with a health care provider, and one of the most common causes of male LUTS is benign prostatic hyperplasia (BPH). In recent decades, medical therapy has established itself as viable and cost effective for the majority of men. For the treatment of male LUTS in the United States, the 5 currently available α-adrenergic receptor blockers are alfuzosin, doxazosin, silodosin, terazosin, and tamsulosin. α-Blockers remain one of the mainstays in the treatment of male LUTS and clinical BPH. They exhibit an early onset of efficacy (within less than 1 week) with regard to both symptoms and flow rate improvement, maintain such improvements in open-label and controlled trials for up to 5 years, and have been shown to prevent symptomatic progression.

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Male lower urinary tract symptoms (LUTS) are one of the most common causes for a consultation with a health care provider, and their treatment is a significant contributor to the overall health care expenditure in the United States and most developed countries. Male LUTS is commonly stratified into 3 different symptom categories: voiding or obstructive (hesitancy, slow stream, intermittency, incomplete emptying), storage or irritative (frequency, urgency, nocturia, urge urinary incontinence), and postmicturition (postvoid dribbling).[1] One of the most common, but by no means the only, cause of male LUTS is benign prostatic hyperplasia (BPH), the stromoglandular hyperplasia of the prostate gland that develops after age 40 in the majority of men, and is present

on tissue samples in about 50% of all men over the age of 50 years.[2] At least as frequently is the bladder the source of male LUTS; symptoms of overactive bladder (urgency, frequency, nocturia, and urge urinary incontinence) are as common in men as they are in women, although they are less often labeled as such and more often treated as BPH-related symptoms in men.[3] Due to the increase in life expectancy worldwide, and the aging of the Baby Boom Generation in the United States, a considerable increase in the population of men seeking care for male LUTS is forecast that will require adjustments on the part of the health care provider and cost-effective management algorithms.[4]

Whereas in decades past the only available treatment option was a transurethral resection of the prostate, in the past 20 years medical therapy has established itself firmly as a viable and cost-effective alternative for the majority of men.[5,6] In addition to the 2 major classes of drugs, the α-adrenergic receptor blockers (or α-blockers) and the 5α-reductase inhibitors, antimuscarinics, phytotherapeutic agents, and combinations thereof are in widespread use. None, however, are more often used than α-blockers, which were introduced for the treatment of male LUTS in the early 1990s.[7]

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α_1-Adrenergic Receptors

Adrenergic receptors (ARs) were originally divided into α-AR and β-AR categories,[8] but application of molecular biologic methods has confirmed 9 total AR subtypes: α_{1A} (formerly named α_{1C}), α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, and β_3.[9] α_1 ARs generally mediate their actions through members of the $G_{q/11}$ family of G proteins that stimulate inositol phosphate (membrane phospholipid) hydrolysis, with each subtype demonstrating different efficacy of coupling to phosphoinositide hydrolysis: $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$.[10] In addition, α_1-AR subtypes can be pharmacologically distinguished on the basis of differential binding to α_1-antagonists (blockers),[11] as well as differential inactivation by the alkylating agent chloroethylclonidine.[10,12]

Tissue Distribution of α_1-Adrenoceptor Subtypes

All 3 α_1-AR subtypes exist in a wide range of human tissues.[13] The α_{1A}-AR subtype shows highest levels of expression in human liver, followed by slightly lower levels in heart, cerebellum, and cerebral cortex; the α_{1B}-AR subtype has highest expression in human spleen, kidney, and fetal brain; α_{1D}-AR has highest levels in the cerebral cortex and human aorta.[13]

In terms of male LUTS, α_1-AR expression in prostate, urethra, spinal cord, and bladder is important. Molecular and contraction studies in human prostate tissue demonstrate the α_{1A}-AR subtype predominance (70%-100%) in prostate stroma.[14,15] Because baseline tone is present in prostate smooth muscle (due to its rich sympathetic innervation), blockade of prostate α_{1A}-ARs results in relaxation of prostate smooth muscle. Hence, α_1-AR blockade is capable of modifying the dynamic (prostate smooth muscle contraction) component in BPH. Another tissue important in LUTS is the urethra. To date, most studies show that all regions of human urethra (including bladder neck and intraprostatic urethra) contain only α_{1A}-ARs. Because of reflex arcs, spinal cord α_1-AR expression may be important in LUTS.[16]

Normal detrusor (bladder smooth muscle tissue) obtained from surgical patients expresses predominantly α_{1D}-ARs, although other subtypes are present to a lesser extent.[17] Studies demonstrating increased α_{1D}-AR expression and function in models of bladder hypertrophy provide a mechanistic explanation for increased irritability symptoms associated with LUTS.[18,19]

α_1-AR antagonists mediate vasodilation in vasculature; therefore, one of the side effects of treating LUTS with α_1-AR antagonists is hypotension. α_{1A}-ARs predominate in human splanchnic (mesenteric, splenic, hepatic, and distal omental) resistance arteries.[20] Interestingly, α_1-AR expression increases 2-fold in representative (mammary) arteries with aging, with the ratio of α_{1B}:α_{1A} increasing, whereas no alteration occurs in veins.[20] Studies of pharmacy databases in Europe suggest that the administration of α_1-AR blockers increases the incidence of hip fractures (chosen as a surrogate for clinically important orthostatic hypotension)[18]; further analysis with regard to the precise α_1-AR antagonists prescribed suggests that avoidance of α_{1B}-AR blockade may result in fewer overall hip fractures.[21]

Clinical Use of α-Adrenoceptor Antagonists for the Treatment of LUTS

Efficacy of α-Blockers

For the treatment of male LUTS in the United States today, alfuzosin, doxazosin, silodosin, terazosin, and tamsulosin are the 5 available α_1-AR antagonists (Table 1). Terazosin, doxazosin, and alfuzosin are non–subtype selective in that they block all 3 α_1-AR subtypes. In contrast, tamsulosin blocks α_{1A}- and α_{1D}-ARs with 10-fold greater affinity than α_{1B}-ARs, and is

Table 1
Clinical Pharmacology of Currently Available α_1-Blockers Used to Treat Male Lower Urinary Tract Symptoms

	Alfuzosin	Doxazosin	Silodosin	Tamsulosin	Terazosin
α_1-AR Subtype Selectivity*	Non–Subtype Selective	Non–Subtype Selective	$\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$	$\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$	Non–Subtype Selective
Pharmacologic selectivity	N	N	Y	Y	N
Clinical selectivity†	N	N	Y	Y	N
Registered for use in hypertension?	N	Y	N	N	Y
Reduces elevated blood pressure?	Y	Y	N	N	Y
Usual daily dose (mg)	7.5-10	1-8	8 mg	0.4	1-10
Regimen (doses/d)	1	1	1	1	1
Modified-release formulation	Y	Y	N	Y	N

AR, adrenergic receptor; N, no; Y, yes.
*Alfuzosin, doxazosin, and terazosin demonstrate similar selectivities for all 3 α_1-AR subtypes.
†Differentiation of desired urological and unwanted cardiovascular α_1-blockade (data from Richardson et al.[11]).
Modified from Schwinn and Roehrborn.[46]

therefore considered α_1-AR subtype selective. The newest compound, silodosin, blocks α_{1A} with 162-fold greater affinity than α_{1B}-ARs and is also subtype selective (Table 2).[22]

Many authoritative reviews have been published suggesting that the efficacy of the α-blockers alfuzosin, doxazosin, tamsulosin, and terazosin is comparable.[7,23,24] Many randomized, placebo-controlled trials, as well as open-label studies, suggest that an improvement in the International Prostate Symptom Score (IPSS) of 4 to 6 points may be expected, as well as an improvement in the single disease-specific quality of life (QoL, scale from 1-6) question of 1 to 1.5 points. Changes in the maximum urinary flow rate (Q_{max}) of 2 to 3 mL/s are in general the results of α-blocker therapy (Table 3). These 4 α-blocking agents have been shown to be superior to placebo in pivotal phase III trials leading to their approval by the regulatory agencies worldwide.

Table 2
Uroselectivity: Inhibition of Hypogastric Nerve Stimulation in Decerebrate Dogs

	Urethral Pressure (ID_{50}) (μγ/kg)	Blood Pressure (ED_{15}) (μγ/kg)	Uroselectivity (BP/UP)
Intravenous Injection			
Silodosin	3.15	8.03	2.55
Tamsulosin	1.73	0.59	0.35
Prazosin	11.8	2.46	0.21
Intraduodenal Injection			
Silodosin	26.4	266.3	10.1
Tamsulosin	5.48	5.95	1.09
Prazosin	–	–	–

BP, blood pressure; ED_{15}, dose required to reduce BP by 15%; ID_{50}, dose required to inhibit the increase in intraurethral pressure by 50%; UP, urethral pressure.
Adapted with permission from Akiyama K et al.[47]

The newest entry in the class is silodosin, a highly selective α-blocker for the α_{1A} receptor, which was studied in the United States in 2 pivotal phase III studies of 12 weeks duration followed by a common open-label extension study of 40 weeks duration.[25,26] The 2 12-week studies randomized 457 and 466 patients, respectively, to receive placebo versus

Table 3
Efficacy and Adverse Events of α-Blockers

	Alfuzosin*	Doxazosin*	Silodosin†	Tamsulosin*	Terazosin*
IPSS 3-9 mo/10-16 mo	−4.44	−5.10/−5.63	−6.4/−7.8	−4.63/−7.53‡	−6.22/−5.99
Q_{max} 3-9 mo/10-16 mo	2.05	3.11/2.98	2.6	1.85/1.86‡	2.51/1.94
QoL 3-9 mo/10-16 mo	−1.10	−1.25/−1.47		−1.43	−1.70‡/−1.37
BPH II 3-9 mo/10-16 mo		−2.0/−2.47			1.45‡/−2.09
Asthenia	4	15	NR	7	12
Cardiovascular	1	2	NR	8	2
Dizziness	5	13	3.2	12	15
Gastrointestinal system	10	10	2.6	11	5
Headache	5	8	2.4	12	7
Nasal congestion/rhinitis	6	8	2.1	11	6
Ejaculation problem		0	28.1	10	1
Erection problem	3	4	NR	4	5
Hypotension, asymptomatic	NR	5		7	8
Hypotension, symptomatic	1				3
Hypotension, symptomatic postural		4	2.6	3	6
Hypotension, symptomatic syncope	1	0		1	1

BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; Q_{max}, peak urine flow rate.
*Based on randomized clinical trials (data from American Urological Association Practice Guidelines Committee[48]).
†From 2 randomized, controlled trials lasting 12 weeks and open-label extension trial of 52 weeks in length (data from Marks et al[25]).
‡Data based on single-arm meta-analyses.
Adapted from American Urological Association Practice Guidelines Committee.[48]

silodosin, 8 mg, daily, and enrolled men with an average IPSS score of 21.2 to 21.4 points and a Q_{max} between 8.4 and 9.0 mL/s. The IPSS improvements were 6.3 and 6.5 points versus 3.4 and 3.6 improvements in the placebo arms, respectively, and the flow rate improvements were 2.2 and 2.9 versus 1.2 and 1.9 mL/s, respectively. The data from these 2 trials were pooled by Marks and colleagues.[25] Of the 661 participants in the 40-week open-label extension study, 435 (65.8%) completed the study and experienced an improvement in IPSS of 6.8 (crossover from placebo) and 7.8 (continuation on 8 mg silodosin) points, respectively.[26]

Early Onset of Efficacy

A double-blind, placebo-controlled study was conducted to investigate whether alfuzosin, 10 mg once daily, improves the Q_{max} and LUTS from BPH after 1 week and 1 month of treatment. A total of 372 men age 50 years or older with symptomatic BPH received alfuzosin or placebo for 28 days. Q_{max} increased significantly from baseline at day 8 with alfuzosin ($P < .001$ vs placebo); this improvement was evident within 24 hours after the first dose and was maintained at day 29. LUTS improved from baseline with alfuzosin at day 8 ($P = .07$ vs placebo) and day 29 ($P = .003$ vs placebo). Alfuzosin, 10 mg once daily, exhibits a rapid onset of action, with improvements in Q_{max} and LUTS maintained through 1 month of treatment.[27] Similar studies have been performed using tamsulosin[28] and doxazosin gastrointestinal therapeutic system (GITS).[29]

Early onset of activity using silodosin was assessed by administering the IPSS score 0.5 weeks after initiation of treatment in the 2 12-week trials, resulting in an improvement of 3.9 and 4.4 points, respectively, which proved superior to placebo.

Early onset of activity using silodosin was assessed by administering the IPSS score 0.5 weeks after initiation of treatment in the 2 12-week trials, resulting in an improvement of 3.9 and 4.4 points, respectively, which proved superior to placebo. Similarly, in a subset of patients, a flow rate

measurement was performed 2 to 6 hours after the first morning dose, and a 2.8 mL/s improvement was noted, suggesting that the onset of efficacy is indeed quite rapid.[25]

Urodynamic Effects of α-Blockers

Urodynamic effects of the compounds were assessed in 2 studies employing invasive pressure flow studies in Japan. Yamanishi and coworkers[30] treated 36 patients with LUTS and BPH and performed pressure flow studies at baseline and at 3 months, noting a decrease in the detrusor pressure at maximal flow (p_{det} @ Q_{max}) from 80.6 to 48.6 cm H_2O and a decrease in the bladder outlet obstruction index (BOOI) from 70.2 to 32.6 ($P < .0001$ for both). In a similar study, Matsukawa and coauthors[31] treated 57 patients with silodosin, 8 mg, for 4 weeks and performed pressure flow studies before and after. Similar to the previous study, they found a decrease in $p_{det}Q_{max}$ (cm H_2O) from 72.5 to 51.4 and in the BOOI from 60.6 to 33.8 ($P < .0001$). These findings are particularly remarkable as meta-analyses of urodynamic studies using α-blocking agents had failed to show a significant effect of the other α-blocking agents on these parameters,[32,33] raising the possibility that the highly selective effect on the $\alpha 1_A$ receptor at the bladder neck might be responsible for the observed reduction in obstruction, which is nearly commensurate with the effect of a surgical intervention.

Long-Term Effects of α-Blocker Therapy

Although the onset of action of all α-blockers is rather quick (ie, within 1 week), controlled long-term efficacy and safety data are not as widely available. There are many open-label extension studies, often following a placebo-controlled, double-blinded study, in which patients are asked to participate voluntarily. These studies are sometimes criticized because of the so-called responder enrichment bias. This effect implies that only those patients who had good results with the drug are interested in continuing in the open-label extension portion of the study. Despite this potential bias, the resulting data allow at least a comparison between the patients who were originally on placebo and switched to open-label active drug and those who were on active drug (but did not know it) and continued on it. In the case of silodosin, the results of such open-label extension studies suggest that the active-active patients had a 7.8-point improvement at 1 year as compared with the placebo-active patients who experienced a 6.8-point improvement.[26]

For the older α-blockers, controlled clinical trial data are available that in aggregate suggest that the efficacy in terms of symptom improvement in unselected patient populations with LUTS is maintained. The Veterans Administration Cooperative Study combination medical therapy study[34] randomized 1229 patients to placebo versus finasteride versus terazosin versus combination for 12 months. The IPSS improvements were 2.6, 3.2, 6.1, and 6.2 points, respectively ($P < .001$ for the comparisons of both terazosin and combination therapy with finasteride and with placebo). The mean changes at 1 year in Q_{max} rates were increases of 1.4, 1.6, 2.7, and 3.2 mL/s, respectively ($P < .001$ for the comparisons of both terazosin and combination therapy). The results of a very similar study in 1095 patients randomized in Europe (Prospective European Doxazosin and Combination Therapy [PREDICT])[35] to placebo versus finasteride versus doxazosin versus combination were very similar. ALTESS (the Alfuzosin Long-Term Efficacy and Safety Study)[36] enrolled more than 1500 men at risk for progression to be randomized to alfuzosin, 10 mg daily, versus placebo. Symptom score and flow rate improvements in the alfuzosin arms were significantly superior to placebo and maintained for 2 years. Tamsulosin was tested in the CombAT (Combination Therapy with Avodart and Tamsulosin) study,[37] in which more than 4500 men at risk for progression were randomized to tamsulosin versus dutasteride versus combination for 4 years. The adjusted mean change in IPSS from baseline to year 4 was −6.3 points for combination therapy versus −3.8 points ($P < .001$) for tamsulosin and −5.3 points ($P < .001$) for dutasteride. At month 48, the adjusted mean increase in Q_{max} from baseline was 2.4 mL/s for combination therapy versus 0.7 mL/s ($P < .001$) for tamsulosin and 2.0 mL/s ($P = .05$) for dutasteride. Lastly, the MTOPS (Medical Therapy of Prostatic Symptoms) study[38,39] enrolled more than 3000 patients randomized to placebo versus doxazosin versus finasteride versus combination therapy in a progression prevention study over 5 years. The 4-year mean reduction in symptom score was 4.9 in the placebo group, 6.6 in the doxazosin group, 5.6 in the finasteride group, and 7.4 in the combination therapy group. The mean improvement in flow rate was 4.0 mL/s in the doxazosin group, 3.2 mL/s in the finasteride group, and 5.1 mL/s in the combination therapy group.

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Acute Urinary Retention and Trial Without Catheter

Several randomized trials have studied whether the administration of α-blockers at the time of an acute urinary retention (AUR) event would

be beneficial and improve the outcome of a trial without catheter (TWOC). Two studies performed randomizing patients in AUR to placebo versus alfuzosin suggest that the success rates may be improved from 47.9% to 61.9% and from 29% to 55%, respectively.[40,41] Similar success was found by others using tamsulosin with an improvement from 26% to 48% of successful voiding.[42] A Cochran meta-analysis concluded that "the limited available evidence suggests that alpha-blockers increase success rates of TWOC."[43] It may be assumed that this represents a class effect and applies to all α-blockers.

Prevention of Progression of LUTS/BPH

Three controlled studies focused on the prevention of certain elements of progression of LUTS and clinical BPH using medical therapy, which are the 2-year ALTESS study (placebo vs alfuzosin),[36] the 4-year CombAT study (tamsulosin vs dutasteride vs combination),[37] and the 5-5.5 year MTOPS study (placebo vs doxazosin vs finasteride vs combination).[40] These 3 studies use 3 different α-blocking agents, are of different duration (2 vs 4 vs 5 years), and enroll different patient populations (MTOPS enrolled patients independent of prostate size and serum prostate-specific antigen, whereas ALTESS and CombAT enrolled patients at risk for progression based on prostate size and/or serum prostate-specific antigen). The findings are remarkably consistent among the studies.

In the ALTESS trial, alfuzosin did not reduce the risk of AUR (alfuzosin 2.1% vs placebo 1.8%; $P = .82$) but tended to reduce the risk of surgery (5.1% vs 6.5%; $P = .18$); the reduction in risk (RR) and 95% confidence interval with alfuzosin was 22% (−18-48); and significantly reduced the risk of symptom deterioration (11.7% vs 16.8%; $P = .0013$); the RR was 30% (10-46). The overall clinical progression of BPH was significantly lower with alfuzosin than with placebo (16.3% vs 22.1%; $P < .001$); RR 26% (9-40).[36]

In the CombAT trial, the time to first AUR or BPH-related surgery was significantly lower with combination therapy when compared with tamsulosin ($P < .001$); there was no significant difference between combination therapy and dutasteride ($P = .18$).[37] Time to first BPH clinical progression was significantly different in favor of combination therapy versus tamsulosin and dutasteride ($P < .001$ for both comparisons). Combination therapy reduced the relative risk of BPH clinical progression by 44.1% compared with tamsulosin and 31.2% compared with dutasteride.

In the MTOPS trial, the rate of overall clinical progression among men in the placebo group was 4.5 per 100 person-years. As compared with placebo, doxazosin reduced the risk of progression by 39%, to 2.7 per 100 person-years ($P < .001$), and finasteride by 34%, to 2.9 per 100 person-years ($P = .002$). Treatment with finasteride and combination therapy significantly reduced the risk of receiving invasive therapy by 64% ($P < .001$) and 67% ($P < .001$), respectively, as compared with placebo. In contrast, doxazosin did not significantly reduce the cumulative incidence of invasive therapy.[39]

Medical Expulsive Therapy for Ureteral Stones

An interesting use of α-blockers in medical expulsive therapy for ureteral stones is beyond the scope of this review. However, likely due to the presence of α receptors in the upper urinary tract, stone passage appears facilitated by the use of α-blocking agents.[44,45]

Safety and Adverse Events

Safety issues and adverse events spectra differ considerably between the available α-blockers and are discussed in another contribution in this supplement [Kaplan SA. Side effects of α-blocker use: retrograde ejaculation. *Rev Urol.* 2009;11(suppl 1): S14–S18].

Due to the presence of α receptors in the upper urinary tract, stone passage appears facilitated by the use of α-blocking agents.

Conclusions

α-Blockers remain a mainstay in the treatment of male LUTS and clinical BPH. They exhibit an early onset of efficacy (within less than 1 week) with regard to both symptoms and flow rate improvement, maintain such improvements in open-label and controlled trials for up to 5 years, are useful adjuncts in the management of patients in AUR prior to a TWOC and in the management of ureteral stones, and have been shown to prevent symptomatic progression (although not progression to AUR and subsequent surgery, which appears to be driven by prostate volume increases and the natural history of BPH, which is not affected by α-blockers). The efficacy appears to be similar across all α-blockers, although some drugs simply have not been tested in certain situations. The new compound silodosin has excellent early efficacy and distinguishes itself by a strong effect not only on symptoms but on obstruction as measured by pressure

flow studies, a finding perhaps explained by the strong selectivity to the α_{1A} receptor.

References

1. Chapple CR, Roehrborn CG. A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. *Eur Urol*. 2006;49:651-659.
2. Roehrborn C, McConnell J. Etiology, pathophysiology, epidemiology and natural history of benign prostatic hyperplasia. In: Walsh P, Retik A, Vaughan E, et al, eds. *Campbell's Urology*. 8th ed. Philadelphia: Saunders; 2002:1297-1336.
3. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol*. 2006;50:1306-1315.
4. Jacobsen SJ, Girman CJ, Guess HA, et al. New diagnostic and treatment guidelines for benign prostatic hyperplasia. Potential impact in the United States. *Arch Intern Med*. 1995;155:477-481.
5. McConnell JD, Barry MJ, Bruskewitz RC, et al. *Benign Prostatic Hyperplasia: Diagnosis and Treatment. Quick Reference Guide for Clinicians*. AHCPR Publication No. 95-0583. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services; 1994.
6. McConnell J, Abrams P, Denis L, et al. *Male Lower Urinary Tract Symptoms: Evaluation and Management*. 6th ed. Paris, France: Health Publications; 2006.
7. Clifford GM, Farmer RD. Medical therapy for benign prostatic hyperplasia: a review of the literature. *Eur Urol*. 2000;38:2-19.
8. Docherty JR. Subtypes of functional alpha1- and alpha2-adrenoceptors. *Eur J Pharmacol*. 1998;361:1-15.
9. Hieble JP, Bylund DB, Clarke DE, et al. International Union of Pharmacology. X. Recommendation for nomenclature of alpha 1-adrenoceptors: consensus update. *Pharmacol Rev*. 1995;47:267-270.
10. Hawrylyshyn KA, Michelotti GA, Coge F, et al. Update on human alpha1-adrenoceptor subtype signaling and genomic organization. *Trends Pharmacol Sci*. 2004;25:449-455.
11. Richardson CD, Donatucci CF, Page SO, et al. Pharmacology of tamsulosin: saturation-binding isotherms and competition analysis using cloned alpha 1-adrenergic receptor subtypes. *Prostate*. 1997;33:55-59.
12. Schwinn DA, Johnston GI, Page SO, et al. Cloning and pharmacological characterization of human alpha-1 adrenergic receptors: sequence corrections and direct comparison with other species homologues. *J Pharmacol Exp Ther*. 1995;272:134-142.
13. Price DT, Lefkowitz RJ, Caron MG, et al. Localization of mRNA for three distinct alpha 1-adrenergic receptor subtypes in human tissues: implications for human alpha-adrenergic physiology. *Mol Pharmacol*. 1994;45:171-175.
14. Price DT, Schwinn DA, Lomasney JW, et al. Identification, quantification, and localization of mRNA for three distinct alpha 1 adrenergic receptor subtypes in human prostate. *J Urol*. 1993;150:546-551.
15. Andersson KE, Lepor H, Wyllie MG. Prostatic alpha 1-adrenoceptors and uroselectivity. *Prostate*. 1997;30:202-215.
16. Smith MS, Schambra UB, Wilson KH, et al. Alpha1-adrenergic receptors in human spinal cord: specific localized expression of mRNA encoding alpha1-adrenergic receptor subtypes at four distinct levels. *Brain Res Mol Brain Res*. 1999;63:254-261.
17. Malloy BJ, Price DT, Price RR, et al. Alpha1-adrenergic receptor subtypes in human detrusor. *J Urol*. 1998;160:937-943.
18. Ishizuka O, Persson K, Mattiasson A, et al. Micturition in conscious rats with and without bladder outlet obstruction: role of spinal alpha 1-adrenoceptors. *Br J Pharmacol*. 1996;117:962-966.
19. Bouchelouche K, Andersen L, Alvarez S, et al. Increased contractile response to phenylephrine in detrusor of patients with bladder outlet obstruction: effect of the alpha1A and alpha1D-adrenergic receptor antagonist tamsulosin. *J Urol*. 2005;173:657-661.
20. Lee E, Lee C. Clinical comparison of selective and non-selective alpha 1A-adrenoreceptor antagonists in benign prostatic hyperplasia: studies on tamsulosin in a fixed dose and terazosin in increasing doses. *Br J Urol*. 1997;80:606-611.
21. de Mey C, Michel MC, McEwen J, et al. A double-blind comparison of terazosin and tamsulosin on their differential effects on ambulatory blood pressure and nocturnal orthostatic stress testing. *Eur Urol*. 1998;33:481-488.
22. Tatemichi S, Kobayashi K, Maezawa A, et al. [Alpha1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213).] *Yakugaku Zasshi*. 2006;126(Spec no):209-216.
23. 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;36:1-13.
24. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J Urol*. 2003;170:530-547.
25. Marks LS, Gittelman MC, Hill LA, et al. 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;181:2634-2640.
26. Marks LS, Gittelman MC, Hill LA, et al. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study [published online ahead of print October 8, 2009]. *Urology*. doi:10.1016/j.urology.2009.06.072.
27. Resnick MI, Roehrborn CG. Rapid onset of action with alfuzosin 10 mg once daily in men with benign prostatic hyperplasia: a randomized,

Main Points

- Male lower urinary tract symptoms (LUTS) are commonly stratified into 3 different symptom categories: voiding or obstructive, storage or irritative, and postmicturition. One of the most common causes of male LUTS is benign prostatic hyperplasia (BPH).
- In the past 20 years medical therapy has established itself firmly as viable and cost effective in the treatment of LUTS due to BPH. In addition to the 2 major classes of drugs, the α-adrenergic receptor blocker (or α-blocker), and the 5α-reductase inhibitors, antimuscarinics, phytotherapeutic agents, and combinations thereof are in widespread use.
- α_1-Adrenoceptor blockade is capable of modifying the dynamic (prostate smooth muscle contraction) component in BPH.
- Many randomized placebo-controlled trials, as well as open-label studies, suggest that an improvement in the International Prostate Symptom Score and changes in the peak urinary flow rate are in general the results of α-blocker therapy.
- α-Blockers exhibit an early onset of efficacy (within $<$ 1 week) with regard to both symptoms and flow rate improvement, and maintain such improvements in open-label and controlled trials for up to 5 years.
- α-Blockers are useful adjuncts in the management of patients with acute urinary retention and in the management of ureteral stones, and have been shown to prevent symptomatic progression.

placebo-controlled trial. *Prostate Cancer Prostatic Dis*. 2007;10:155-159.
28. Dunn CJ, Matheson A, Faulds DM. Tamsulosin: a review of its pharmacology and therapeutic efficacy in the management of lower urinary tract symptoms. *Drugs Aging*. 2002;19:135-161.
29. Roehrborn CG, Prajsner A, Kirby R, et al. A double-blind placebo-controlled study evaluating the onset of action of doxazosin gastrointestinal therapeutic system in the treatment of benign prostatic hyperplasia. *Eur Urol*. 2005;48: 445-452.
30. Yamanishi T, Mizuno T, Tatsumiya K, et al. Urodynamic effects of silodosin, a new alpha(1A)-adrenoceptor selective antagonist, for the treatment of benign prostatic hyperplasia [published online ahead of print August 19, 2009]. *Neurourol Urodyn*. doi: 10.1002/nau.20802.
31. Matsukawa Y, Gotoh M, Komatsu T, et al. Efficacy of silodosin for relieving benign prostatic obstruction: prospective pressure flow study. *J Urol*. 2009;182:2831-2835.
32. Rossi C, Kortmann BB, Sonke GS, et al. alpha-Blockade improves symptoms suggestive of bladder outlet obstruction but fails to relieve it. *J Urol*. 2001;165:38-41.
33. Bosch JL. Urodynamic effects of various treatment modalities for benign prostatic hyperplasia. *J Urol*. 1997;158:2034-2044.
34. Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *N Engl J Med*. 1996;335:533-539.
35. Kirby RS, Roehrborn C, Boyle P, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology*. 2003;61: 119-126.
36. Roehrborn CG. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. *BJU Int*. 2006;97:734-741.
37. Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study [published online ahead of print September 19, 2009]. *Eur Urol*. doi: 10.1016/j.eururo.2009.09.035.
38. Roehrborn CG. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. *BJU Int*. 2008;101(suppl 3):17-21.
39. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effects of doxazosin, finasteride and the combination on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349:2387-2398.
40. McNeill SA, Hargreave TB, Roehrborn CG. Alfuzosin 10 mg once daily in the management of acute urinary retention: results of a double-blind placebo-controlled study. *Urology*. 2005;65:83-89.
41. McNeill SA, Daruwala PD, Mitchell ID, et al. Sustained-release alfuzosin and trial without catheter after acute urinary retention: a prospective, placebo-controlled trial. *BJU Int*. 1999;84: 622-627.
42. Lucas MG, Stephenson TP, Nargund V. Tamsulosin in the management of patients in acute urinary retention from benign prostatic hyperplasia. *BJU Int*. 2005;95:354-357.
43. Zeif HJ, Subramonian K. Alpha blockers prior to removal of a catheter for acute urinary retention in adult men. *Cochrane Database Syst Rev*. 2009; CD006744.
44. Seitz C, Liatsikos E, Porpiglia F, et al. Medical therapy to facilitate the passage of stones: what is the evidence? *Eur Urol*. 2009;56:455-471.
45. Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of ureteral calculi. *Ann Emerg Med*. 2007;50:552-563.
46. Schwinn DA, Roehrborn CG. Alpha1-adrenoceptor subtypes and lower urinary tract symptoms. *Int J Urol*. 2008;15:193-199.
47. Akiyama K, Noto H, Nishizawa O, et al. Effect of KMD-3213, an alpha1A-adrenoceptor antagonist, on the prostatic urethral pressure and blood pressure in male decerebrate dogs. *Int J Urol*. 2001;8:177-183.
48. American Urological Association Practice Guidelines Committee. *Diagnosis and Treatment Recommendations*. In: Guideline on the Management of Benign Prostatic Hyperplasia (BPH). American Urological Association Education and Research; 2006:1-54. Available at: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chapt_1_appendix.pdf. Accessed November 12, 2009.