Medical Management of Lower Urinary Tract Symptoms

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Lower urinary tract symptoms (LUTS) are a common complaint among aging men and are often caused by benign prostatic hyperplasia (BPH). A number of medical treatments for LUTS/BPH exist, such as α-blockers, 5α-reductase inhibitors, anticholinergics, phosphodiesterase type 5 (PDE5) inhibitors, and combination therapies. Agonist binding of the α_{1A}-adrenergic receptor (AR), causing prostatic smooth muscle contraction, has been attributed to cause some LUTS. Therefore, medical therapy has aimed to block the α_{1A}-AR and improve LUTS. Determining which therapy to choose must take into account individual patient factors as well as cost and patient choice.
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Lower urinary tract symptoms (LUTS) are a common complaint among aging men. These symptoms are often caused by benign prostatic hyperplasia (BPH), and include nocturia, urinary frequency, urgency, decreased urine flow rates, incomplete bladder emptying, and hesitancy. These symptoms are common, and their prevalence increases as men age. They are present in 8% of men age 31 to 40 years, 50% in those age 51 to 60 years, 70% in those age 61 to 70 years, and 90% in those age 81 to 90 years.[1] A number of medical treatments for LUTS/BPH exist, such as α-blockers, 5α-reductase inhibitors, anticholinergics, phosphodiesterase type 5 (PDE5) inhibitors, and combination therapies.

α-Blockers

There are 2 main groups of adrenergic receptors (ARs), α and β, with several subtypes (Figure 1). The different AR subtypes are distributed unequally though the body. α_{1A}-ARs are the predominant subtype in human prostate stroma. α_{1B}-ARs are found in human heart, spleen, kidney, vascular smooth muscle, and lung tissue. α_{1D}-ARs are found in the central nervous system and are the predominant subtype in the bladder.[2,3] Agonist binding of the α_{1A}-AR, causing prostatic smooth muscle contraction, has been attributed to cause some LUTS.[4] Therefore, medical therapy has aimed to block the α_1-AR and improve LUTS.

A number of α_1-blocking agents are currently approved for treating LUTS due to BPH. α-Blockers are the most commonly used medical therapy for BPH. They are well tolerated and have been shown to decrease the overall and symptomatic progression of BPH.[5] The common side effects reported are dizziness, headache, asthenia, postural hypotension, rhinitis, and sexual dysfunction.[6] Side effects are usually attributed to action of the drug at extraurinary receptors; in fact, the main difference among α-blockers is their affinity for the specific α-AR subtypes.

α_1-AR Selective Antagonists

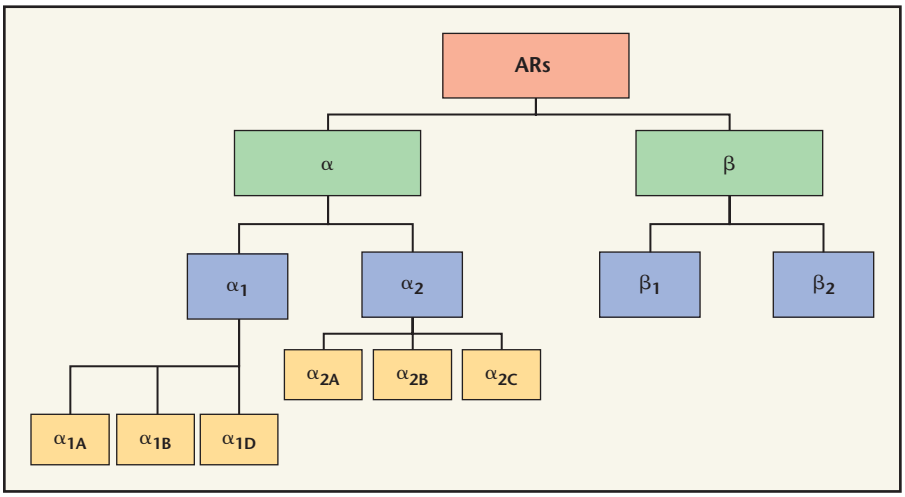
Agents that are selective α_1 antagonists include prazosin, terazosin, doxazosin, and alfuzosin (Table 1).[7] These agents bind selectively to α_1- versus α_2-ARs, but they do not exhibit in vitro selectivity among the different α_1-AR subtypes. At prescribed doses they appear to have comparable levels of efficacy.[8] Prazosin is limited by its short half-life (2.5 h), which requires dosing 2 to 3 times daily. Because these agents have affinity for both the α_{1A}-AR and the α_{1B}-AR, vasodilatory side effects are more common. In fact, doxazosin and terazosin have been used to treat essential hypertension.

α-Blockers are the most commonly used medical therapy for BPH.

Subtype-Selective α_1-AR Antagonists

In contrast with the previously mentioned agents, tamsulosin and silodosin exhibit selectivity among the different α_1-AR subtypes. Tamsulosin selectively blocks the α_{1A}- and α_{1D}-ARs via high-affinity binding.[9] Silodosin has a higher affinity for the α_{1A}-AR compared with the α_{1D}- and α_{1B}-ARs.[7] Both tamsulosin and silodosin significantly improve LUTS when compared with placebo.[10,11] Because of their selectivity for the α_{1A}-AR, vasodilatory side effects are limited. Tamsulosin has been associated with a low incidence of vasodilatory side effects, whereas the incidence of vasodilatory side effects associated with silodosin is no different than placebo.[11,12] A summary of all the side effects of the different α_1-blockers can be found in Table 2.[10,13-15]

Figure 1. *α and β adrenergic receptor (AR) subdivisions.*



5α-Reductase Inhibitors

5α-reductase inhibitors (5ARIs) are compounds that block the conversion of the main male androgenic steroid hormone testosterone (T) to dihydrotestosterone (DHT). This conversion is enabled by the enzyme 5AR, of which there are 2 isoenzymes, known as type I and type II. Both T and DHT bind to the AR, although DHT does so with greater affinity and is thus considered the more potent androgenic steroid hormone.[16] The T/DHT-AR complex within the nucleus of the prostate cells initiates transcription and translation, thus promoting cellular growth and ultimately contributing to BPH with an imbalance between growth and apoptosis (cellular death in favor of growth) and subsequent cellular mass or volume increase.

Type II 5AR is principally found in the prostate and other genital tissues. Type I is found throughout the body, including the skin, liver, and prostate. Both type I and type II 5AR have been shown as present in all prostate zones (peripheral, transition, and central).[17]

Currently, 2 5ARIs are used in the treatment of BPH—finasteride and dutasteride. Finasteride is a selective

Table 1
Pharmacologic Selectivity of α-Blockers

α_1-Blocker	α_1-Receptor Selectivity
Doxazosin	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Terazosin	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Alfuzosin	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Tamsulosin	$\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$
Silodosin	$\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$

Data from Schwinn DA and Roehrborn CG.[7]

Table 2
Treatment-Related Adverse Events of α-Blockers Used for Benign Prostatic Hyperplasia

	Terazosin[13] (%)	Tamsulosin[10] (%)		Alfuzosin[14] (%)	Silodosin[15] (%)
		0.4 mg	0.8 mg		
Asthenia/fatigue	7.4	7.8	8.5	2.7	Not reported
Positive orthostatic test	Not reported	16.0	19.0	6.6	2.6
Rhinitis/nasal congestion	3.9	13.1	17.9	0.4	2.1
Dizziness	9.1	14.9	17.1	5.7	3.2
Retrograde ejaculation	Not reported	8.4	18.1	Not reported	28.1

inhibitor of type II 5AR. At a dose of 5 mg/d, it reduces plasma DHT by 60% to 70% and prostatic DHT concentrations by approximately 85%.[18] Dutasteride differs from finasteride in that it blocks both isoenzymes of 5AR (type I and type II). This results in a 90% to 95% decrease in circulating DHT.[19,20] Side effects of both drugs include decreased libido, erectile dysfunction (ED), decrease in ejaculate volume, and gynecomastia. Tolerability improves with prolonged usage (Tables 3 and 4).[18,20]

At this time there appears to be no clinical benefit of the greater suppression of serum DHT seen with dutasteride as compared with finasteride.

5ARIs are appropriate and effective treatment options for men with LUTS/BPH who have demonstrable prostate enlargement.

Both have been shown to decrease prostate volume, improve urinary symptoms, decrease the risk of urinary retention, and decrease the risk of BPH surgery (Table 5).[18,21] 5ARIs are appropriate and effective treatment options for men with LUTS/BPH who have demonstrable prostate enlargement. (In different studies different thresholds have been proposed for the definition of prostate enlargement [25, 30, or 40 mL].) Dutasteride is untested in glands smaller than 30 g. There are no data from direct comparator trials or other sources to suggest that the clinical efficacy of the 2 5ARIs in the appropriate indication is different. Comparisons are difficult if not impossible, as inclusion and exclusion criteria do not match for any of the trials performed with finasteride or dutasteride.

In the Medical Therapy of Prostatic Symptoms (MTOPS) and Combination Therapy With Avodart and Tamsulosin (CombAT) studies, 5ARIs were shown as useful in preventing progression of LUTS/BPH and reducing the risk of urinary retention and future prostate-related surgery. However, in this and all settings, 5ARIs should not be used in men with LUTS/BPH if there is no demonstrable prostatic enlargement.

Anticholinergics

The rationale for the use of anticholinergic medications in treating BPH is based on LUTS including overactive bladder (OAB) symptoms, such as frequency, urgency, and incontinence. OAB symptoms are attributed to detrusor overactivity (DO), which may be induced by bladder outlet obstruction. DO is thought to contribute to symptoms in 40% to 70% of patients with bladder outlet obstruction.[22] Bladder contractions are stimulated by the action of acetylcholine on muscarinic receptors in the smooth muscle of the bladder. Anticholinergic medications such as tolterodine, flavoxate, propiverine, and oxybutynin[23] are widely used to treat OAB symptoms, especially in women, but only recently has their role in treating LUTS secondary to BPH been explored.[24]

Table 3
Side Effects of Finasteride and Dutasteride from Clinical Trials With Treatment up to 1 Year

	Finasteride[21]		Dutasteride[19]	
	Treatment (%)	Placebo (%)	Treatment (%)	Placebo (%)
Decreased libido	6.4	3.4	3.7	1.9
Erectile dysfunction	8.1	3.7	6.0	3.0
Gynecomastia	0.5	0.1	1.3	0.5
Decreased ejaculate volume	3.7	0.8	1.8	0.7

Table 4
Side Effects of Finasteride and Dutasteride from Clinical Trials With Treatment Longer Than 1 Year

	Finasteride[21]		Dutasteride[19]	
	Treatment (Patients, %)	Placebo (Patients, %)	Treatment (Patients, %)	Placebo (Patients, %)
Decreased libido	2.6	2.6	0.6	0.3
Erectile dysfunction	5.1	5.1	1.7	1.2
Gynecomastia	1.1	1.8	1.3	0.3
Decreased ejaculate volume	1.5	0.5	0.5	0.1

Table 5
Data From Clinical Trials of Finasteride and Dutasteride

	Finasteride[21]		Dutasteride[19]	
	Treatment	Placebo	Treatment	Placebo
Volume change (%)	−18	14	−26	−2
Decrease in IPSS	3.3	1.3	4.5	2.3
Improvement in flow rate (mL/s)	1.9	0.2	2.2	0.6
Patients developing acute urinary retention (%)	3	7	1.8	4.2
Patients requiring BPH surgery (%)	5	10	2.2	4.1

BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score.

Complete inhibition of bladder contractions would result in urinary retention, a serious unwanted side effect. However, this occurrence is exceedingly rare with clinically effective dosing of antimuscarinic medications in a highly select cohort with low baseline postvoid residual volumes.[25] This risk was addressed in a study in which 221 men with urodynamically confirmed bladder outlet obstruction and DO were randomized to tolterodine compared with placebo for 12 weeks.[26] Postvoid residual volume increased to a significantly greater extent in the tolterodine group relative to placebo (+25 mL), but this was not accompanied by an

increase in adverse events. Urinary retention was reported by 1 patient treated with placebo. Also demonstrated in this study were significant clinical effects in the bladder outlet obstruction index (a urodynamic measure of the degree of obstruction), volume to first detrusor contraction, and maximum cystometric capacity, favoring tolterodine over placebo.[25]

Phosphodiesterase Type 5 Inhibitors

Newer evidence suggests a role for using phosphodiesterase type 5 (PDE5) inhibitors to treat LUTS due to BPH. A possible mechanism by which PDE5 inhibitors can influence LUTS is through nitric oxide (NO) and cyclic guanosine monophosphate (cGMP). The NO/cGMP system generally has an inhibitory effect on the lower urinary tract.[27,28] Additionally, men with BPH have been shown to have a decrease in NO-mediated relaxation of prostate smooth muscle.[29] PDE5 inhibitors are known to exert their effects by increasing levels of cGMP and NO. A number of isoforms of PDE have been found in the prostate, bladder, and urethra.[30] PDE5 inhibitors should improve LUTS by acting at these sites.

Studies using daily dosing of both sildenafil and tadalafil have shown improvement in International Prostate Symptom Score (IPSS)[31,32]; erectile function improved as well, although urinary flow rates did not increase in either study. To date, the exact mechanism and site of action of PDE5 inhibitors on LUTS is unknown. Nonetheless, using PDE5 inhibitors to treat LUTS is especially attractive because LUTS and ED are often found in the same patient populations.[33]

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Combination Therapy

Although the previously mentioned drugs are effective alone, they can also be used in combination. The MTOPS trial is the largest trial to evaluate combination therapy with α-blockers and 5ARIs. This trial found that combination therapy (finasteride and doxazosin) reduced the overall progression of BPH more than either agent alone.[5] Progression of BPH was defined as the first occurrence of an increase over baseline of at least 4 points in the IPSS, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence. The risk of clinical progression was reduced by 39% in the doxazosin-treated group, 34% in the finasteride-treated group, and 66% in the group on combination therapy. In addition, the risk of acute urinary retention and the need for BPH-related surgery was decreased by both the finasteride-treated group and the combination therapy group (but not by the doxazosin only group).

Combination therapy with anticholinergics and α-blockers has also been studied. Although the length of follow-up in each of the studies is short, there appears to be consensus that combination therapy is more effective than either α-blockers or anticholinergics alone in the treatment of LUTS due to BPH (Table 6)[34-37]

Table 6
A Summary of Trials With α-Blockers/Anticholinergic Combination Therapy

Study	Agents	N	Duration	Primary Outcome	Combination Therapy Efficacy vs α_1-ARA Alone
Athanasopoulos et al.[36]	Tamsulosin and tolterodine	50	3 mo	QoL questionnaire, urodynamic studies	Improved QoL scores, some urodynamic variables
Lee et al.[37]	Doxazosin CR and propiverine CR	211	8 wk	Urinary frequency, urodynamic studies, patient satisfaction rates	Improved urinary frequency, average micturition volume, storage symptoms, urgency severity
Kaplan et al.[35]	Tamsulosin and tolterodine ER	879	12 wk	Bladder diaries	Improved urgency incontinence
Yang et al.[34]	Terazosin and tolterodine	191	6 wk	IPSS score, peak urinary flow rate, postvoid residual volume	Reduced IPSS score

ARA, adrenergic agent; CR, controlled release; ER, extended release; IPSS, International Prostate Symptom Score; QoL, quality of life.

More recently, combining both PDE5 inhibitors and α-blockers has been evaluated. A study by Kaplan and colleagues[38] compared the impact of alfuzosin, sildenafil, or the combination of alfuzosin and sildenafil on LUTS. The results indicated that combination therapy (24.1% improvement) improved LUTS more than treatment with alfuzosin (15.6% improvement) or sildenafil (11.8% improvement) alone.

Conclusions

Currently, multiple treatment modalities exist for the treatment of LUTS due to BPH. At this time α-blockers, 5ARIs, and PDE5 inhibitors appear effective. Determining which therapy to choose must take into account individual patient factors as well as cost and patient choice. No single medical therapy available appears to be superior to the others. The role of PDE5 inhibitors, both alone and in combination with other forms of LUTS treatment, is a new area and requires further study. ■

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Main Points

- Lower urinary tract symptoms (LUTS) are a common complaint among aging men and are often caused by benign prostatic hyperplasia (BPH). A number of medical treatments for LUTS/BPH exist, including α-blockers, 5α-reductase inhibitors, anticholinergics, phosphodiesterase type 5 (PDE5) inhibitors, and combination therapies.
- There are 2 main groups of adrenergic receptors (ARs), α and β, with several subtypes. The different AR subtypes are distributed unequally through the body; α_{1A}-ARs are the predominant subtype in human prostate stroma. Agonist binding of the α_{1A}-AR, causing prostatic smooth muscle contraction, has been attributed to cause some LUTS; therefore, medical therapy has aimed to block the α_1-AR and improve LUTS.
- 5α-reductase inhibitors are compounds that block the conversion of the main male androgenic steroid hormone testosterone to dihydrotestosterone. Both dutasteride and finasteride have been shown to decrease prostate volume, improve urinary symptoms, decrease the risk of urinary retention, and decrease the risk of BPH surgery.
- The rationale for the use of anticholinergic medications in treating BPH is based on LUTS including overactive bladder (OAB) symptoms. OAB symptoms are attributed to detrusor overactivity, which may be induced by bladder outlet obstruction. Anticholinergic medications are widely used to treat OAB symptoms, and recently their role in treating LUTS secondary to BPH has been explored.
- A possible mechanism by which phosphodiesterase type 5 (PDE5) inhibitors can influence LUTS is through nitric oxide (NO) and cyclic guanosine monophosphate (cGMP). The NO/cGMP system generally has an inhibitory effect on the lower urinary tract. Studies using daily dosing of both sildenafil and tadalafil have shown improvement in International Prostate Symptom Score and erectile function, but not urinary flow rates.
- Several large trials have proven that combination therapy reduced the overall progression of BPH more than one agent alone.

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