Lower Urinary Tract Symptoms (LUTS) In Men: Thinking Beyond the Prostate

Sammy Elsamra, MD, and Pamela S. Ellsworth, MD

Lower Urinary Tract Symptoms (LUTS) in men are commonly thought to be related to **benign enlargement of the prostate, BPE**, a term that replaces the term, **BPH (benign prostatic hyperplasia)**, which is a pathologic diagnosis. However, LUTS is not exclusive to men, nor is it only related to BPE. More recently, the role of underlying **overactive bladder (OAB)** has been highlighted in the etiology of male LUTS.

LUTS is a symptom complex composed of storage and voiding phase symptoms. The storage phase symptoms consist of urinary urgency (a sudden compelling desire to void that is difficult to defer) with or without urinary urgency incontinence, urinary frequency (voiding 8 or more times per day), and nocturia (awakening one or more times at night to void) and the voiding phase symptoms include hesitancy, intermittent urinary stream, feeling of incomplete emptying, straining to void and post-void dribbling. The storage phase symptoms are those of OAB, a symptom complex, suggestive of underlying vesicourethral dysfunction. **The National Overactive Bladder Evaluation (NOBLE)** study, using a validated, computer-assisted telephone interview of 5204 adults in the United States > 18 yrs of age, identified the overall prevalence of OAB as 16.9% in women and 16.0% in men.[1] The Males Attitudes Regarding Sexual Health Study demonstrated the overall prevalence of LUTS among US men ≥ 40 yrs to be 13%, 9% and 6% for storage symptoms, mixed symptoms and voiding symptoms, respectively. [2] OAB symptoms in women are easily recognized and treated, but those in men, despite a similar prevalence, are not. In two large studies utilizing medical and pharmacy data from IMS Health, only 16-24% of men diagnosed with OAB were treated medically.[3, 4] Simply treating the BPE and BOO symptoms of LUTS leaves a subset of male patients with inadequate control. Lee et al demonstrated that 65% of patients with BOO and overactive bladder treated with an alpha-blocker for 3 months did not show symptomatic improvement.[5] Furthermore, 25 to 30% of males have persistent OAB symptoms after prostate surgery and OAB symptoms may return even after initial resolution of LUTS after TURP.[6, 7]

Men with LUTS are more commonly treated with agents directed at **bladder outlet obstruction (BOO)** secondary to BPE, alpha-blockers (tamsulosin (flowmax), terazosin (hytrin), doxazosin (cardura), alfuzosin (uroxatral) and silodosin (rapaflo) and 5 alpha-reductase inhibitors (finasteride (proscar) and dutasteride (avodart), even if BPE is not documented. General practice prescribing data supports that antimuscarinics are not given to men, due to a theoretical concern that the inhibitory effect of antimuscarinic agents on detrusor contraction may aggravate voiding difficulties or precipitate acute urinary retention. Abrams et al. demonstrated that short term use of tolterodine (Detrol IR) 2mg orally twice a day compared to placebo in males with urodynamically proven OAB and BOO did not adversely affect urinary function. There was a significant increase in volume to first detrusor contraction and maximum cystometric capacity, favoring tolterodine over placebo. There was a statis-

Table 1: Dosing and Metabolism of Currently Approved OAB Agents

Drug	Half-life (hr)	Time to Peak (hr)	Route of Metabolism	Adult Dose	Dose frequency
Darifenacin (Enablex)	7-20	5-8	CYP450 CYP2D6 CYP3A4	7.5mg 15mg	QD
Fesoterodine (Toviaz)	7-8	5	Ester hydrolysis CYP450 CYP2D6 CYP3A4	4mg – 8mg	QD
Oxybutynin (Ditropan)	2-3	<1	CYP450 CYP3A4	2.5 to 5.0mg	BID to TID
Oxybutynin XL (Ditropan XL)	12-13	3-6	CYP450 CYP3A4	5mg-30mg	QD
Oxybutynin chloride 10% gel (Gelnique)	64 At steady state	Steady state concentrations achieved within 7 days of steady dosing	Liver CYP450 CYP3A4	1gm dose of 100mg/g oxybutynin chloride gel 1.14ml	QD
Solifenacin (Vesicare)	45-68	3-8	CYP450 CYP3A4	5mg-10mg	QD
Tolterodine IR (Detrol IR)	2-4	1-2	CYP450 CYP2D6 CYP3A4	1mg-2mg	BID
Tolterodine LA (Detrol LA)	7-18	2-6	CYP450 CYP2D6 CYP3A4	2mg 4mg	QD
Transdermal oxybutynin (Oxytrol)	7-8	10-48	CYP450 CYP3A4	36mg patch delivers 3.9mg/day	Twice weekly
Trospium chloride (Sanctura)	18	5-6	Renal excretion Minimal hepatic metabolism	20mg	BID 1 hr before meals
Trospium Chloride XR (Sanctura XR)	36	5	Ester hydrolysis Renal excretion	60mg	QD – 1 hr before breakfast

tically significant increase in post-void residual in patients on tolterodine, compared to placebo, however, the one patient who experienced acute urinary retention was in the placebo group.[8] Athanasopoulos et al demonstrated that combined treatment with an alpha-blocker plus an antimuscarinic in males with urodynamically proven OAB and BOO improved quality of life compared to monotherapy with an alpha-blocker. There was no acute urinary retention in the combination therapy group, nor was there a change in the flow rate or increase in post-void residual.[9] Kaplan et al. evaluated the efficacy and safety of tolterodine extended release (ER), tamsulosin, or both in men with OAB and BPH. Patients receiving tolterodine ER plus tamsulosin compared to placebo experienced significant reduction in urgency urinary incontinence, urgency episodes without incontinence, maturations per 24 hours and maturations per night. In addition, patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements on the total International Prostate Symptom Score versus placebo and QOL item. The incidence of acute urinary retention requiring catheterization was low (tolterodine ER plus tamsulosin 0.4%, tolterodine ER 0.5%, tamsulosin 0%, and placebo 0%).[10]

In clinical practice, men with LUTS are often started on one or a combination of agents directed at BOO secondary to BPE, an alpha-blocker and/or 5 alpha-reductase inhibitor. (Table 3) Those individuals who fail to respond to this therapy who have persistent OAB symptoms, who empty their bladders well (usually documented by bladder scanner post-void residual, bladder ultrasound or catheterized PVR determination) are suitable candidates for the addition of an antimuscarinic agent, provided there are no medical contraindications. A variety of antimuscarinic agents that vary in dose flexibility, method of administration, and safety and tolerability profiles exist, such that one can select an antimuscarinic agent most appropriate for each individual patient. (Tables 1and 2) The antimuscarinic agents share similar efficacy; however, if an individual fails one agent from either an efficacy or tolerability standpoint, it is reasonable to try another agent.

Behavioral therapy is a useful adjunct to the treatment of LUTS in both men and women, particularly with respect to management of OAB symptoms. Behavioral therapy focuses on education, dietary and lifestyle changes, bladder training and pelvic floor muscle exercises to improve symptoms. In some individuals, caffeinated (tea, coffee, soda, chocolate) and acidic foods may exacerbate OAB symptoms and thus avoidance of such foods/drinks may improve symptoms. Fluid restriction in the evening may improve nocturia symptoms. Pelvic floor muscle exercises (quick flicks) may help decrease urgency urinary incontinence episodes and suppress detrusor overactivity.

Lastly, an association between LUTS and **erectile dysfunction (ED)** is being increasingly identified. Studies have demonstrated that the presence and severity of LUTS are associated with sexual dysfunction and decreased sexual activity and satisfaction.[11] The presence of LUTS is an independent risk factor for sexual dysfunction and the close association between LUTS and sexual dysfunction is not attributable to age or to co-morbidities and lifestyle factors such as hypertension, diabetes, cardiac disease, hypercholesterolemia, pelvic operations, obesity, smoking, and alcohol consumption. Irwin et al demonstrated that OAB, as defined by the International Continence Society, was significantly associated with increased prevalence of ED, reduced sexual activity

Table 2 Adverse Events of the Antimuscarinic Agents Approved for OAB

DRUG	SIDE EFFECT	DRUG	PLACEBO	DRUG/PLACEBO ratio
Darifenacin (Enablex) 7.5 mg	Dry mouth	20.2%	8.2%	2.5
	Constipation	14.8%	6.2%	2.4
	Dizziness	0.9%	1.3%	0.7
15mg	Dry mouth	35.3%	8.2%	4.3
	Constipation	21.3%	6.2%	3.4
	Dizziness	2.1%	1.3%	1.6
Fesoterodine (Toviaz) 4mg	Dry mouth	18.8%	7.0%	2.7
	Constipation	4.2%	2.0%	2.1
	Insomnia	1.3%	0.5%	2.6
8mg	Dry mouth	34.6%	7.0%	4.9
	Constipation	6.0%	2.0%	3.0
	Insomnia	0.4%	0.5%	0.8
Oxybutynin chloride 10% gel (Gelnique)	Dry mouth	7.5%	2.8%	3.3
	Constipation	1.3%	Not reported	-
	Application site reaction	5.4%	1.0%	5.4
Solifenacin (Vesicare) 5mg	Dry mouth	10.9%	4.2%	2.6
	Constipation	5.4%	2.9%	1.9
	Dizziness	1.9%	1.8%	1.1
	Blurred vision	3.8%	1.8%	2.1
10mg	Dry mouth	27.6%	4.2%	6.6
	Constipation	13.4%	2.9%	4.6
	Dizziness	1.8%	1.8%	1.0
	Blurred vision	4.8%	1.8%	2.7
Tolterodine LA 4mg (Detrol LA 4mg)	Dry mouth	23%	8%	2.9
	Constipation	6%	4%	1.5
	Headache	6%	4%	1.5
	Dizziness	2%	1%	2.0
	Abnormal vision	1%	0%	
Transdermal oxybutynin (Oxytrol)	Dry mouth	9.6%	8.3%	1.2
	Constipation	3.3%	0%	
	Application site			
	Puritis	16.8%	6.1%	2.8
	Erythema	5.6%	2.3%	2.4
Trospium chloride IR (Sanctura)	Dry mouth	20.1%	5.8%	3.5
	Constipation	9.6%	4.6%	2.1
	Headache	4.2%	2.0%	2.1
Trospium chloride XR (Santura XR)	Dry mouth	10.7%	3.7%	2.9
	Constipation	8.5%	1.5%	5.7
	Dry eyes	1.6%	0.2%	8.0

*Oxybutynin IR and ER not included as prescribing information reports Aes from multiple doses
Information is derived from prescribing information for each drug.

Table 3: BPE Drugs and Dosing

DRUG	DOSE	Tmax Hrs	Half-Life Hrs	Metab	Contraindications
Alpha-blocker					
Alfuzosin (Uroxatral)	10mg	8 hrs	10 hrs	Liver metabolism, CYP3A4	Contraindicated in moderate to severe hepatic impairment, should not be used with co administration of potent CYP3A4 inhibitors. Intraoperative Floppy Iris Syndrome has been reported in patients taking uroxatral while undergoing cataract surgery.
Doxazosin (Cardura)	1mg, 2mg, 4mg, 8mg	2-3 hrs	22 hrs	Liver metabolism mainly by O-demethylation of quinazoline nucleus or hydroxylation of the benzodioxan moiety	Administer with caution if impaired hepatic function. Intraoperative Floppy Iris Syndrome has been reported in patients taking doxazosin while undergoing cataract surgery.
Doxazosin XL (Cardura XL)	4mg, 8mg With breakfast	4mg: 8±3.7 hrs 8mg: 9±4.7 hrs	15 to 19 hrs	CYP3A4 primary elimination pathway but also CYP2D6 and CYP2C19	Use with caution in pts with mild or moderate hepatic impairment, not recommended with severe hepatic impairment. Intraoperative Floppy Iris Syndrome has been reported in patients taking doxazosin while undergoing cataract surgery.
Silodosin (Rapaflo)	4mg and 8mg capsule, once daily with meal	2.6±0.90 hrs	13.3±8.07 hrs	Glucuronidation, alcohol and aldehyde dehyrogenase, and Cyt P450 pathways	Severe renal impairment Severe liver impairment Concomitant admin strong CytP3A4 inhibitors Silodosin is not recommended in patients taking strong P-gp inhibitors such as cyclosporine. As with other alpha-blockers individuals taking silodosin should discuss this with ophthalmologist prior to undergoing cataract surgery due to risk of Intraoperative Floppy Iris Syndrome
Tamsulosin (Flomax)	0.4mg, 0.8 mg	0.4mg : 4 hrs (fasted) 6 hrs (light breakfast) 0.8mg: 5.0 hrs (fasted) 7.0 hrs (light breakfast)	0.8mg: 14.9± 3.9	Cyt P45- CYP3A4 and CYP2D6	Use with caution in combination with moderate or strong CYP2D6 or CYP3A4 inhibitors; If pt has a serious or life-threatening sulfa allergy, caution warranted when using tamsulosin. Intraoperative Floppy Iris Syndrome, a complication in cataract surgery has been reported in patients taking flomax prior to cataract surgery.
Terazosin (Hytrin)	1mg, 2mg, 5mg, 10 mg capsules, with or without food	1 hr	12 hrs	Extensively metabolized by liver with little parent drug excreted in urine and feces	Contraindicated in those with known sensitivity to terazosin. Same concerns apply regarding use and risk of Intraoperative Floppy Iris Syndrome in patients undergoing cataract surgery.
5-alpha-reductase inhibitors					
Dutasteride (Avodart)	0.5mg with or without food	2-3 hrs	5 wks at steady state	Liver metabolized by CYP3A4 and CYP3A5	Caution when co administration with potent, chronic CYP3A4 inhibitors
Finasteride (Proscar)	5 mg	1.8 hrs	6 hrs (3-16 hrs) 8.2 hrs in those ≥ 70 yrs	Liver Metabolized by CYP3A4	Caution with use in those pts with liver function abnormalities

and sexual enjoyment because of urinary symptoms, and reduced sexual satisfaction.[12] Other studies have suggested that voiding problems, including obstructive urination, might be an independent risk factor for ED. Conversely, Shiri et al noted that ED is associated with an increased incidence of LUTS and bother.[13] Several hypotheses are being evaluated to explain the relation between LUTS and ED: (1) an increased Rho-kinase activation, (2) an alpha-adrenergic receptor imbalance, (3) a decrease in NOS/NO in the endothelium, (4) atherosclerosis affecting small vessels in the pelvis and (5) autonomic hyperactivity, each affecting simultaneously bladder, prostate and penis.[14] In a study evaluating sildenafil for erectile dysfunction and lower urinary tract symptoms in men with the 2 conditions, in addition to improving the erectile function domain score and all other International Index of Erectile Function domains, sildenafil significantly improved the International Prostate Symptom Score, the Benign Prostatic Hyperplasia Impact Index, the mean International Prostate Symptom Score quality of life score and total self-esteem and relationship questionnaire scores compared to placebo, although there was no difference in urinary flow between the 2 groups. Conversely, in separate studies 0.4mg tamsulosin or 10mg alfuzosin daily improved sexual function in men with LUTS associated with BPH.[15] Prescribing information for the oral PDE-5 inhibitors indicates that they should not be used in males taking alpha-blockers until they are on stable doses of alpha-blocker and tolerate the alpha-blocker.

Conclusion

No longer can male LUTS be viewed as a problem related to only the prostate. A careful history can help determine whether or not coexistent OAB symptoms are present with BPE with BOO symptoms. Use of antimuscarinic agents in males treated for LUTS with persistent OAB symptoms has been demonstrated to be safe over the short term and associated with improved QOL and patient satisfaction. Furthermore, the impact of LUTS extends beyond storage and voiding symptoms and men presenting with LUTS should be screened for underlying erectile dysfunction and vice versa. Pelvic health in men

can no longer be viewed as distinct, separate conditions, the interactions between the prostate, bladder and sexual function require that an assessment of each of these conditions be made in an individual presenting with one to achieve maximal quality of life impact. For further information regarding OAB and the management of male OAB patients one can go www.urologyuniversitycme.com, a CME website presented by the office of Continuing Medical Education at the Warren Alpert School of Medicine of Brown University in collaboration with Health and Wellness Education Partners and chaired by Pamela Ellsworth, MD.

References

1. Stewart W, Herzog R, et al. The prevalence and impact of overactive bladder in the United States. *Neurourol Urodynam* 2001; 20: 406-8.
2. Glasser DB, Carson III C, et al. Prevalence of storage and voiding symptoms among men aged 40 years and older in a US population-based study. *Int J Clin Pract* 2007; 61: 1294-300.
3. Helfand BT, Evans RM, McVary KT. Prevalence of medical therapies in men and women with overactive bladder symptoms. Poster presentation at 2009 American Urological Association Meeting. April 25-30, 2009. Chicago, IL. Poster 1942.
4. Helfand BT, Evans RM, McVary KT. Medical treatment of LUTS/BPH. Poster presented at 2009 American Urological Association Annual Meeting. April 25-30, 2009. Chicago, IL. Poster 1939.
5. Lee JY, Kim HW, et al. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int* 2004; 95: 1117-8.
6. Abrams PH, Farrar DJ, et al. The results of prostatectomy. *J Urol* 1979; 121: 640-2.
7. Mitterberger M, Pallwein L, et al. Persistent detrusor overactivity after transurethral resection of the prostate is associated with reduced perfusion of the urinary bladder. *BJU Int* 2007; 99: 831-5.
8. Abrams P, Kaplan S,et al. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol* 2006; 999-1004.
9. Athanasopoulos A, Gyftopoulos K, et al. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction. *J Urol* 2003; 169: 2253-6.
10. Kaplan SA, Roehrborn CG, et al. Tolterodine and tamsulosin in men with LUTS including OAB. *JAMA* 2006; 296: 2319-28.
11. Wein AJ, Coyne KS, et al. The impact of lower urinary symptoms on male sexual health. *BJU Int* 2009; 103: 33-41.
12. Irwin DE, Milsom I, et al. Overactive bladder is associated with erectile dysfunction and reduced sexual quality of life in men. *J Sex Med* 2008; 5: 2904-10.
13. Shiri R, Hakkinen J, et al. Erectile dysfunction influences the subsequent incidence of lower urinary tract symptoms and bother. *Int J Impot Res* 2007; 19: 317-20.
14. Ponholzer A, Madersbacher S. Lower urinary tract symptoms and erectile dysfunction. *Int J Impot Res* 2007; 19: 544-50.
15. McVary KT, Monnig W, et al. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia. *J Urol* 2007; 177: 1071-7.

Sammy Elsamra, MD, is a resident, Department of Urology, The Warren Alpert Medical School of Brown University.

Pamela Ellsworth, MD, is Associate Professor of Urology/Surgery, The Warren Alpert Medical School of Brown University.

Disclosure of Financial Interests

Sammy Elsamra, MD, and spouse/significant other have no financial interests to disclose.

Pamela S. Ellsworth, MD. Consultant: Pfizer, Novartis. Speaker's Bureau: Pfizer, Novartis. Other Financial or Material Interest: Pfizer.

Correspondence

Pamela Ellsworth, MD
Associate Professor of Urology/Surgery
Division of Urology
Rhode Island Hospital
2 Dudley Street, Suite 174
Providence, RI 02905
phone (401) 421-0710 ext 1323
E-mail: pamelaellsworth@aol.com

Information for Contributors, *Medicine & Health/Rhode Island*

Medicine & Health/Rhode Island is peer-reviewed, and listed in the *Index Medicus*. We welcome submissions in the following categories.

Contributions – Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be submitted as separate electronic files (jpeg, tif, or pdf).

Creative Clinician – Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

Point of View – Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

Advances in Pharmacology – Authors discuss new treatments. Maximum length: 1200 words.

Advances in Laboratory Medicine – Authors discuss a new laboratory technique. Maximum length: 1200 words.

Images in Medicine – Authors submit an interesting Image, with a 300-400 word explanation.

For the above articles: Please submit an electronic version (Microsoft Word or Text) with the author's name, mailing address, phone, fax, e-mail address, and clinical and/or academic positions to the managing editor, Joan Retsinas, PhD, e-mail: joan.retsinas@gmail.com For additional information, phone: (401) 272-0422.