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Medical Management of Male Lower Urinary Tract Symptoms: What's New?

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to define the main categories into which male lower urinary tract symptoms medications are stratified, describe the similarities and differences in newer classes of medication compared to older ones, and utilize different pharmacotherapy options tailored to specific needs of men with lower urinary tract symptoms.

This AUA Update aligns with the American Board of Urology Module on Neurogenic Bladder, Voiding Dysfunction, Female Urology, BPH, and Urethral Stricture. Additional information on this topic can be found in the AUA Core Curriculum section on BPH.

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KEY WORDS: male LUTS, alpha-blockers, 5-alpha-reductase, β3-adrenoceptor, desmopressin

INTRODUCTION

Benign prostatic hyperplasia (BPH) contributes significant morbidity to the aging male population.[1] Outlet obstruction from the growing prostate and bladder dysfunction can both contribute to lower urinary tract symptoms (LUTS) in men. Fortunately, the treatment options of male LUTS are broad and can be tailored to the specific complaint or preference of the patient with male LUTS. Due to its variety of symptoms, however, treatment of male LUTS can be convoluted. Although both surgical and medical therapy can offer patients much-needed relief, this Update will focus on the medical management options available to clinicians for treating male LUTS.

ALPHA BLOCKER

Alpha-adrenergic receptor blockers (ABs) reduce smooth-muscle tone in the prostate and bladder neck and are often used in the treatment of LUTS. There are 2 types of adrenoceptors: A1 and A2 receptors. **The predominant adrenoceptors in the human prostate, bladder neck, and urethra are A1a and A1d subtypes.** Some of the side effects of ABs come from nonselective inhibition of A1b receptor subtypes, which are predominantly expressed in the peripheral vasculature.[2] Theoretically, selective subtype adrenoreceptor blockade should relieve LUTS without cardiovascular adverse symptoms such as dizziness, headache, and orthostatic hypotension, as these are mediated by A1b receptors.[2]

Relatively new subtype selective ABs with high affinity for A1a (silodosin) or A1d (naftopidil) receptors have a similar effect on the International Prostate Symptom Score (IPSS), and quality of life (QoL) scores compared with other ABs.[3,4] In a Cochrane review, silodosin was as effective as tamsulosin (mean difference −0.04, 95% CI −1.31 to 1.24) in IPSS reduction, and the incidence of cardiovascular adverse events (AEs) was similar to tamsulosin. However, sexual AEs such as retrograde ejaculation and anejaculation were more common in the silodosin group compared with tamsulosin (RR 1.96, 95% CI 1.12 to 3.44) though this did not affect treatment withdrawal.[4]

Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use), which is the first oral antiviral medication approved for the treatment of mild to moderate COVID-19, was recently deemed a contraindicated medication to AB use because coadministration may result in increased effects of adrenergic blockade.

For the majority of male patients complaining of LUTS, AB therapy is an effective starting point to achieve relief. These drugs have a well-known side effect profile and hold an established role in initial LUTS therapy.

5ALPHA-REDUCTASE INHIBITORS

5Alpha-reductase inhibitors (5ARIs) represent a widely utilized means of treating male LUTS. Finasteride competitively inhibits type 2 5alpha-reductase (5AR) but is only weakly active against type 1. Dutasteride is a dual inhibitor of both type 1 and type 2 5AR.[5] A result of manipulation of the steroid's structure, dutasteride is the most recent development and was approved by the Food and Drug Administration (FDA) in 2001 for BPH treatment. Dual inhibition of 5AR with dutasteride results in near-complete and consistent suppression of serum dihydrotestosterone compared to finasteride (100% vs 70%).[1,6] Further detail of the mechanism of action for 5ARI can be found in *AUA Update Series*, volume 41, Lesson 12.[7] **In a meta-analysis of 8 randomized, controlled trials with a total of 2,116 patients, dutasteride was found to be just as effective as finasteride in improving IPSS and QoL scores; however, urinary flow rate showed greater improvement in the dutasteride group compared to finasteride.**[8] Until dutasteride and finasteride are compared in a randomized, controlled trial, the effect of additional type 1 isoenzyme inhibition will be undetermined. Theoretically, there may be advantages, but whether these are at the expense of additional side effects remains to be seen.[8] **It is prudent to consider that the patients who benefit most from 5ARI therapy are those with prostate gland size greater than 30 mL on imaging, a PSA greater than 1.5 ng/dL, or palpable prostatic enlargement on digital rectal exam.**[9] As the mechanism results in glandular size reduction, patient selection and gland morphology are key in setting the expectation of outcomes.[5] Other patients who should be considered for 5ARI therapy are those who are seeking simultaneous treatment of alopecia as they may benefit from concurrent deceleration of male pattern baldness.

PHOSPHODIESTERASE-5 INHIBITORS

Phosphodiesterase-5 inhibitors (PDE-5Is) such as tadalafil, sildenafil, and vardenafil have been proposed as effective treatments in the management of male LUTS. They are thought to blunt inflammatory cytokines like interleukin-8 and subsequently suppress human myofibroblast prostatic cells, relax smooth muscle, and reduce bladder afferent nerve activity. However, the exact mechanism remains elusive. In one Cochrane review comparing placebo to PDE-5Is, PDE-5Is demonstrated a greater improvement in IPSS (mean difference −1.89).[10] When compared to ABs, PDE-5Is did not improve IPSS or Benign Prostatic Hyperplasia Impact Index symptoms more than AB monotherapy, meanwhile demonstrating a similar AE profile.[10]

Randomized, controlled trials have shown that sildenafil, when taken on demand for erectile dysfunction (ED), improved LUTS. All severe LUTS in one trial became moderate and 60% of moderate LUTS became mild over the course of 3 months; however, 18% of mild LUTS progressed to moderate.[11,12] Tadalafil seems to have similar improvement of LUTS when compared to an AB like tamsulosin.[13] Vardenafil also has been shown to improve maximal urine flow (Qmax), International Index of Erectile Function, and the irritative

ABBREVIATIONS: 5alpha-reductase (5AR), 5alpha-reductase inhibitor (5ARI), alpha-adrenergic receptor blocker (AB), adverse event (AE), β3-adrenoceptor (B3AR), benign prostatic hyperplasia (BPH), desmopressin (DDAVP), erectile dysfunction (ED), Food and Drug Administration (FDA), International Prostate Symptom Score (IPSS), lower urinary tract symptoms (LUTS), phosphodiesterase-5 inhibitor (PDE-5I), post-void residual (PVR), quality of life (QoL), maximal urine flow (Qmax)

IPSS subscore.[14] In isolation, it is evident that many variations on dosage and type of PDE-5I offer improvement of symptoms, but to better understand the relative efficacy of these drugs, a broader picture is required.

A large meta-analysis in 2020 compared 15 combinations of PDE-5I medications and dosages including sildenafil, tadalafil, and vardenafil at common dosages of sildenafil 25 mg; tadalafil 5 mg, 10 mg, and 20 mg; and vardenafil at 10 mg; as well as 0.4 mg tamsulosin. In this analysis sildenafil 25 mg with tamsulosin demonstrated the greatest improvement of LUTS with or without ED. The next most efficacious regimen was tadalafil 5 mg with tamsulosin in improving IPSS. Sildenafil 25 mg with tamsulosin also demonstrated the greatest improvement in Qmax. Interestingly, sildenafil 25 mg when combined with tamsulosin demonstrated improved outcomes with a 4-times-weekly dosage when compared to a daily dosage of sildenafil 25 mg.[15]

Dose dependency has been shown with regard to the effect of tadalafil in treating male LUTS. Therapeutic effect increased with regard to IPSS parameters with increased dosage from 2.5 mg to 5 mg to 10 mg; however, 20 mg did not demonstrate further improvement. This ceiling effect was not observed in improvement of symptom scores, which continued to improve with increased dosages of tadalafil. AEs, however, also increased with an increase in dosage. **The ideal candidates for PDE-5I treatment of LUTS would be men with concomitant mild ED.** Generally, tadalafil 5 mg daily is an appropriate starting point for these men.[10]

ANTIMUSCARINICS

It is proposed that male LUTS cannot be attributable exclusively to the prostate because of a similar prevalence in women.[16] Thus, the focus has shifted from the prostate to the bladder as an alternative source of male LUTS and as a therapeutic target. The most prolific acetylcholine receptor in the bladder is the M3 muscarinic receptor, and the modulation of such has proven successful in treating a variety of LUTS symptoms.[17] Since 1999, antimuscarinic therapy has been studied in male LUTS, including bladder outlet obstruction and detrusor dysfunction.[18] The most studied antimuscarinics and anticholinergics, hereafter referred to as antimuscarinics, are solifenacin (Vesicare, Vesitirim), darifenacin (Enablex), fesoterodine (Toviaz), propantheline (Pro-Banthine), propiverine, trospium (Sanctura), tolterodine (Detrol), and oxybutynin (Ditropan, Gelnique).

Antimuscarinics have an established role in the treatment of male LUTS. Ongoing trials presently will help define the future of Vesitirim, a solifenacin compound, as well as other exciting avenues like combination solifenacin and mirabegron after transurethral resection of the prostate. Balanced by the side effect profile, the benefits of antimuscarinic therapy are impactful for storage and voiding symptoms and are most pronounced in urgency and frequency relief. In men with a high risk of acute urinary retention, caution should be used and close monitoring applied particularly for the first month of treatment.

In patients where the primary component of their symptoms can reasonably be attributed to detrusor overactivity, antimuscarinics can afford a great deal of relief. An example of this type of patient would be one with Parkinson's disease, multiple sclerosis, or a cerebral vascular accident with little to no evidence of obstruction on uroflow, ie, Qmax greater than 15 mL/s.

β3-ADRENOCEPTOR AGONIST

β3-adrenoceptor (B3AR) is the dominant β-adrenoreceptor in the lower urinary tract (including the bladder, prostate, and urethra). **It causes smooth muscle relaxation in the detrusor, which leads to increased storage and a decrease in storage LUTS.**[18] Animal-based studies suggest that B3AR also induces relaxation of the urethra, providing possible physiology for relief of voiding LUTS.[19] In a phase 4 study of 352 men who were given mirabegron as an add-on therapy with overactive bladder symptoms while receiving tamsulosin for LUTS secondary to BPH, the addition of mirabegron did not translate to clinically meaningful changes in post-void residual (PVR) or Qmax.[20] Additionally, there were no clinically significant changes in blood pressure between the 2 cohorts. In terms of AE, the mirabegron group had a higher incidence of drug-related events (11.9% vs 5.9%).[20] The urinary retention rate was higher in the mirabegron group compared to placebo (1.7% vs 0.3%).[20]

Vibegron differs from mirabegron with regard to its pharmacological profile. Because it is metabolized independently by CYP2D6 (and approximately 25% of all drugs are metabolized by this pathway), it is less likely to cause a drug-drug interaction and less likely to affect blood pressure.[21] Vibegron received FDA approval for use in overactive bladder in 2020.[21] In the EMPOWUR phase 3 clinical trial and subsequent extension study, vibegron was shown to have a better reduction in urge incontinence and a comparable decrease in urgency compared to placebo and tolterodine.[21]

Similar to antimuscarinics, B3ARs also tend to benefit patients with underlying detrusor overactivity. Either in combination with AB or as monotherapy, B3ARs are an effective medium in managing patients with storage-related LUTS. The role of B3ARs as combination therapy is unclear; however, they may be more favorable than antimuscarinics given reported neuropsychiatric side effects. Storage-related LUTS requires diligent management with frequent PVR. Generally asymptomatic PVR of less than 150 mL can be followed; however, storage-related disease should be considered when an asymptomatic PVR reaches 300 mL. The impact of such PVRs must be interpreted in the clinical context.

DESMOPRESSIN (DDAVP)

Nocturia is one of the most frequently reported male LUTS and is multifactorial in origin. There are several causes such as nocturnal polyuria, global polyuria, functional bladder storage problems, and sleep disorders. Because of its multifactorial pathophysiology, it responds poorly to traditional therapies for LUTS including ABs and 5ARIs.[22] **DDAVP is the only medication with grade A level evidence provided by the International Consultation on Incontinence and the European Association of Urology for refractory nocturia of polyuria origin.**[21-23] DDAVP is a synthetic analog of vasopressin, which is secreted by the posterior pituitary to increase water permeability by acting on renal collecting ducts through arginine vasopressin V2 receptors, leading to water reabsorption and decreased urine volume.

DDAVP may be prescribed orally, nasally, or intravenously. The route of administration (intranasal, sublingual, or oral) did not increase the risk of major AEs such as symptomatic hyponatremia, arrhythmia, need for hospital admission, or respiratory insufficiency. A Cochrane review showed that mean change in the number of nocturnal voids was lowest in the intranasal formulation compared to the oral formulation (intranasal was −0.20 [95% CI −0.34 to −0.06], sublingual was −0.37 [95% CI −0.71 to −0.03], and oral was −1.14 [95% CI −1.41 to −0.86]; $P < .001$).[24]

A bladder diary is a valuable tool in the evaluation of male LUTS and especially nocturnal polyuria. Patients should diligently keep both diurnal and nocturnal voiding diaries to aid clinicians and patients in understanding their disease as well as setting expectations of treatment. Prior to therapy, voiding diaries can provide valuable insight into the degree of symptoms and aid in accurate diagnostics. After initiation of therapy, incremental improvements in male LUTS can be better elucidated with a voiding diary, and aid in outpatient titration of prescription dosing. Men with nocturnal polyuria greater than 33% of total urine output benefit most from the initiation of DDAVP. Serum sodium must be monitored for all patients on DDAVP as hyponatremia is an untoward side effect.

COMBINATION THERAPY

Male LUTS is a quality-of-life disease in the majority of cases. It can have dramatic effects on the everyday routines, physiology, and psychological health of patients. When considering which candidates are appropriate for initiation of which therapies, the entire patient must be considered. As mentioned, concomitant diagnoses like ED, alopecia, or neurological disorders would direct a clinician to favor initiating one drug class over another. Similarly, when considering using drugs in combination, the simultaneous treatment of other disorders must be accounted for.

Multidrug combination therapies approved by the FDA are dutasteride with tamsulosin (Jalyn) and finasteride with tadalafil (Entadfi). Certain landmark studies have validated the safety and efficacy of combination therapy for male LUTS including the Symptom Management After Reducing Therapy (SMART-1) trial, the Medical Therapy of Prostatic Symptoms (MTOPS) trial, and the Combination of Avodart and Tamsulosin (CombAT) trial.[25] In 2007, the CombAT trial demonstrated that 0.5 mg dutasteride with 0.4 mg tamsulosin was superior to monotherapy at reducing BPH progression and improvement of IPSS including both storage and voiding symptoms. The combination therapy proved superior to tamsulosin alone, but not dutasteride alone, at reducing acute urinary retention events and progression to BPH surgery. Of note, men with prostates ≥58 cm^3 showed similar symptom improvement for combination therapy and dutasteride alone.[25] The MTOPS trial has demonstrated many valuable angles to combination therapy of male LUTS. In this trial men were divided into groups of placebo, 4 mg or 8 mg doxazosin, 5 mg finasteride, or a combination of doxazosin and finasteride. These data demonstrated that men treated with both medications had superior placebo-corrected risk reduction than either group alone. This study also demonstrated the benefits of 5ARI for men with prostate size 30 mL or greater.[26] Continued effort in the realm of combination therapy has led to the recent development of a drug combining tadalafil with finasteride. Clinical trials are underway investigating exciting new avenues for combination drug therapy to aid the treatment of the prolific and compromising disorder of male LUTS.

CONCLUSIONS

Male LUTS continues to contribute greatly to the clinical urologist's daily repertoire. Treatment of male LUTS should be patient focused and diagnosis driven. In considering the multitude of treatment options available to patients, their priorities and concomitant diagnoses can be valuable tips as to what would most benefit the patient. Consider the impact the symptoms have on QoL and routinely ask patients whether or not they would like to initiate, alter, or discontinue pharmacotherapy for their LUTS. Many options are available to aid the suffering patient in what can be a devastating constellation of symptoms contained within male LUTS.

DID YOU KNOW?

- Male LUTS has many viable options for treatment, with alpha blockers as the preferred first-line solo therapy.
- Additional pharmacotherapy of male LUTS can be variable dependent on the priorities of the patient.
- Certain therapies can be employed to better treat concurrent diseases of male LUTS.

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Study Questions Volume 42 Lesson 13

1. What new COVID-19 medication needs special considerations when co-administered with alpha blocker per the FDA?
   a. Ivermectin
   b. Ritonavir-boosted nirmatrelvir (Paxlovid)
   c. Remdesivir (BIIa)
   d. Sotrovimab

2. PDE-5Is show the best improvement of symptoms when combined with what other medication class?
   a. DDAVP
   b. Alpha blocker
   c. 5-Alpha-reductase inhibitor
   d. β3 agonist

3. What type of lower urinary tract symptom is most improved with desmopressin?
   a. Obstructive
   b. Storage
   c. Irritative
   d. Nocturia

4. Which B3AR is currently approved by the FDA for use in LUTS?
   a. Vibegron
   b. Sildosin
   c. Solabegron
   d. Ritobegron

5. What concomitant diagnosis may lead a clinician to initiate LUTS treatment with a 5ARI?
   a. Diabetes
   b. Polydypsia with polyuria
   c. Alopecia
   d. Ejaculatory dysfunction