# Medical and Surgical Treatment Modalities for Lower Urinary Tract Symptoms in the Male Patient Secondary to Benign Prostatic Hyperplasia: A Review

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## Abstract

Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) is one of the most common ailments affecting aging men. Symptoms typically associated with BPH include weak stream, hesitancy, urgency, frequency, and nocturia. More serious complications of BPH include urinary retention, gross hematuria, bladder calculi, recurrent urinary tract infection, obstructive uropathy, and renal failure. Evaluation of BPH includes a detailed history, objective assessment of urinary symptoms with validated questionnaires, and measurement of bladder function parameters, including uroflowmetry and postvoid residual. In general, treatment of LUTS associated with BPH is based on the effect of the symptoms on quality of life (QOL) and include medical therapy aimed at reducing outlet obstruction or decreasing the size of the prostate. If medical therapy fails or is contraindicated, various surgical options exist. As the elderly population continues to grow, the management of BPH will become more common and important in maintaining patient's QOL.

**Keywords**

- benign prostatic hyperplasia
- lower urinary tract symptoms
- transurethral resection of the prostate
- interventional radiology

**Objectives**: Upon completion of this article, the reader will be able to define LUTS and differentiate severity classes of LUTS; describe conservative and medical management of LUTS secondary to BPH; describe surgical options for management of LUTS secondary to BPH and when to pursue these options.

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## Benign Prostatic Hyperplasia—An Overview

Benign prostatic hyperplasia (BPH) refers to the proliferation of smooth muscle and epithelial cells within the transition zone of the prostate.[1,2] "Lower urinary tract symptoms" (LUTS) is a term used to describe bladder storage and voiding disturbances. Storage symptoms experienced during the storage phase of bladder filling include daytime frequency and urgency as well as nocturia. Detrusor overactivity (DOA) is thought to be a contributor to storage symptoms seen in LUTS.[3] Voiding symptoms experienced during the voiding phase may include straining to urinate, intermittent urinary stream, and weak urinary stream. BPH has been proposed to contribute to overall LUTS via at least two routes: direct bladder outlet obstruction (BOO) from enlarged prostatic tissue and increased smooth muscle tone and resistance within an enlarged prostate gland. LUTS may also be due to

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structural or functional abnormalities of the peripheral and/or central nervous system that provide neural control to the lower urinary tract.

The prevalence of moderate-to-severe LUTS rises to nearly 50% by the eighth decade of life.[4] Another study has estimated that 90% of men between 45 and 80 years of age suffer some degree of LUTS.[5] The impact of LUTS and BPH on a patient's quality of life (QOL) can be significant. Traditionally, the primary goal of treatment has been to alleviate bothersome LUTS that result from prostatic enlargement. Recently, treatment has additionally focused on the alteration of disease progression and prevention of complications associated with BPH and LUTS.[6]

Importantly, LUTS and BPH have been shown to be associated with other comorbidities including acute urinary retention, renal insufficiency, development of gross hematuria, bladder calculi, urinary incontinence, and recurrent urinary tract infections (UTIs).[7,8]

Objective measures of a patient's urinary symptoms include the American Urological Association-Symptom Index (AUA-SI) and International Prostate Symptom Score (IPSS) templates. These are short, self-administered questionnaires used to assess the severity of three storage urinary symptoms (urgency, frequency, and nocturia) and four voiding symptoms (incomplete emptying, intermittency, straining, and weak stream). Each of the seven variables is assessed on a 0- to 5-point scale. The IPSS form also assesses the degree that urinary symptoms affect the patient's QOL.[9,10] A total score of 0 to 7 on the IPSS correlates with mild symptoms, 8 to 19 correlates with moderate symptoms, and 20 to 35 correlates with severe symptoms.

Lifestyle factors such as exercise, weight gain, and obesity appear to have an impact on LUTS. Encouraging activity, regulating fluid intake (especially in the evening), and limiting bladder irritants in the diet are advisable. Bladder irritants include excessive amounts of alcohol, caffeine, and highly seasoned or irritative foods.[11] As the prevalence of LUTS increases with age, the overall burden and number of men complaining of LUTS will continue to rise with increases in life expectancy and growth of the elderly population.

## Recommendations from the American Urological Association Guideline on BPH

- Baseline renal insufficiency appears to be no more common in men with BPH than in men of the same age group in the general population. Therefore, the routine measurement of serum creatinine levels is not indicated in the initial evaluation of men with LUTS secondary to BPH.
- If a patient's LUTS is not significantly bothersome or if the patient does not desire treatment, no further evaluation of LUTS is recommended (if LUTS is considered secondary to BPH and no other causes). Patients who have LUTS that not bothersome are unlikely to experience significant health problems in the future due to their condition.
- If a patient has predominant significant nocturia and is awakened two or more times a night to void, a frequency volume chart should be completed for 2 to 3 days. This will show 24-hour polyuria ($>$ 3 L urine output) or nocturnal polyuria (when more than 33% of 24-hour urine output occurs at night) when present.
- Patients with bothersome LUTS are advised to aim for a total urine output of 1 L over 24 hours.
- If pharmacologic treatment is necessary for management of a patient's LUTS, it is recommended that the patient be followed to assess treatment success and potential adverse effects. If a treatment is successful and a patient is satisfied, once yearly follow-up is satisfactory and should include a repeat of the initial evaluation.
- α-Antagonists are the first-line medical treatment of choice for moderate-to-severe LUTS due to BPH.
- Transurethral resection of the prostate (TURP) is still considered the gold standard of interventional treatment, if required.

## Treatment Options for Mild Urinary Tract Symptoms (IPSS $<$ 8)

Watchful waiting should be employed for mild LUTS secondary to BPH and in patients with moderate or severe symptoms that are not bothered by LUTS or do not wish to pursue treatment. Watchful waiting includes monitoring patients for adverse effects related to LUTS and BPH, including renal insufficiency, acute urinary retention, and/or recurrent UTIs.

Symptom distress may be improved with weight loss, increased exercise, decreased fluid intake (especially at bedtime), and decreased bladder irritant intake (e.g., caffeine and alcohol). Avoidance of decongestants (α agonists can cause further increase in smooth muscle tone of prostate) and antihistamines may also improve symptoms. Patients should be examined yearly with re-evaluation of symptoms and examination, including digital rectal exam (DRE) and prostate specific antigen (PSA), as indicated.

## Complementary and Alternative Medicines for LUTS Secondary to BPH

The AUA Guideline on BPH does not currently recommend phytotherapy as treatment for LUTS secondary to BPH as data are lacking on the efficacy of these products. However, some men may still benefit from phytotherapy. For example, β-sitosterol is thought to be one of the ingredients in phytotherapy that improves BPH symptoms, although its mechanism of action remains unknown. The most commonly used alternative medicine is saw palmetto. Current available data do not suggest that saw palmetto has a clinically meaningful effect on LUTS secondary to BPH.[12,13] Other alternatives include African plum tree, stinging nettle (*Urtica dioica*), pumpkin seed, African star grass, and rye grass pollen.

## Medical Therapy for Patients with Moderate-to-Severe LUTS (IPSS $\geq$ 8)

### α-Antagonists

α-antagonists are effective treatment for patients with bothersome, moderate-to-severe LUTS secondary to BPH and are

considered first-line medical therapy in patients without a contraindication. These medications inhibit α-1 adrenergic receptors and lead to relaxation of the smooth muscle in the bladder neck and prostate. With activation of these receptors, a subsequent increase in prostatic smooth muscle tone with urethral contraction and impaired flow of urine results.[14] This mechanism is thought to be a major contributor to the pathophysiology of LUTS secondary to BPH. α-1A receptors are the primary subtype of α-1 receptors in the prostate.

Up to 98% of α-adrenergic receptors are associated with stromal elements of the prostate. Therefore, α-antagonists are thought to have the greatest influence on prostatic smooth muscle tone.[15] These medications act in a dose-dependent manner with a concomitant improvement in urinary symptom score and maximum urinary flow rate ($Q_{max}$). With relaxation of the smooth muscle in the prostate, bladder neck, seminal vesicles, and vas deferens, α antagonists may cause the adverse effect of retrograde ejaculation.

Nonselective α-1 antagonists include terazosin (Hytrin (AbbVie), Chicago, IL), doxazosin (Cardura, Pfizer, New York, NY), and alfuzosin (Uroxatral, Covis Pharmaceuticals, Inc., Cary, NC). α-1A–specific antagonists include tamsulosin (Flomax, Boehringer Ingelheim, Ridgefield, CT) and silodosin (Rapaflo, Actavis, Inc., Piscataway, NJ). Silodosin has the highest affinity for α-1A receptors. Improvement can occur within a few days of medication initiation; however, maximal improvement is generally established by 1 to 3 months. α-antagonists produce a significant symptom improvement compared with placebo. Average benefits seen with α-antagonist therapy include a reduction in symptom score by 6 points and an increase in $Q_{max}$ by 2 to 3 mL/s. The minor differences in efficacy noted earlier between the different α-antagonists are not statistically or clinically significant. Side effects include dizziness (2–14%, higher in terazosin and immediate release doxazosin), fatigue, nasal congestion, orthostatic hypotension, syncope, and retrograde ejaculation. Retrograde ejaculation can occur in up to 28% of patients treated with silodosin and 18% of patients treated with tamsulosin. A recent publication noted a $< 10\%$ risk of retrograde ejaculation with tamsulosin.[16]

Another side effect specific to α-antagonists includes intraoperative floppy iris syndrome as first described in 2005.[17] Patients should be asked about planned cataract surgery before initiation of α-antagonist therapy to prevent intraoperative floppy iris syndrome. The risk of intraoperative floppy iris syndrome is highest in those on tamsulosin therapy, ranging from approximately 43 to 90%. α-antagonists should be avoided until planned cataract surgery is completed as permanent visual problems can arise when cataract surgery is not modified to account for this.

## 5-α-Reductase Inhibitors

5-α-Reductase inhibitors (5-ARIs) may be used to prevent the progression of LUTS secondary to BPH and decrease the risk of acute urinary retention and future prostate-related surgery. 5-α-reductase is an enzyme that converts testosterone to dihydrotestosterone, the main active androgen within the prostate. Medication options include finasteride (Proscar, Merck, Whitehouse Station, NJ) and dutasteride (Avodart, GlaxSmithKline, Research Triangle Park, NC). Finasteride inhibits type II 5-α-reductase, whereas dutasteride inhibits types I and II 5-α-reductase. The difference in activity leads to a reduction in the serum levels of dihydrotestosterone by approximately 70% with finasteride compared with approximately 95% with dutasteride.[18] However, type II 5-α-reductase is far more common than type I in the prostate and specifically in BPH tissues, and the reduction of DHT in prostatic tissue has been measured at approximately 80% with finasteride and 94% with dutasteride.[19–21] The Proscar Long-term Efficacy and Safety Study showed that 5-ARIs improve urinary symptoms and flow rate mainly in men with PSA $\geq 1.4$ and prostate volume $>$ 40 mL.[22–25] Therefore, the use of 5-ARIs for LUTS secondary to BPH is often restricted to men with these characteristics.

Symptom improvement may begin within several weeks of initiation of medication; however, it usually takes 6 to 9 months to achieve a very noticeable change in symptoms after starting 5-ARIs. Adverse effects noted while taking these medications include erectile dysfunction (ED) ($< 5\%$), decreased libido ($< 4\%$), decreased volume of ejaculate ($< 3\%$), and gynecomastia ($< 1\%$). These adverse effects are reversible and uncommon after the first year of therapy.

5-ARIs decrease DHT and reduce prostate volume by 15 to 25%, increase $Q_{max}$ by approximately 10%, improve symptom score by 20 to 30% (reduction of $\sim$3–4 points), and reduce the risk of urinary retention and need for surgical BPH therapy by 50%.[22–26] These medications also reduce the risk of BPH progression and decrease total PSA levels by approximately 50% after 9 to 12 months of treatment. They can assist in the prevention of gross hematuria or treatment of refractory hematuria due to prostatic bleeding by suppression of vascular endothelial growth factor.[27–30] Clinically insignificant increases in serum testosterone by 10 to 20% are also noted. Notably, these medications are less effective than α-antagonists in improving LUTS when used as monotherapy.

## Phosphodiesterase-5 Inhibitors

Tadalafil (Cialis) is the only phosphodiesterase-5 inhibitor that has been approved by the Food and Drug Administration for the treatment of LUTS related to BPH. This therapy may be ideal for men with LUTS secondary to BPH and ED, as it can improve both conditions. Daily tadalafil therapy (5 mg) significantly improves erectile function, voiding symptoms, and QOL. Improvement in voiding symptoms can occur within a week, but maximal improvement may take up to 2 months. The combination of tadalafil and an α-antagonist significantly improves $Q_{max}$, voiding symptoms, and ED compared with an α-antagonist alone, and combination of tadalafil with a 5-ARI improves symptom scores more than 5-ARIs alone.[31–33]

## Combination of Medical Therapy with α-Antagonist and 5-α-Reductase Inhibitor

The Medical Therapy of Prostate Symptoms and Combination Avodart and Tamsulosin (CombAT) trials showed that a

combination of an α-antagonist and a 5-ARI improves voiding symptoms and $Q_{max}$ more than either agent alone.[6,16] The combination of α-antagonist and 5-ARI is appropriate and effective for patients with LUTS associated with prostatic enlargement with prostate volumes $> 40$ mL and PSA values $> 1.5$. Combination therapy showed a reduced risk of acute urinary retention, need for BPH surgery, and progression to worse voiding symptoms. It did not reduce renal insufficiency, recurrent UTIs, or incontinence. Approximately 80% of men will not experience a significant worsening of voiding symptoms when the α-antagonist is withdrawn after 6 to 9 months of combination therapy; however, the AUA Guideline on BPH states that the optimal duration of combination therapy prior to discontinuation of α-antagonist remains in doubt.[34] Of note, there was a significant increase noted in drug-related adverse effects with combination therapy versus monotherapies noted in the CombAT trial.

## Combination Medical Therapy with α-Antagonist and Anticholinergics

Combination medical therapy with an α-antagonist and anticholinergic can be used for coexisting BOO symptoms and overactive bladder (OAB) symptoms. The symptoms of OAB (urinary urgency, frequency) may not be treated adequately with an α-antagonist alone. Addition of an anticholinergic results in a statistically significant improvement in voiding symptoms, QOL, urgency, frequency, and nocturia than either agent alone. Patients should be tested for postvoid residual before start of anticholinergic therapy to prevent acute urinary retention. Anticholinergic therapy should not be initiated in patients with postvoid residuals $> 200$ mL, $Q_{max} < 5$ mL/s, or patients with a history of acute urinary retention requiring catheterization. In most studies, adding an anticholinergic to an α-antagonist did not significantly alter PVR or $Q_{max}$. Randomized controlled trials have only investigated tolterodine as the anticholinergic agent, and the most common adverse event was dry mouth in 7 to 24% of patients. The rate of acute urinary retention in these patients was similar to placebo, as was the occurrence of constipation, diarrhea, and somnolence.[35–38]

## Surgical Therapy for Patients with Moderate-to-Severe LUTS Secondary to BPH

Surgical therapy is indicated for patients with moderate-to-severe LUTS secondary to BPH who have failed medical therapy for more than 6 months. However, medical therapy before surgical management of patients with LUTS secondary to BPH is not absolutely required. It is also indicated for patients who experience refractory urinary retention, recurrent UTIs, refractory gross hematuria, recurrent or large bladder stones, renal insufficiency, or hydronephrosis. The presence of a bladder diverticulum is not an absolute indication for surgery unless associated with recurrent UTIs or progressive bladder dysfunction.

## Minimally Invasive Surgical Therapies

Minimally invasive surgical options exist for treatment of LUTS secondary to BPH and include transurethral needle ablation of the prostate and transurethral microwave thermotherapy. An in-depth description of these procedures is beyond the scope of this review. Although significant improvements are noted in voiding symptoms (9- to 11-point reduction), QOL, and $Q_{max}$ (3–4 mL/s), these do not match the results seen with TURP. In general, the minimally invasive treatment approaches mentioned lack sufficient durability of effect when compared with TURP and therefore do not play a greater role in management of LUTS secondary to BPH.

## Transurethral Resection of the Prostate

TURP remains the gold standard and benchmark for surgical therapy for treatment of LUTS secondary to BPH. This procedure involves the resection of prostatic tissue circumferentially from the bladder neck to just cephalad to the verumontanum. The success rate of TURP is higher in patients with preoperative $Q_{max} < 15$ mL/s (consistent with obstructed voiding) and men substantially bothered by urinary symptoms. This procedure is most suitable for patients with prostate volumes $< 80$ mL, due to the limitations of successfully performing surgery as prostate volume size increases.

Historically, monopolar technology was used to perform TURP. The transurethral resection (TUR) syndrome was a complication of monopolar TURP in 1% of cases secondary to the excessive absorption of hypotonic irrigation fluid from the prostatic vascular bed. TUR syndrome led to hyponatremia, hypervolemia, hypertension, altered mental status, nausea with vomiting, and visual changes. The risk of TUR syndrome is higher when the duration of monopolar TURP surgery is long, irrigation pressures are high, and the resection bed contains open venous sinuses.

Bipolar TURP is now available which can be used to resect, coagulate, vaporize, and transect tissue. Bipolar technology uses a specialized resectoscope loop that incorporates both the active and return electrodes, which reduces the effects of stray current flow during the procedure. Importantly, normal saline irrigation may be used with bipolar technology, which allows for an isotonic irrigant and thereby eliminates the risk of TUR syndrome.

Average improvement in symptoms score demonstrates a 15-point reduction in the IPSS along with an average increase in $Q_{max}$ of 11 mL/s. TURP should be approached with caution in patients who have received prior prostate cryotherapy or radiation as the risk of postoperative urinary incontinence is significantly increased in these patients. Complications associated with TURP include postoperative bleeding requiring blood transfusion, ED, irritative voiding symptoms, bladder neck contracture, hematuria, UTI, TUR syndrome, and identification of prostate cancer in prostate specimen sent for pathology (up to 10%). The Veterans Affairs Cooperative Study found a 1% risk of urinary incontinence, which was similar to the incidence in the control group (watchful waiting) and an

overall decline in sexual function identical to the control treatment group.[39]

Historically, the TURP procedure was the most common active treatment for BPH. However, potential morbidities, the desire to shorten Foley catheter indwelling time course, and the pressure to reduce hospital length of stay have stimulated research into alternative procedures.

## Transurethral Incision of the Prostate

Transurethral incision of the prostate (TUIP) is an effective treatment in men with moderate-to-severe LUTS secondary to BPH when the prostate size is less than 30 mL. This procedure is most effective in men with smaller prostate size associated with a "high-riding" bladder neck. TUIP is typically an outpatient procedure involving one or two incisions in the prostate from the bladder neck to just cephalad to the verumontanum, which thereby reduces constriction of the urethra. Symptomatic improvement in the appropriately selected patient is equivalent to those attained after TURP, showing an average of 15-point reduction in symptom score and 7 mL/s improvement in $Q_{max}$.[40–43] There is a significantly reduced risk of ejaculatory disturbance compared with TURP. However, TUIP is associated with a slightly higher rate of required secondary procedures.

## Transurethral Laser Surgical Management

Transurethral laser therapies for LUTS secondary to BPH involve the use of a laser to resect or vaporize the prostatic tissue. The choice of approach should be based on the patient's presentation, anatomy, surgeon's level of training and experience, and risks versus benefits of the procedure. When compared with TURP, laser therapies show a comparable improvement in voiding symptoms with a lower risk of bleeding, shorter postoperative catheterization time, and shorter length of stay in the hospital. However, information concerning certain outcomes including retreatment has been limited due to short follow-up time. The AUA Guideline on transurethral laser surgeries for LUTS secondary to BPH states that emerging evidence suggests a possible role of transurethral enucleation and laser vaporization as options for men with very large prostates (100 g).[34]

Photoselective vaporization of the prostate involves the use of potassium titanyl phosphate and/or lithium borate lasers, referred to as "green light lasers," as the wavelength is in the green portion of the visible spectrum. This wavelength is absorbed by water irrigation as well as hemoglobin and results in a penetration depth of 0.8 mm. The procedure is typically performed using normal saline irrigation and a continuous flow scope. Symptom scores have improved consistently in all studies with an average of approximately 14-point reduction[44,45] with an improvement in $Q_{max}$ of approximately 11 mL/s.[46,47]

Holmium laser enucleation of the prostate (HoLEP) separates the prostatic adenoma from the surgical capsule from apex to base and after any median lobe has been freed from the bladder neck. A tissue morcellator can be used to morcellate tissue within the bladder allowing for shorter operative times. This procedure is typically used for larger glands that historically would have been treated with open prostatectomy. The results are generally comparable to open prostatectomy, depending on the surgeon's experience.[48–50]

Other HoLEP studies have shown improvements in symptom scores, QOL, and $Q_{max}$ that approach those after TURP (up to 18-point reduction in symptom score with 11 mL/s increase in $Q_{max}$).[51,52] Long-term data remain lacking, and therefore, the widespread use of HoLEP has been limited. The procedure also requires specialized training with a learning curve that appears to be greater than that of other surgical interventions.

## Simple Prostatectomy

Simple prostatectomy is typically reserved for men with large prostates ($>$ 80 mL) or men who cannot tolerate a transurethral procedure. Surgical approaches include a suprapubic, retropubic, or perineal approach. The suprapubic approach is the most common approach for patients with very large prostate glands and is ideal for patients who require concomitant removal of bladder stones or excision of bladder diverticula. Minimally invasive laparoscopic and robotic approaches to simple prostatectomy have been described, with open simple prostatectomy typically associated with a longer hospital stay and larger loss of blood when compared with the robotic approach. When compared with TURP, open prostatectomy is associated with an increased risk of blood loss, transfusion, and longer hospital stay. Open prostatectomy shows an average 10-point reduction in symptom scores and 14 mL/s improvement in $Q_{max}$.

## Surgical Considerations

Symptoms can persist in up to 15 to 20% of men after invasive treatment for BPH. Video urodynamics can be employed when voiding symptoms persist after invasive treatment to assess for obstructive voiding indices or DOA. DOA may take as long as 1 year to resolve after surgical interventions for BPH. The most common causes of urinary incontinence after invasive treatment are DOA and urinary sphincteric damage during the surgical procedure. Overall, surgery improves symptom scores and $Q_{max}$ more than any other therapies employed for LUTS secondary to BPH.

## Conclusion

LUTS secondary to BPH is an important health issue in the aging male patient who can have significant impacts on QOL. Mild LUTS can be treated with lifestyle factors and watchful waiting. Moderate-to-severe LUTS can be given a trial of medical therapy when appropriate, with α-antagonists being the first-line medical therapy with an average 6-point reduction in symptom scores. 5-ARI therapy is useful for patients with prostate volumes $>$ 40 mL and PSA $>$ 1.5. Tadalafil is an optimal therapeutic option for patients with BPH and concomitant ED. For patients who fail medical therapy or

experience complications secondary to LUTS and BPH (e.g., acute urinary retention, recurrent UTIs, bladder calculi, renal insufficiency), surgical intervention may be pursued. TURP is still considered the gold standard surgical intervention for patients with moderate-to-severe LUTS; however, there are myriad surgical options with varying side effect profiles and success rates. As the average life expectancy and elderly population continue to increase, LUTS secondary to BPH should be expected to increase in incidence. It is, therefore, imperative to understand the medical and surgical options available to patients for treatment of LUTS secondary to BPH.

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