# *Chapter 1: Guideline on the Management of Benign Prostatic Hyperplasia (BPH)*

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## Introduction

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.[1, 2] The exact etiology is unknown; however, the similarity between BPH and the embryonic morphogenesis of the prostate has led to the hypothesis that BPH may result from a "reawakening" in adulthood of embryonic induction processes. The enlarged gland has been proposed to contribute to the overall lower urinary tract symptoms (LUTS) complex via at least two routes: (1) direct bladder outlet obstruction (BOO) from enlarged tissue (static component) and (2) from increased smooth muscle tone and resistance within the enlarged gland (dynamic component). Voiding symptoms have often been attributed to the physical presence of BOO. Detrusor overactivity is thought to be a contributor to the storage symptoms seen in LUTS.[3] This Guideline attempts to globally encompass the concept of LUTS in a broad spectrum of etiologies, and focuses treatment (e.g., active surveillance, medical and surgical) on the management of such symptoms.

The prevalence and the severity of LUTS in the aging male can be progressive, and is an important diagnosis in the healthcare of our patients and the welfare of society. In assessing the burden of disease, the Urologic Diseases in America BPH Project examined the prevalence of moderate-to-severe LUTS reported in U.S. population-based studies that used the definition of an American Urological Association (AUA) Symptom Index (SI) score of ≥7.[4] Results from the Olmsted County Study showed a progressive increase in the prevalence of moderate-to-severe LUTS, rising to nearly 50% by the eighth decade of life. The presence of moderate-to-severe LUTS was also associated with the development of acute urinary retention (AUR) as a symptom of BPH progression, increasing from a prevalence of 6.8 episodes per 1000 patient years of follow-up in the overall population to a high of 34.7 episodes in men aged 70 and older with moderate to severe LUTS. Another study has estimated that 90% of men between 45 and 80 years of age suffer some type of LUTS.[5]

Although LUTS secondary to BPH (LUTS/BPH) is not often a life-threatening condition, the impact of LUTS/BPH on quality of life (QoL) can be significant and should not be underestimated.[4] When the effect of BPH-associated LUTS on QoL was studied in a number of community-based populations, for many, the most important motivations for seeking treatment were the severity and the degree of bother associated with the symptoms. These were also important considerations when assessing BPH and deciding when treatment is indicated.[6]

Traditionally, the primary goal of treatment has been to alleviate bothersome LUTS that result from prostatic enlargement. More recently, treatment has additionally been focused on the alteration of disease progression and prevention of complications that can be associated with BPH/LUTS.[7] A variety of pharmacologic classes are employed including alpha-adrenergic antagonists (alpha-blockers), 5-alpha-reductase inhibitors (5-ARIs), anticholinergics and phytotherapeutics. Choosing the correct medical treatment for BPH is truly complex and ever-changing.

In the management of bothersome LUTS, it is important as healthcare providers that we recognize the complex dynamics of the bladder, bladder neck, prostate and urethra, and that symptoms may result from interactions of these organs as well as with the central nervous system. It is the hope that this revised clinical Guideline will provide a useful reference on the effective evidence-based management of male LUTS secondary to BPH. This 2010 Guideline reviews a number of important

aspects in the management of LUTS presumed secondary to BPH including available diagnostic tests to identify the underlying pathophysiology and to assist in symptom management. Pharmacotherapies--including complementary and alternative medications (CAM) and watchful waiting, as well as lifestyle issues-- are addressed. The current literature on the standard surgical options as well as on minimally invasive procedures was similarly reviewed. Despite the rigorous methodology and detail used in these various areas, supporting high-quality data (i.e., randomized controlled trials) could not be identified for some topics. In these situations, the Panel, not surprisingly, was forced to suggest best practices based on expert opinion.

In more recent years, the association between LUTS and erectile dysfunction (ED) has been clarified. Lifestyle factors – such as exercise, weight gain and obesity –appear to have an impact on LUTS. We expect these concerns to grow in importance with the aging of our nation and the obesity epidemic. Because prevalence of LUTS increases with age, the burden and number of men complaining of LUTS will rise with the increasing life expectancy and growth of our elderly population. This will place increased demands for treatment services, and necessitate the incorporation of evidence-based medicine in treatment therein.

## Definitions and Terminology

For this Guideline, the **Index Patient** is a male aged 45 or older who is consulting a qualified healthcare provider for his LUTS. He does not have a history suggesting non-BPH causes of LUTS and his LUTS may or may not be associated with an enlarged prostate gland, BOO, or histological BPH. Although the Index Patient defined in the 2003 Guideline was aged 50 or older, the Panel has lowered the age for inclusion in this Guideline, as this lower age group can present with LUTS.

**LUTS** include storage and/or voiding disturbances common in aging men. Storage symptoms are experienced during the storage phase of the bladder and include daytime frequency and nocturia; voiding symptoms are experienced during the voiding phase. LUTS may be due to structural or functional abnormalities in one or more parts of the lower urinary tract that comprises the bladder, bladder neck, prostate, distal sphincter mechanism, and urethra. Of note, LUTS may result from abnormalities of the peripheral and/or central nervous systems that provide neural control to the lower urinary tract. LUTS may also be secondary to cardiovascular, respiratory or renal dysfunction or disease. Thus, this disease entity is particularly complex to evaluate, survey and treat. In men, enlargement of the prostate gland from hyperplasia can cause BOO and be a major cause of LUTS or mimicked by other issues, such as infection, malignancy, central-peripheral neurologic disease or overactivity/hypoactivity of detrusor muscles.

In the past, a number of terms have been used to describe these LUTS in the male. These have varied from BPH, clinical BPH, BOO, prostate enlargement, or prostatism. It is becoming widely accepted that the symptoms we relate in many older males may not have an etiology in prostate enlargement. For that reason, the term "**LUTS independent of BPH"** has been introduced and is gaining worldwide acceptance. Regardless, the concept of **LUTS secondary to BPH (LUTS/BPH)** is meaningful to clinicians. Less frequently, LUTS/BPH has been associated with other comorbidities including AUR, renal insufficiency, and the development of gross hematuria, bladder calculi, urinary incontinence and recurrent urinary tract infection (UTI).[8, 9]

The **overactive bladder syndrome** is defined as urgency with or without urge incontinence, usually with frequency and nocturia.

**Detrusor overactivity** is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase. These contractions may be spontaneous or provoked.

The term **"benign prostatic hyperplasia"** is reserved for the histological pattern it describes. **Benign prostatic enlargement** is used when there is gland enlargement and is usually a presumptive diagnosis based on the size of the prostate. **Benign prostatic obstruction (BPO)** is used when obstruction has been proven by pressure flow studies, or is highly suspected from flow rates and if the gland is enlarged. **Bladder outlet obstruction (BOO)** is the generic term for all forms of obstruction to the bladder outlet (e.g., urethral stricture) including BPO.

**The AUA-SI and the International Prostate Symptom Score (I-PSS)** (Appendix A6)[10, 11] are nearly identical, validated short, self-administered questionnaires, used to assess the severity of three storage symptoms (frequency, nocturia, urgency) and four voiding symptoms (feeling of incomplete emptying, intermittency, straining, and a weak stream). The I-PSS also assesses the degree of bother associated with the seven symptoms in the aforementioned symptom severity score with one additional QoL question: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" A three-point improvement in the AUA-SI is considered meaningful. For consistency in this Guideline, the term "AUA-SI" will be used when discussing the tools unless specifically differentiated in a study being cited. The **BPH Impact Index (BII)** (Appendix A5) is a questionnaire that assesses the effect of symptoms on everyday life and their interference with daily activities, thus capturing the impact of the condition. This questionnaire can be administered in conjunction with the AUA-SI and provides useful additional information to the single QoL question.

This Guideline does not apply when other disease pathologies are known to be responsible for LUTS, such as prostate cancer or other genitourinary tract malignancies, or when LUTS are due to significant comorbidities (e.g., severe diabetes mellitus or neurologic disease), concomitant medications, UTIs, prior pelvic surgery, or trauma. In addition to being responsible for the symptoms, these excluded clinical scenarios, diseases and/or conditions may affect treatment in a manner outside the purview of this Guideline.

## Methodology

The clinical guideline statements presented in this document were based on a systematic review and synthesis of the clinical literature on current and emerging therapies for the treatment of BPH. The methodology followed the same process used in the development of the 2003 Guideline and, as such, did not include an evaluation of the strength of the body of evidence as will be instituted in future Guidelines produced by the AUA. The full description of the methodology presented in Chapter 2 can be accessed at http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm.

The expert Panel examined three overarching key questions for pharmacotherapeutic, surgical and alternative medicine therapies: (1) What is the comparative efficacy (the extent to which an intervention produces a beneficial result under ideal conditions such as clinical trials) and effectiveness (the extent to which an intervention in ordinary conditions produces the intended result) of currently available and emerging treatments for BPH? What are the predictors of beneficial effects from

treatments? (2) What are the adverse events associated with each of the included treatments, and how do the adverse events compare across treatments? (3) Are there subpopulations in which the efficacy, effectiveness, and adverse event rates vary from those in general populations?

The guideline statements were drafted by the Panel based on the outcomes data and tempered by the Panel's expert opinion. As in the previous Guideline, statements were graded using three levels with respect to the degree of flexibility in their application. A "standard" has the least flexibility as a treatment policy; a "recommendation" has significantly more flexibility; and an "option" is even more flexible. These three levels of flexibility are defined as follows:

1. **Standard**: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and (2) there is virtual unanimity about which intervention is preferred.
2. **Recommendation**: A guideline statement is a recommendation if: (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred.
3. **Option**: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.

The guideline was examined by 69 peer reviewers, and approved by the Practice Guidelines Committee and the Board of Directors of the AUA. The Guideline is published on the AUA website (http://www.auanet.org). A summary version of the Guideline will be published in *The Journal of Urology.*

## Diagnostic Evaluation

The Panel decided that the diagnostic section of the 2003 Guideline required updating. After review of the recommendations for diagnosis published by the 2005 International Consultation of Urologic Diseases[12] and reiterated in 2009 in an article by Abrams et al (2009), the Panel unanimously agreed that the contents were valid and reflected "best practices". [13] The diagnostic guidelines by Abrams et al (2009) are revisited in Appendix A7. [13] Two treatment algorithms, one on the basic management of LUTS in men and one on the detailed management for persistent bothersome LUTS— were adapted for this Guideline and are included in Appendix A1 as Figures 1.1 and 1.2, respectively. [13]

## Basic Management

The algorithm describing basic management of BPH/LUTS classifies diagnostic tests as either recommended or optional. A "recommended test" should be performed on every patient during the initial evaluation whereas an "optional test" is a test of proven value in the evaluation of select patients. In general, optional tests are performed during a detailed evaluation by a urologist.

If the initial evaluation demonstrates the presence of LUTS associated with results of a digital rectal exam (DRE) suggesting prostate cancer, hematuria, abnormal prostate-specific antigen (PSA)

levels, recurrent infection, palpable bladder, history/risk of urethral stricture, and/or a neurological disease raising the likelihood of a primary bladder disorder, the patient should be referred to a urologist for appropriate evaluation before advising treatment (Figure 1.1 in Appendix A7). 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.

**Not Recommended: The routine measurement of serum creatinine levels is not indicated in the initial evaluation of men with LUTS secondary to BPH. [Based on review of the data and Panel consensus.]**

When initial evaluation demonstrates the presence of LUTS only, with or without some degree of nonsuspicious prostate enlargement, if the symptoms are not significantly bothersome or if the patient does not want treatment, no further evaluation is recommended. The patient should be reassured and can be seen again if necessary. This recommendation is based on the opinion that patients with nonbothersome LUTS are unlikely to experience significant health problems in the future due to their condition.

In patients with bothersome symptoms, it is now recognized that LUTS has a number of causes that may occur singly or in combination. Among the most important are BPO, overactive bladder, and nocturnal polyuria. The physician can discuss with the patient treatment alternatives based on the results of the initial evaluation with no further tests being needed (See Figure 1.1 Recommended Tests in Appendix A7). There should be a discussion of the benefits and risks involved with each of the recommended treatment alternatives (e.g., watchful waiting, medical, surgical, or minimally invasive surgical treatments). Then the choice of treatment is reached in a shared decision-making process between the physician and patient.

If the patient has predominant significant nocturia and is awakened two or more times per night to void, it is recommended that the patient complete a frequency volume chart for two to three days. The frequency volume chart will show 24-hour polyuria or nocturnal polyuria when present, the first of which has been defined as greater than three liters total output over 24 hours. In practice, patients with bothersome symptoms are advised to aim for a urine output of one liter per 24 hours. Nocturnal polyuria is diagnosed when more than 33% of the 24-hour urine output occurs at night. Nocturia should be managed according to the algorithm in Figure 1.1 in Appendix A7 in that fluid intake should be reduced; other treatments, such as desmopressin, can also be considered. If symptoms do not improve sufficiently, these patients can be managed similarly to those without predominant nocturia.

If the patient has no polyuria and medical treatment is considered, the physician can proceed with therapy by focusing initially on modifiable factors such as concomitant drugs, regulation of fluid intake (especially in the evening), lifestyle (increasing activity) and diet (avoiding excess of alcohol and highly seasoned or irritative foods).[14] If pharmacological treatment is necessary, it is recommended that the patient be followed to assess treatment success and possible adverse events. The time from initiation of therapy to treatment assessment varies according to the pharmacological agent prescribed. An interval of two to four weeks is recommended for alpha-blockers and at least a three-month interval is recommended for 5-ARIs.

If treatment is successful and the patient is satisfied, once yearly follow-up should include a repeat of the initial evaluation. The follow-up strategy will allow the physician to detect any changes

that have occurred -- more specifically, if symptoms have progressed or become more bothersome, or if a complication has developed that requires surgery.

## Detailed Management

If the patient's LUTS are being managed by a primary care giver and the patient has persistent bothersome LUTS after basic management, then a urologist should be consulted. The urologist may use additional testing beyond those recommended for basic evaluation (Figure 1.2 in Appendix A7).

If drug therapy is considered, decisions will be influenced by coexisting overactive bladder symptoms and prostate size or serum PSA levels. If there are coexisting BOO and overactive bladder symptoms then the patient can be treated with combination alpha-blocker and anticholinergic therapy. When BOO symptoms predominate, alpha-adrenergic blocking agents are the first treatment of choice for LUTS due to BPH. However, alpha-blockers alone, 5-ARIs alone, and/or combination alpha-blocker and 5-ARI therapy have shown the most efficacy when the prostate is enlarged as assessed by PSA levels, transrectal ultrasound (TRUS) or on DRE (Figure 1.2 in Appendix A7). As always, the decision for choice of therapy should be decided in concert with the patient's wishes and concerns.

If storage symptoms predominate, an overactive bladder due to idiopathic detrusor overactivity is the most likely cause if there is no indication of BOO from flow study. The treatment options of lifestyle intervention (fluid intake alteration), behavioral modification and pharmacotherapy (anticholinergic drugs) should be discussed with the patient. **It is the expert opinion of the Panel that some patients may benefit using a combination of all three modalities. Should improvement be insufficient and symptoms severe, then newer modalities of treatment such as botulinum toxin and sacral neuromodulation can be considered.** The patient should be followed to assess treatment success or failure and possible adverse events according to the section on basic management above.

**Interventional Therapy**

If the patient elects interventional therapy and there is sufficient evidence of obstruction, the patient and urologist should discuss the benefits and risks of the various interventions. Transurethral resection is still the gold standard of interventional treatment but, when available, new interventional therapies could be discussed. The techniques accepted for clinical use are summarized below.

If the patient's condition is not sufficiently suggestive of obstruction (e.g., peak urinary flow (Qmax) >10 mL/sec) pressure flow studies are optional as treatment failure rates are somewhat higher in the absence of obstruction. If interventional therapy is planned without clear evidence of the presence of obstruction, the patient needs to be informed of possible higher failure rates of the procedure.

***Treatment Alternatives***

**Standard: Information on the benefits and harms of treatment alternatives for LUTS secondary to BPH should be explained to patients with moderate to severe symptoms (AUA-SI score ≥8) who are bothered enough to consider therapy.**
**[Based on Panel consensus.]**

The patient must be informed of all available and acceptable treatment alternatives applicable to his clinical condition, as well as the related benefits, risks and costs of each modality so that he may actively participate in the choice of therapy (shared decision-making). Some patients with bothersome symptoms might opt for surgery, while others might opt for watchful waiting or medical therapy depending on individual views of benefits, risks and costs. The treatment choices (Table 1) are discussed in this chapter with the supporting evidence presented in Chapter 3.

**Table 1.1. Treatment alternatives for patients with moderate to severe symptoms of BPH**

| |
|---|
| **Watchful Waiting** |
| **Medical Therapies**<br>*Alpha-Blockers*<br>- Alfuzosin<br>- Doxazosin<br>- Tamsulosin<br>- Terazosin<br>- Silodosin*<br><br>*5- Alpha-reductase inhibitors (5-ARIs)*<br>- Dutasteride<br>- Finasteride<br><br>*Combination Therapy*<br>- Alpha blocker and 5-alpha-reductase inhibitor<br>- Alpha blocker and anticholinergics<br><br>*Anticholinergic Agents* |
| **Complementary and Alternative Medicines (CAM)** |
| **Minimally Invasive Therapies**<br>- Transurethral needle ablation (TUNA)<br>- Transurethral microwave thermotherapy (TUMT) |
| **Surgical Therapies**<br>- Open prostatectomy<br>- Transurethral holmium laser ablation of the prostate (HoLAP)<br>- Transurethral holmium laser enucleation of the prostate (HoLEP)<br>- Holmium laser resection of the prostate (HoLRP)<br>- Photoselective vaporization of the prostate (PVP)<br>- Transurethral incision of the prostate (TUIP)<br>- Transurethral vaporization of the prostate (TUVP)<br>- Transurethral resection of the prostate (TURP) |

*Silodosin was approved by the US Food and Drug Administration but there were no published articles in the peer reviewed literature prior to the cut-off date for the literature search.

**Watchful Waiting**

**Standard: Patients with mild symptoms of LUTS secondary to BPH (AUA-SI score <8) and patients with moderate or severe symptoms (AUA-SI score ≥8) who are not bothered by their LUTS should be managed using a strategy of watchful waiting (active surveillance).**
**[Based on review of the data and Panel consensus.]**

Watchful waiting (active surveillance) is the preferred management strategy for patients with mild symptoms. It is also an appropriate option for men with moderate-to-severe symptoms who have not yet developed complications of LUTS and BOO (e.g., renal insufficiency, urinary retention or recurrent infection).

Watchful waiting is a management strategy in which the patient is monitored by his physician but currently receives no active intervention for BPH. The level of symptom distress that individual patients are able to tolerate is highly variable so watchful waiting may be a patient's treatment of choice even if he has a high AUA-SI score. Symptom distress may be reduced with simple measures such as avoiding decongestants or antihistamines, decreasing fluid intake at bedtime and decreasing caffeine and alcohol intake generally. Watchful waiting patients usually are reexamined yearly, repeating the initial evaluation as previously outlined in Figure 1.1 in Appendix A7.

As prostate volume assessed by DRE and/or serum PSA predicts the natural history of symptoms, flow rate and risk for AUR and surgery, patients may be advised, depending on the outcomes of these assessments, as to their individual risk. Measures to reduce the risk, such as medical intervention, may be offered depending on the circumstances.

**Medical Management**

***Alpha-adrenergic Blockers (Alpha Blockers)***

**Option: Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatment alternatives for patients with bothersome, moderate to severe LUTS secondary to BPH (AUA-SI score ≥8). Although there are slight differences in the adverse events profiles of these agents, all four appear to have equal clinical effectiveness. As stated in the 2003 Guideline, the effectiveness and efficacy of the four alpha blockers under consideration appear to be similar. Although studies directly comparing these agents are currently lacking, the available data support this contention.[*]**
**[Based on review of the data and Panel consensus.]**

**Option: The older, less costly, generic alpha blockers remain reasonable choices. These require dose titration and blood pressure monitoring.**
**[Based on Panel consensus.]**

[*] Silodosin was approved by the U.S. Food and Drug Administration but there were no relevant published articles in the peer-reviewed literature prior to the cut-off date for the literature search.

**Recommendation: As prazosin and the nonselective alpha-blocker phenoxybenzamine were not reviewed in the course of this Guideline revision, the 2003 Guideline statement indicating that the data were insufficient to support a recommendation for the use of these two agents as treatment alternatives for LUTS secondary to BPH has been maintained.**
**[Based on Panel consensus.]**

Alpha-blockers are a widely used class of medications for the treatment of LUTS secondary to BPH. Noradrenergic sympathetic nerves have been demonstrated to effect the contraction of prostatic smooth muscle.[15] Ninety-eight percent of alpha-blockers are associated with the stromal elements of the prostate and are thus thought to have the greatest influence on prostatic smooth muscle tone.[16] Activation of these receptors and the subsequent increase in prostatic smooth muscle tone with urethral constriction and impaired flow of urine is thought to be a major contributor to the pathophysiology of LUTS secondary to BPH.

For the purposes of this Guideline, the specific agents reviewed included alfuzosin, doxazosin, tamsulosin and terazosin as they theoretically act in the location that will have the greatest benefit for symptoms with the fewest side effects. As these agents remain a mainstay of LUTS/BPH therapy, they were considered individually rather than by class. Alpha-blockers produce a significant symptom improvement compared to placebo, which the average patient will appreciate as a moderate improvement from baseline. The minor differences in efficacy noted between the different alpha-blockers are not statistically (when tested) or clinically significant.

The 2003 Guideline suggested that some patients treated with tamsulosin require the 0.8 mg dose to achieve the results obtained with doxazosin and terazosin titrated to response. This may present a cost-effectiveness problem for tamsulosin because the 0.8 mg daily dose requires two tablets and, thus, twice the expense of the lower dose, while the terazosin and doxazosin recommended dosages are available as one unit generic products and priced accordingly. However, during guideline development (March 2010), the Panel became aware that tamsulosin was available as a generic product which may have obviated this problem.

In clinical studies, rates for specific adverse events were low and similar between treatment and placebo groups. Dizziness was the most common adverse event, with rates reported between 2% and 14% in patients receiving alpha-blockers and somewhat lower rates with placebo. With regard to tamsulosin, the ~10% risk of ejaculatory disturbance cited in the 2003 Guideline appears to be lower in a more recent study noted in this review, understanding that this study used alternate metrics to gauge ejaculation alterations.[17]

Although doxazosin and terazosin require dose titration and blood pressure monitoring, they are inexpensive, are dosed once daily, and appear to be equally effective to tamsulosin and alfuzosin. In addition, they have generally similar side effect profiles, except ejaculatory dysfunction which has been reported less frequently with alfuzosin. Moreover, these older agents do not appear to increase the risk of the intraoperative floppy iris syndrome (IFIS), and doxazosin has demonstrated efficacy relative to placebo over four years of follow-up. The Panel wishes to remind clinicians that these agents remain excellent choices for the management of bothersome LUTS attributed to BPH.

In the expert opinion of the Panel, the caveat remains that alpha-blocker monotherapy is not considered optimal therapy for hypertension. LUTS/BPH and hypertension should be managed separately.

**Option: The combination of an alpha-blocker and a 5-ARIs (combination therapy) is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, PSA level as a proxy for volume, and/or enlargement on DRE.**
**[Based on review of the data and Panel consensus.]**

In previous studies of one-year duration or less, combination therapy proved equal to alpha blocker therapy in efficacy and safety, but superior to 5-ARI therapy.[18, 19] However, the Medical Therapy of Prostate Symptoms (MTOPS) Study demonstrated that in the long term, among men with larger prostates, combination therapy is superior to either alpha-blocker or 5-ARI therapy in preventing progression and improving symptoms.[7] It was the opinion of the Panel that there is insufficient information to gauge the utility of alpha-blocker withdrawal among men initially treated with combination therapy. Although not an unreasonable strategy, clinicians need to recognize that the optimal duration of combination therapy prior to discontinuation of the alpha-blocker remains in doubt.

Data from the long-term MTOPS Study suggests a time-limited impact of alpha-blockers on the outcomes of AUR and crossover to surgery. That is, while AUR and surgery rates were lower with doxazosin compared to placebo in the early years of follow-up, by five years rates of these outcomes were similar in both groups.[7] The time-limited effect noted for doxazosin in MTOPS on these outcomes is likely a class effect.

The second major combination therapy study was the four-year, CombAT trial comparing tamsulosin, dutasteride and a combination of both; at present only the two-year data are available and published.[17] In contrast to prior studies, eligible men had a prostate volume > 30 mL by TRUS and a serum PSA level of >1.5 ng/mL. Combination therapy resulted in significantly greater improvements in symptoms compared to dutasteride from month three and tamsulosin from month nine, and in BPH-related health status from months three and 12, respectively. A significantly greater improvement from baseline in peak urinary flow for combination therapy vs. dutasteride and tamsulosin monotherapies from month six was also noted. There was a significant increase in drug-related adverse events with combination therapy vs. monotherapies. The primary endpoints of the four-year analysis are similar to the MTOPS Study and include progression to urinary retention and need for prostate surgery as well as symptom progression.

When comparing results from the MTOPS and CombAT studies, the following important differences must always be considered as they affect many aspects of the trials, including the outcomes (Table 1.2).

**Table 1.2. Differences in MTOPS and CombAT Study Characteristics**

| | Medical Therapy of Prostate Symptoms Study (MTOPS) | Combination of Avodart and Tamsulosin (CombAT) |
|---|---|---|
| *Treatments* | Placebo vs finasteride vs doxazosin vs combination | Dutasteride vs. tamsulosin vs. combination |
| *Setting* | United States; select centers | International > 100 centers |
| *Total number enrolled* | *N*=3047 | *N*=4844 |
| *Follow-up time* | Up to 5.5 years | 4 years (2-year data available) |
| *Endpoints* | Composite progression | International Prostate Symptom Score at 2 years; progression at 4 years |
| *Prostate size (mean)* | 36.3 mL | 55.0 mL |
| *Prostate-specific antigen (mean)* | 2.4 ng/mL | 4.0 ng/mL |

***Intraoperative Floppy Iris Syndrome***

**Recommendation: Men with LUTS secondary to BPH for whom alpha-blocker therapy is offered should be asked about planned cataract surgery. Men with planned cataract surgery should avoid the initiation of alpha-blockers until their cataract surgery is completed.**
**[Based on review of the data and Panel consensus.]**

**Recommendation: In men with no planned cataract surgery, there are insufficient data to recommend withholding or discontinuing alpha blockers for bothersome LUTS secondary to BPH.**
**[Based on review of the data and Panel consensus.]**

Intraoperative floppy iris syndrome (IFIS) was first described by Chang and Campbell in 2005 as a triad of progressive intraoperative miosis despite preoperative dilation, billowing of a flaccid iris, and iris prolapse toward the incision site during phacoemusification for cataracts.[20] Operative complications in some cases included posterior capsule rupture with vitreous loss and postoperative intraocular pressure spikes, though visual acuity outcomes appeared preserved. The original report linked this condition with the preoperative use of tamsulosin; iris dilator smooth muscle inhibition has been suggested as a potential mechanism.[20, 21]

To better understand the implications of IFIS for the use of alpha-blocker therapy for men with LUTS attributed to BPH, two focused literature searches were conducted covering the period 1/1/1999 – 2/5/2009. Reference lists of the retrieved papers were reviewed for additional original reports. A total of 32 unique articles were identified with 11 studies published in 10 reports providing the requisite information on the risk of IFIS. A review of these data supports the following conclusions:

- The risk of IFIS was substantial among men taking tamsulosin, ranging from about 43% to 90% in 10 retrospective and prospective studies (sometimes the denominator for these risks was patients, and sometimes eyes).[20, 22-31]
- The risk of IFIS appears to be lower with older, generic alpha-blockers such as terazosin and doxazosin, with IFIS occurring in 0/11 patients (0%), 3/49 patients (6.1%), 1/51 eyes (2.0%) and 1/4 eyes (25%) in the four studies reporting on the risk of IFIS with these agents.[20, 23, 28, 31]
- There is insufficient exposure data to estimate the risk of IFIS with alfuzosin.
- The dose or duration of alpha-blocker treatment that influences the risk of IFIS is unclear.
- Whether stopping alpha-blocker treatment at any time before surgery mitigates the risk of IFIS is unclear.
- If experienced ophthalmologists are aware of preoperative alpha-blocker use, pre- and intraoperative precautions can be taken to reduce the risk of IFIS complications and attain excellent visual outcomes,[21, 24] though it remains unclear if the residual risk and outcomes are any worse than among patients without IFIS.

It is important to note that after the IFIS literature search and review was completed, a study was published in the Journal of the American Medical Association examining the association of recent tamsulosin use with serious postoperative complications (e.g., retinal detachment, lost lens or lens fragment, or endophthalmitis) requiring reintervention within 14 days of cataract surgery.[32] The study found that for every 255 men receiving tamsulosin in the immediate preoperative period, one of these complications would result. The study had insufficient power to determine whether discontinuation of tamsulosin reduced the risk of these complications, and no separate estimate of the risk was provided for other alpha blockers, including alfuzosin. Therefore, the Panel believed that these new findings were supportive of their original conclusions.

***5-Alpha-reductase Inhibitors (5-ARIs)***

**Option: 5-ARIs may be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery.**
**[Based on review of the data and Panel consensus.]**

**Recommendation: 5-ARIs should not be used in men with LUTS secondary to BPH without prostatic enlargement.**
**[Based on review of the data and Panel consensus.]**

**Option: The 5-ARIs are appropriate and effective treatment alternatives for men with LUTS secondary to BPH who have demonstrable prostate enlargement.**
**[Based on review of the data and Panel consensus.]**

The compounds in this class approved for the treatment of BPH, finasteride at a dose of 5 mg daily, and dutasteride at a dose of 0.5 mg tablet daily, differ in two important pharmacological characteristics.[33-35]

- Finasteride inhibits exclusively the 5-AR type II isoenzyme, while dutasteride inhibits both types I and II. This difference in activity leads to a reduction in serum levels of dihydroxytestosterone (DHT) by approximately 70% with finasteride compared to approximately 95% with dutasteride.[34] However, in the prostate, and specifically in BPH tissues, type II 5-AR is far more common than type I.[36] The reduction of DHT in prostate tissues relative to placebo is therefore less pronounced and has been measured at approximately 80% (finasteride)[37] and approximately 94% (dutasteride)[38].
- The serum half life of finasteride ranges from six to eight hours whereas that of dutasteride is five weeks. This pharmacokinetic difference may have implications in terms of treatment compliance as well as persistence of side effects.[39]

There are no data from direct comparator trials or other sources to suggest that the clinical efficacy of the two 5-ARIs used for the appropriate indication is different. Comparisons are difficult if not impossible due to the fact that inclusion and exclusion criteria do not match for any trials of finasteride or dutasteride. In different studies, various thresholds have been proposed for the definition of prostate enlargement (25, 30 or 40 mL). In some studies, serum PSA has been recommended as a proxy for prostate size (using usually a threshold of 1.5 ng/dL).

The Panel was not charged with addressing the use of 5-ARIs for chemoprevention but understands the controversies for and against use in that indication.[40, 41]

**Finasteride**

In the 2003 Guideline finasteride was found to be an appropriate BPH treatment option based on a thorough review of a large body of evidence consisting of randomized, placebo-controlled studies of one, two and four years duration. With finasteride, the average patient experiences a three-point improvement in the AUA-SI. Finasteride is less effective than an alpha-blocker in improving LUTS and is not an appropriate treatment for men with LUTS who do not have prostatic enlargement. Due to the more progressive nature of the disease in men with larger glands and/or higher PSA values, conservatively treated patients (watchful waiting or placebo groups) face an increasingly worse prognosis, enhancing the difference over time in outcomes between finasteride and no treatment or placebo groups. Finasteride reduces the risk of subsequent AUR and the need for BPH-related surgery with the absolute benefit increasing with rising prostate volume or serum PSA. Reported adverse events are primarily sexually related and include decreased libido, ejaculatory dysfunction, and ED. These events are reversible and uncommon after the first year of therapy.

The majority of studies with finasteride were published before the 2003 Guideline and since then the compound has lost patent protection. Only a small number of subset or post hoc analyses and open-label extension studies have been reported since the 2003 Guideline.

**Dutasteride**

Dutasteride is the second 5-ARI approved by the U.S. Food and Drug Administration for the use in men with LUTS and BPH.[42] Its pharmacological characteristics produce a more profound reduction in both serum and intraprostatic DHT levels compared with finasteride. Whether these differences are clinically important is unknown; there are no published trials directly comparing the two agents. Indirect comparisons of efficacy outcomes are limited in that only patients with baseline prostate volumes > 30

mL by TRUS and serum PSA levels > 1.5 ng/mL were eligible for enrollment in dutasteride clinical trials, thus enriching the population for potential responders to 5-ARI treatment.

The clinical database for dutasteride consists mainly of three trials: the phase III randomized, placebo-controlled trial of two-year duration[43] with an open-label extension[44]; a study evaluating the effect of a placebo-controlled withdrawal of an alpha-blocker from a combination therapy arm (SMART 1)[45]; and a four-year study comparing dutasteride vs. tamsulosin vs. their combination of the two (CombAT) for which only the two-year interim data are published[17]. Dutasteride is untested among men with prostate volumes < 30 mL. Reported treatment-related adverse events include ED, decreased libido, gynecomastia and ejaculation disorders.

**Combination Therapy with Alpha-adrenergic Antagonists**

See Guideline Statement and text in section on alpha-adrenergic antagonists.

***5-Alpha-reductase Inhibitors for Other Indications***

**Hematuria**

**Option: Finasteride is an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding (i.e., after exclusion of any other causes of hematuria). A similar level of evidence concerning dutasteride was not reviewed; it is the expert opinion of the Panel that dutasteride likely functions in a similar fashion. [Based on review of the data and Panel consensus.]**

One of the early intraprostatic effects of finasteride has been the suppression of vascular endothelial growth factor (VEGF).[46-49] Initially anecdotally,[50] and then in long-term follow-up studies[51-53] it was noted that men with prostate-related bleeding (e.g., all other causes of hematuria had been excluded) responded to finasteride therapy with a reduction or cessation of such bleeding and a reduced likelihood of recurrent bleeding. A prospective study verified these observations.[46]

**Prevention of Bleeding During Transurethral Resection of the Prostate (TURP)**

**Option: Overall, there is insufficient evidence to recommend using 5-ARIs preoperatively in the setting of a scheduled TURP to reduce intraoperative bleeding or reduce the need for blood transfusions.**
**[Based on review of the data and Panel consensus.]**

Based on the effect of 5-ARIs on prostate-related bleeding, several investigators studied the effect of presurgical treatment with a 5-ARI on bleeding during TURP. Four studies were randomized, placebo-controlled and well executed.[54-57] Other studies were either uncontrolled[58, 59] or randomized but used poorly defined methods of measuring the blood loss.[60] One of the randomized and the two nonrandomized studies found a reduction in blood loss or transfusion requirements.

***Anticholinergic Agents***

**Option: Anticholinergic agents are appropriate and effective treatment alternatives for the management of LUTS secondary to BPH in men without an elevated post-void residual and when LUTS are predominantly irritative.**

**[Based on Panel consensus.]**

**Recommendation: Prior to initiation of anticholinergic therapy, baseline PVR urine should be assessed. Anticholinergics should be used with caution in patients with a post-void residual greater than 250 to 300 mL.**
**[Based on Panel consensus.]**

Anticholinergic (antimuscarinic) agents block the neurotransmitter acetylcholine in the central and the peripheral nervous system. This class of medication reduces the effects mediated by acetylcholine on its receptors in bladder neurons through competitive inhibition. Five muscarinic subclasses (M1 through M5) of cholinergic receptors have been described in the human bladder muscle, the majority comprises subtypes M2 and M3. While M2 receptors predominate, M3 receptors are primarily responsible for bladder contraction.[61]

Three randomized controlled trials (RCTs) evaluating the use of tolterodine either as monotherapy or in combination with an alpha-blocker in men with LUTS related to BPH were identified on the literature review.[62-64] Although, these trials do not sufficiently demonstrate the efficacy or effectiveness of tolterodine, the Panel concluded that the use of anticholinergic could benefit some patients. The use of PSA measurements does not appear applicable to predicting or monitoring the effectiveness of tolterodine for the treatment of BPH/LUTS. Randomized controlled trials investigating anticholinergic agents other than tolterodine for the treatment of LUTS secondary to BPH have not been published. The most common adverse event reported with tolterodine monotherapy in men with BPH related LUTS was dry mouth, ranging in frequency from seven to 24%.[62, 63, 65] The rate of urinary retention was similar to placebo in two of the largest RCTs. The occurrence of constipation, diarrhea, and somnolence were also similar in frequency to placebo.[62, 63]In available RCTs, the overall withdrawal rate from tolterodine therapy ranged from 11% -- 12%.[62, 63] Withdrawal due to adverse events ranged from 0.02% to 0.3%.[62, 64] ED and ejaculation disorders were not reported with the use of tolterodine alone or in combination with tamsulosin. Significant morbidity and mortality resulting from tolterodine use was not reported in any of these RCTs.

***Complementary and Alternative Medicines (CAM)***

**Recommendation: No dietary supplement, combination phytotherapeutic agent or other nonconventional therapy is recommended for the management of LUTS secondary to BPH.**
**[Based on review of the data and Panel consensus.]**

**Recommendation: At this time, the available data do not suggest that saw palmetto has a clinically meaningful effect on LUTS secondary to BPH. Further clinical trials are in progress and the results of these studies will elucidate the potential value of saw palmetto extracts in the management of patients with BPH.**
**[Based on review of the data and Panel consensus.]**

**Recommendation: The paucity of published high quality, single extract clinical trials of Urtica dioica do not provide a sufficient evidence base with which to recommend for or against its use for the treatment of LUTS secondary to BPH.**

**[Based on review of the data and Panel consensus.]**

Nonconventional approaches to the management of LUTS due to BPH have been of great interest to patients for many years. Of particular appeal are dietary supplements, which include extracts of the saw palmetto plant (Serenoa repens) and stinging nettle (Urtica dioica), among several others. Since the publication of the last version of this Guideline, higher-quality evidence has begun to appear and assessments of the efficacy of the dietary supplements are beginning to evolve.

By far the most commonly studied extract is that of the saw palmetto plant. Systematic reviews of the earlier evidence suggested that saw palmetto extracts may have modest efficacy in the treatment of LUTS.[66, 67] However, more recent studies with more rigorous methods have generally failed to confirm a clinically important role for saw palmetto in the management of BPH.[68, 69] Further studies are ongoing, and more definitive evidence regarding the use of saw palmetto will be forthcoming.

**Minimally Invasive Therapies**

**Standard: Safety recommendations for the use of transurethral needle ablation of the prostate (TUNA) and transurethral microwave thermotherapy (TUMT) published by the U.S. Food and Drug Administration should be followed: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/default.htm.**
**[Based on review of the data.]**

***Transurethral Needle Ablation (TUNA) of the Prostate***

**Option: TUNA of the prostate is an appropriate and effective treatment alternative for bothersome moderate or severe LUTS secondary to BPH.**
**[Based on review of the data and Panel consensus.]**

TUNA is described in detail in Chapter 3. Since the development of the 2003 Guideline, little new information on effectiveness and safety has been published. There are only three prospective, randomized trials (one trial reports outcomes at two time points).[70-72] Improvements in symptoms, QoL, and urinary flow rates are significant but do not generally match the result of TURP and, taken together, lack sufficient detail on comorbidity of subjects. The remainder are cohort studies from which the reporting of outcomes varies considerably. In addition, the bulk of the literature suggests a high long-term retreatment rate. TUNA is safe with low peri-operative complications (such as bleeding) and has a low to nonexistent rate of associated ED for which this therapy is attractive. The Panel concluded that a degree of uncertainty remains regarding TUNA because of a paucity of high-quality studies.

***Transurethral Microwave Thermotherapy (TUMT)***

**Option: TUMT is effective in partially relieving LUTS secondary to BPH and may be considered in men with moderate or severe symptoms.**
**[Based on review of the data and Panel consensus.]**

TUMT heats the prostate using a microwave antennae mounted on a urethral catheter. This interventional therapy is effective in partially relieving the symptoms and bother believed secondary to BPH. TUMT is the least operator-dependent of the BPH interventions and predicting responders is difficult and inconsistent.

A systematic review of TUMT data (see Table 3.6 in Appendix A8) reveals a heterogeneous mix of studies of various sample sizes and TUMT protocols often using different outcome measures with varying durations of follow-up. This leads to conflicting results, as may be seen in studies of shorter versus longer follow-up. There is no compelling evidence from comparator trials to conclude that one device is superior to another.

Earlier, low-energy TUMT devices similarly possessed comparatively less clinical efficacy than later, higher energy counterparts but also carried a lower risk of side effects. The durability of TUMT treatment appears to have improved with the advent of higher energy, later generation devices. One should also note, however, that the concept of durability with TUMT may be misleading, as the data suffer from selection bias. Most studies analyze only those patients who remained in the study at the time of analysis; these patients would tend to represent the best "responders". In many studies, less than half of the initial group of men treated was analyzed at the end of the study period. An intent-to-treat analysis which considers therapeutic failures provides a better measure of the true effectiveness and durability of TUMT. Outpatient capability, lack of sexual side effects and avoidance of actual surgery are attractive to patient and clinician alike. But perhaps there is one issue that has held back greater utilization: the perception that these approaches lack sufficient durability of effect to assume a greater role in the management of LUTS.

**Surgical Procedures**

Surgical intervention is an appropriate treatment alternative for patients with moderate-to-severe LUTS and for patients who have developed AUR or other BPH-related complications. By definition, surgery is the most invasive option for BPH management and generally, patients will have failed medical therapy before proceeding with surgery. However, medical therapy may not be viewed as a requirement because some patients may wish to pursue the most effective therapy as a primary treatment if their symptoms are particularly bothersome. As with other medical treatment alternatives, the decision to elect surgery as the treatment alternative is based upon the patient's own views of treatment risks vs. benefits. The 2003 Guideline recognized that TURP remained the benchmark for therapy. Alternative technologies such as laser-assisted TURP were reported to offer lower morbidities but were typically still performed in the operating room setting and require anesthesia. In addition to open prostatectomy (e.g., retropubic, suprapubic), surgical options for BPH management include:

- Transurethral holmium laser ablation of the prostate (HoLAP)
- Transurethral holmium laser enucleation of the prostate (HoLEP)
- Holmium laser resection of the prostate (HoLRP)
- Photoselective vaporization of the prostate (PVP)
- Transurethral incision of the prostate (TUIP)
- Transurethral vaporization of the prostate (TUVP)
- Transurethral resection of the prostate (TURP)
    - Monopolar
    - Bipolar

- Laparoscopic and robotic prostatectomy (considered investigational)
  **Recommendation: Surgery is recommended for patients who have renal insufficiency secondary to BPH, who have recurrent UTIs, bladder stones or gross hematuria due to BPH, and those who have LUTS refractory to other therapies. The presence of a bladder diverticulum is not an absolute indication for surgery unless associated with recurrent UTI or progressive bladder dysfunction.**
  **[Based on review of the data and Panel consensus.]**

***Open Prostatectomy***

**Option: Open prostatectomy is an appropriate and effective treatment alternative for men with moderate to severe LUTS and/or who are significantly bothered by these symptoms. The choice of approach should be based on the patient's individual presentation including anatomy, the surgeon's experience, and discussion of the potential benefit and risks for complications. The Panel noted that there is usually a longer hospital stay and a larger loss of blood associated with open procedures.**

**[Based on review of the data and Panel consensus.]**

Open prostatectomy involves the surgical removal (enucleation) of the inner portion of the prostate via a suprapubic or retropubic incision in the lower abdominal area. Open prostatectomy typically is performed on patients with prostate volumes greater than 80 to 100 mL.[73-83] The Panel noted that there is significant risk of blood loss, transfusion and a longer hospital stay associated with open prostatectomy than TURP. Open prostatectomies may be needed only for men with very enlarged prostate glands (it may be more effective than TURP in relieving the blockage of urine flow), and for men with bladder diverticula (pockets), or stones.

***Laser Therapies***

**Option: Transurethral laser enucleation (holmium laser resection of the prostate [HoLRP], holmium laser enucleation of the prostate [HoLEP]), transurethral side firing laser ablation (holmium laser ablation of the prostate [HoLAP], and photoselective vaporization [PVP]) are appropriate and effective treatment alternatives to transurethral resection of the prostate and open prostatectomy in men with moderate to severe LUTS and/or those who are significantly bothered by these symptoms. The choice of approach should be based on the patient's presentation, anatomy, the surgeon's level of training and experience, and a discussion of the potential benefit and risks for complications. Generally, transurethral laser approaches have been associated with shorter catheterization time and length of stay, with comparable improvements in LUTS. There is a decreased risk of the perioperative complication of transurethral resection syndrome. Information concerning certain outcomes, including retreatment and urethral strictures, is limited due to short follow-up. As with all new devices, comparison of outcomes between studies should be considered cautiously given the rapid evolution in technologies and power levels. Emerging evidence suggests a possible role of transurethral enucleation and laser vaporization as options for men with very large prostates (> 100 g). There are insufficient data on which to base comments on bleeding.**
**[Based on review of the data and Panel consensus.]**

In general, laser energy can be used to produce a variety of effects within prostate tissue including coagulation necrosis or vaporization and resection of tissue. Today, the holmium and variants of the PVP laser are the most common laser technologies used to treat prostate disease.

**Transurethral Holmium Laser Ablation of the Prostate (HoLAP)**

The holmium:YAG laser may be used to treat prostatic tissue transurethrally using a 550 micron side-firing laser fiber in a noncontact mode. This technology delivers laser energy at a wavelength of 2120 nm (infrared range) which is absorbed primarily by water and results in an optical penetration depth of 0.4 mm. The HoLAP procedure is intended to be comparable to TURP in that the prostatic lobes may be vaporized down to the surgical capsule resulting in a TURP-like effect.

**Transurethral Holmium Laser Enucleation of the Prostate (HoLEP)**

The holmium laser has been used to enucleate the prostate adenoma, separating the adenoma from the surgical capsule, from apex to base, after any median lobe has been freed from the bladder neck. Typically, the technology is utilized for larger glands that previously would have been treated surgically with an open prostatectomy. Generally, the results compare favorably to open prostatectomy in the hands of an experienced surgeon.[84-86] In other trials, improvements in symptom scores, QoL indices, and flow rate, approach those obtained after TURP.[87, 88] Nonetheless, long-term data beyond two years are still lacking[87], and the procedure requires specialized training and equipment. The Panel believes that the learning curve for holmium laser enucleation of the prostate appears to be greater than that of other technologies.

Operative times for holmium enucleation have been improved significantly with the advent of the tissue morcellator. By morcellating tissue within the bladder, the resection technique could be modified to allow complete enucleation of the median and lateral lobes of the prostate.

**Holmium Laser Resection of the Prostate (HoLRP)**

The prostatic adenoma is resected using a holmium laser fiber and a specially adapted resectoscope.[89] Data suggest that the intermediate-term, symptomatic improvement obtained after holmium laser resection may be comparable to that obtained after TURP, with a slightly reduced risk of bleeding, need for blood transfusions, and an absence of transurethral resection (TUR) syndrome.[90]

**Photoselective Vaporization of the Prostate (PVP)**

PVP of the prostate is a form of transurethral prostatectomy performed using a 600 micron side-firing fiber in a noncontact mode. The primary difference from HoLAP is its wavelength of 532 nm (in the green visible spectrum) which is absorbed by both the water irrigation and hemoglobin resulting in an optical penetration depth of 0.8 mm. The other acronyms for this procedure, KTP (potassium tintanyl phosphate) and LBO (lithium borate), identify the crystal used in the laser generator. Typically performed using normal saline irrigation and a continuous flow scope, the goal of PVP is to create a TURP-like cavity after ablating the various prostatic lobes down to the surgical capsule. Symptom scores improved consistently in all studies,[91, 92] as did QoL scores[93, 94] and maximum urinary flow rates.[94, 95]

***Transurethral Incision of the Prostate (TUIP)***

**Option: TUIP is an appropriate and effective treatment alternative in men with moderate to severe LUTS and/or who are significantly bothered by these symptoms when prostate size is less than 30 mL. The choice of approach should be based on the patient's individual presentation including anatomy, the surgeon's experience and discussion of the potential benefits and risks for complications.**
**[Based on review of the data and Panel consensus.]**

TUIP is an outpatient endoscopic surgical procedure limited to the treatment of smaller prostates (30 mL of resected weight or less). In the TUIP procedure, one or two cuts are made in the prostate and prostate capsule, reducing constriction of the urethra. In the appropriate patient, TUIP results in degrees of symptomatic improvement equivalent to those attained after TURP.[96-99] In addition, compared to TURP, TUIP results in a significantly reduced risk of ejaculatory disturbance. TUIP also was associated with a slightly higher rate of secondary procedures.

***Transurethral Electrovaporization of the Prostate (TUVP)***

**Option: TUVP is an appropriate and effective treatment alternative in men with moderate to severe LUTS and/or who are significantly bothered by these symptoms. The choice of approach should be based on the patient's individual presentation including anatomy, the surgeon's experience and discussion of the potential benefit and risks for complications.**
**[Based on review of the data and Panel consensus.]**

Transurethral electrovaporization is an adaptation of an old device, the roller ball electrode. Compared to TURP, transurethral electrovaporization results in equivalent, short-term improvements in symptom scores, urinary flow rate, and QoL indices. There is a decreased risk of the perioperative complication of transurethral resection syndrome compared with traditional monopolar TURP. However, the rates of postoperative irritative voiding symptoms, dysuria and urinary retention, as well as the need for unplanned secondary catheterization, appear to be higher. Reoperation rates were higher with TUVP than with TURP. Long-term comparative trials are needed to determine if the transurethral electrovaporization approach is superior to standard TURP.

***Transurethral Resection of the Prostate (TURP)***

**Option: TURP is an appropriate and effective primary alternative for surgical therapy in men with moderate to severe LUTS and/or who are significantly bothered by these symptoms. The choice of a monopolar or bipolar approach should be based on the patient's presentation, anatomy, the surgeon's experience and discussion of the potential risks and likely benefits.**
**[Based on review of the data and Panel consensus.]**

**Option: Overall, there is insufficient evidence to recommend using 5-ARIs in the setting of a pre-TURP to reduce intraoperative bleeding or reduce the need for blood transfusions.**
**[Based on review of the data and Panel consensus.]**

TURP involves the surgical removal of the prostate's inner portion via an endoscopic approach through the urethra, with no external skin incision. Historically, this procedure was the most common active treatment for symptomatic BPH but potential morbidities, desire to shorten catheter dwell time and pressure to reduce hospital length of stay have stimulated the development of alternative procedures. In the interval since the 2003 Guideline was published, reports concerning TURP that met inclusion criteria for this Guideline were limited to studies focused on TURP as a comparison. Consequently, the Veterans Affairs (VA) Cooperative Study remains the most definitive published study of the efficacy and safety of TURP.[100] The VA Cooperative Study found a 1% risk of urinary incontinence (which was similar to the incidence in the watchful waiting group) and an overall decline in sexual function that was identical to the watchful waiting treatment group. Usually performed under general or spinal anesthesia, TURP requires a hospital stay. One unique complication of TURP is TUR syndrome, a dilutional hyponatremia that occurs when irrigant solution is absorbed into the bloodstream. Other complications that have been reported in more than 5% of patients include (in order of frequency): erectile dysfunction (which may not in all cases be attributable to the surgery); irritative voiding symptoms; bladder neck contracture; the need for blood transfusion; UTI; and hematuria.

Bipolar resection of the prostate utilizes a specialized resectoscope loop that incorporates both the active and the return electrodes. This design limits the dispersal of the current flow in the body which theoretically reduces the deleterious effects of the stray current flow. The bipolar loop can be used to resect tissue as well as coagulate, vaporize and transect tissue. Because the bipolar resectoscope uses 0.9% sodium chloride solution as irrigation fluid, the risk of TUR syndrome is eliminated.

***Laparoscopic and Robotic Prostatectomy***

**Option: Men with moderate to severe LUTS and/or who are significantly bothered by these symptoms can consider a laparoscopic or robotic prostatectomy. There are insufficient published data on which to base a treatment recommendation.**
**[Based on review of the data and Panel consensus.]**

Laparoscopic and robotic prostatectomies are techniques currently associated with the treatment of prostate cancer but a single cohort study has reported on consecutive patients undergoing laparoscopic simple prostatectomy for the treatment of LUTS.[101] The operation can take three to five hours, which is longer than traditional surgery.

## Future Research

Given the increasing aging male population, the health burden of benign prostate disorders such as BPH, will be a major arena for research in the future. Therefore, there is a substantial need to develop a long-range vision to focus and promote efforts to better understand and manage benign prostate disease.[102] In 2010, the AUA launched an initiative to identify national research priorities in urology. Known as the AUA Foundation National Urology Research Agenda (NURA), this document defines the top issues facing urology, and BPH is identified as an area for scientific opportunity.[103] The authors cite the relationship between BPH and co-morbidities as a high priority as well as a more objective method

for diagnosing BPH. Inflammation of the prostate is an important area of study, and the role of diet, lifestyle, and sociodemographics on BPH is important.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a panel of key opinion leaders that included basic researchers, translational scientists, epidemiologists, and clinicians and clinical researchers to develop a comprehensive strategic plan for advancing research in benign prostate disease.[102] This focused group of research and thought leaders identified four major areas of key significance for future investigation: (1) basic science, (2) epidemiology/population-based studies, (3) translational opportunities, and (4) clinical sciences. The following represents a synopsis of their findings and recommendations of the NIDDK Prostate Research Strategic Plan.[102]

There are a host of major clinical opportunities in the future with respect to clinical science development in BPH. This includes:

1. Defining the clinical phenotype: definitions and their importance
2. Measuring disease severity and outcomes
3. Issues in clinical trial design
    a. Study concepts for drug therapy, phytotherapies, behavioral and lifestyle interventions
4. Additional intervention therapies.

These chosen topics illustrate the pressing need for improved methods to diagnose and measure disease symptoms, severity and progression; development of new drug therapies, derived from both synthetic and naturally occurring compounds; and identification and clinical testing of prevention strategies; and for further development of intervention therapies based on non- or minimally invasive approaches. It is anticipated that progress in these areas has the potential to advance clinical care for patients with benign prostate disease beyond current strategies of symptom management, which in many cases are incompletely effective for the individual patient and are not generally effective across patients classified as having the same disorder.

**High Priority Recommendations for Future Research**:

- Make obesity and lifestyle interventions a priority area for BPH disease. This should include studies of specific hypotheses of how LUTS/BPH is impacted by obesity and related diseases; new and enhanced collaborative efforts between urologists, clinical trialists, exercise physiologists and dietary experts; and assessments of the relationship between the various manifestations of metabolic syndrome and LUTS/BPH.
- Develop preventive strategies aimed at underlying common pathophysiology of benign prostate disease.
- Develop studies that assess disease “phenotypes” and lead to better disease definitions (e.g. size versus morphological characteristics and their relative importance in producing symptoms, obstructive versus irritative symptoms relative to prostate morphology and size, and patient phenotypes relative to urologic symptom profiles).
- Encourage the study of primary prevention for LUTS/BPH.
- Develop a plan for a multidisciplinary working group to develop a specific research agenda for symptom and health status measurement related to male LUTS. This effort should include

investigators interested in the broad spectrum of underlying conditions, as well as the developers of the prominent instruments. Professional societies, national and international, and other government organizations are also suggested as participants.

- Development of collaborative network to standardize treatment assessment. This may take the form of a LUTS Treatment Collaborative Network (LTCN) that would allow the critical aggregation of thought leaders, trial design experts, industrial collaborators, and various federal agencies to identify clinically meaningful assessments of promising medical, minimally invasive, and surgical treatments.

## *Conflict of Interest Disclosures*

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## Disclaimer

AUA Guidelines provide guidance only, and do not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, the guideline statements will change. Today these evidence-based guideline statements do not represent absolute mandates, but do represent provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guideline statements do not pre-empt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and in patient tolerances, needs and preferences. Conformance with AUA Guidelines cannot guarantee a successful outcome.

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