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American Urological Association (AUA)

Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE

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EXECUTIVE SUMMARY

Purpose

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. The prevalence and the severity of lower urinary tract symptoms (LUTS) in the aging male can be progressive and is an important diagnosis in the healthcare of patients and the welfare of society. In the management of bothersome LUTS, it is important that healthcare providers recognize the complex dynamics of the bladder, bladder neck, prostate, and urethra. Further, symptoms may result from interactions of these organs as well as with the central nervous system or other systemic diseases (e.g., metabolic syndrome, congestive heart failure). Despite the more prevalent (and generally first line) use of medical therapy for men suffering from LUTS attributed to BPH (LUTS/BPH), there remain clinical scenarios where surgery is indicated as the initial intervention for LUTS/BPH and should be recommended, providing other medical comorbidities do not preclude this approach. It is the hope that this revised Guideline will provide a useful reference on the effective evidence-based management of male LUTS/BPH. Please see the accompanying algorithm for a summary of the procedures detailed in the Guideline.

Methodology

For the surgical management of BPH, the Minnesota Evidence Review Team searched Ovid MEDLINE, the Cochrane Library, and the Agency for Healthcare Research and Quality (AHRQ) database to identify studies indexed between January 2007 and September 2017. Following initial publication in 2018, this Guideline underwent an amendment in 2019 that included literature published through January 2019. An additional literature search was conducted through September 2019 and serves as the basis for a 2020 amendment. The Guideline underwent an additional amendment in 2021 to capture eligible literature published between September 2019 and September 2020.

For the medical management of BPH, the Minnesota Evidence Review Team searched Ovid MEDLINE, Embase, the Cochrane Library, and the AHRQ databases to identify eligible studies published and indexed between January 2008 and April 2019. An updated search was completed to capture studies published between April 2019 and December 2020. Search terms included Medical Subject Headings (MeSH) and keywords for pharmacological therapies, drug classes, and terms related to LUTS or BPH. Limits were used to restrict the search to English language publications. The review team also reviewed articles for inclusion identified by Guideline Panel Members.

When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or

Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

GUIDELINE STATEMENTS

EVALUATION

Initial Evaluation

1. In the initial evaluation of patients presenting with bothersome LUTS possibly attributed to BPH, clinicians should obtain a medical history, conduct a physical examination, utilize the International Prostate Symptom Score (IPSS), and perform a urinalysis. (Clinical Principle)
2. Patients should be counselled on options for intervention, which can include behavioral/lifestyle modifications, medical therapy and/or referral for discussion of procedural options. (Expert Opinion)

Follow-up Evaluation

3. Patients should be evaluated by their providers 4-12 weeks after initiating treatment (provided adverse events do not require earlier consultation) to assess response to therapy. Revaluation should include the IPSS. Further evaluation may include a post-void residual (PVR) and uroflowmetry. (Clinical Principle)
4. Patients with bothersome LUTS/BPH who elect initial medical management and do not have symptom improvement and/or experience intolerable side effects should undergo further evaluation and consideration of change in medical management or surgical intervention. (Expert Opinion)

Preoperative Testing

5. Clinicians should consider assessment of prostate size and shape via transrectal or abdominal ultrasound, cystoscopy, or cross-sectional imaging (i.e., magnetic resonance imaging [MRI]/ computed tomography [CT]) if such studies are available, prior to intervention for LUTS/BPH. (Clinical Principle)
6. Clinicians should perform a PVR assessment prior to intervention for LUTS/BPH. (Clinical Principle)
7. Clinicians should consider uroflowmetry prior to intervention for LUTS/BPH. (Clinical Principle)
8. Clinicians should consider pressure flow studies prior to intervention for LUTS/BPH when diagnostic uncertainty exists. (Expert Opinion)
9. Clinicians should inform patients of the possibility of treatment failure and the need for additional or secondary treatments when considering surgical and minimally-invasive treatments for LUTS/BPH. (Clinical Principle)

MEDICAL THERPAY

Alpha Blockers

10. Clinicians should offer one of the following alpha blockers as a treatment option for patients with bothersome, moderate to severe LUTS/BPH: alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin. (Moderate Recommendation; Evidence Level: Grade A)
11. When prescribing an alpha blocker for the treatment of LUTS/BPH, the choice of alpha blocker should be based on patient age and comorbidities, and different adverse event profiles (e.g., ejaculatory dysfunction [EjD], changes in blood pressure). (Moderate Recommendation; Evidence Level: Grade A)

Alpha Blockers and Intraoperative Floppy Iris Syndrome

12. When initiating alpha blocker therapy, patients with planned cataract surgery should be informed of the associated risks and be advised to discuss these risks with their ophthalmologists. (Expert Opinion)

5α-Reductase inhibitor (5-ARI)

13. For the purpose of symptom improvement, 5-ARI monotherapy should be used as a treatment option in patients with LUTS/BPH with prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a prostate specific antigen (PSA) > 1.5ng/dL, or palpable prostate enlargement on digital rectal exam (DRE). (Moderate

Recommendation; Evidence Level: Grade B)

14. 5-ARIs alone or in combination with alpha blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery. (Strong Recommendation; Evidence Level: Grade A)
15. Before starting a 5-ARI, clinicians should inform patients of the risks of sexual side effects, certain uncommon physical side effects, and the low risk of prostate cancer. (Moderate Recommendation; Evidence Level: Grade C)
16. Clinicians may consider 5-ARIs as a treatment option to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH. (Expert Opinion)

Phosphodiesterase-5 Inhibitor (PDE5)

17. For patients with LUTS/BPH irrespective of comorbid erectile dysfunction (ED), 5mg daily tadalafil should be discussed as a treatment option. (Moderate Recommendation; Evidence Level: Grade B)

Combination Therapy

18. 5-ARI in combination with an alpha blocker should be offered as a treatment option only to patients with LUTS associated with demonstrable prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a PSA >1.5ng/dL, or palpable prostate enlargement on DRE. (Strong Recommendation; Evidence Level: Grade A)
19. Anticholinergic agents, alone or in combination with an alpha blocker, may be offered as a treatment option to patients with moderate to severe predominant storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
20. Beta-3-agonists in combination with an alpha blocker may be offered as a treatment option to patients with moderate to severe predominate storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
21. Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C)

Acute Urinary Retention (AUR) Outcomes

22. Physicians should prescribe an oral alpha blocker prior to a voiding trial to treat patients with AUR related to BPH. (Moderate Recommendation; Evidence Level: Grade B).
23. Patients newly treated for AUR with alpha blockers should complete at least three days of medical therapy prior to attempting trial without a catheter (TWOC). (Expert Opinion)
24. Clinicians should inform patients who pass a successful TWOC for AUR from BPH that they remain at increased risk for recurrent urinary retention. (Moderate Recommendation; Evidence Level: Grade C).

SURGICAL THERAPY

25. Surgery is recommended for patients who have renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross hematuria due to BPH, and/or with LUTS/BPH refractory to or unwilling to use other therapies. (Clinical Principle)
26. Clinicians should not perform surgery solely for the presence of an asymptomatic bladder diverticulum; however, evaluation for the presence of bladder outlet obstruction (BOO) should be considered. (Clinical Principle)

Transurethral Resection of the Prostate (TURP)

27. TURP should be offered as a treatment option for patients with LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)
28. Clinicians may use a monopolar or bipolar approach to TURP as a treatment option, depending on their expertise with these techniques. (Expert Opinion)

Simple Prostatectomy

29. Open, laparoscopic, or robotic assisted prostatectomy should be considered as treatment options by clinicians, depending on their expertise with these techniques, only in patients with large to very large prostates. (Moderate Recommendation; Evidence Level: Grade C)

Transurethral Incision of the Prostate (TUIP)

30. TUIP should be offered as an option for patients with prostates ≤30cc for the surgical treatment of LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)

Transurethral Vaporization of the Prostate (TUVP)

31. Bipolar TUVP may be offered as an option to patients for the treatment of LUTS/BPH. (Conditional Recommendation; Evidence Level: Grade B)

Photoselective Vaporization of the Prostate (PVP)

32. PVP should be offered as an option using 120W or 180W platforms for the treatment of LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)

Prostatic Urethral Lift (PUL)

33. PUL should be considered as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc and verified absence of an obstructive middle lobe. (Moderate Recommendation; Evidence Level: Grade C)

34. PUL may be offered as a treatment option to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

Transurethral Microwave Therapy (TUMT)

35. TUMT may be offered as a treatment option to patients with LUTS/BPH. (Conditional Recommendation; Evidence Level: Grade C)

Water Vapor Thermal Therapy (WVTT)

36. WVTT should be considered as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc. (Moderate Recommendation; Evidence Level: Grade C)

37. WVTT may be offered as a treatment option to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

Transurethral Needle Ablation (TUNA)

38. TUNA is not recommended for the treatment of LUTS/BPH. (Expert Opinion)

Laser Enucleation

39. Holmium laser enucleation of the prostate (HoLEP) or thulium laser enucleation of the prostate (ThuLEP) should be considered as an option, depending on the clinician's expertise with these techniques, as prostate size-independent options for the treatment of LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)

Robotic Waterjet Treatment (RWT)

40. Robotic waterjet treatment (RWT) may be offered as a treatment option to patients with LUTS/BPH provided prostate volume 30-80cc. (Conditional Recommendation; Evidence Level: Grade C)

Prostate Artery Embolization (PAE)

41. PAE for the routine treatment of LUTS/BPH is not supported by current data, and benefit over risk remains unclear; therefore, PAE is not recommended outside the context of clinical trials. (Expert Opinion)

Hematuria

42. After exclusion of other causes of hematuria, 5-ARIs may be an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding. (Expert Opinion)

Medically Complicated Patients

43. HoLEP, PVP, and ThuLEP should be considered as treatment options in patients who are at higher risk of bleeding. (Expert Opinion)

INTRODUCTION

PURPOSE

BPH is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. The prevalence and the severity of LUTS in the aging male can be progressive and is an important diagnosis in the healthcare of patients and the welfare of society. In the management of bothersome LUTS, it is important that healthcare providers recognize the complex dynamics of the bladder, bladder neck, prostate, and urethra. Further, symptoms may result from interactions of these organs as well as with the central nervous system or other systemic diseases (e.g., metabolic syndrome, congestive heart failure). Despite the more prevalent (and often first line) use of medical therapy for men suffering from LUTS/BPH, there remain clinical scenarios where surgery is indicated as the initial intervention for LUTS/BPH and should be recommended, providing other medical comorbidities do not preclude this approach.

It is the hope that this revised Guideline will provide a useful reference on the effective evidence-based management of LUTS/BPH. Please see the accompanying algorithm for a summary of the statements detailed in the Guideline.

METHODOLOGY

The American Urological Association (AUA) Guideline: Management of BPH was last revised in 2010.[1] In preparation for an update of the Guideline, the Panel provided the Minnesota Evidence-based Practice Center with key questions, interventions, comparators, and outcomes to be addressed. The review team worked closely with the Panel to refine the scope, key questions, and inclusion/exclusion criteria.

The key questions were divided into three topics for surgical management of LUTS/BPH: 1. Preoperative parameters that are necessary before surgical intervention is instituted; 2. Surgical management of BOO attributed to BPH; and 3. AUR.

The key questions were divided into two topics for medical management of BPH: 1. Pharmacological management for LUTS/BPH; and 2. Pharmacological management of AUR attributed to BPH. Select newer medications and the long-term side effects of 5-ARIs were the focus of this report.

Panel Formation. The Surgical BPH Panel was created in 2016 by the American Urological Association Education and Research, Inc. The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members with specific expertise in this area. In 2019, additional panel members were added to help aid in the combination of the Surgical and Medical BPH Guidelines. Funding of the Guideline was provided by the AUA; panel members received no remuneration for their work.

Peer Review. The AUA conducted a thorough peer review process. In 2018, the draft Guideline focusing on surgical management was distributed to 130 peer reviewers of which 58 returned comments. In 2019, the draft Guideline focusing on surgical management was distributed to 74 peer reviewers of which 13 returned comments. In 2020, the draft Guideline focusing on surgical management was distributed to 54 peer reviewers of which nine returned comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the Guideline was submitted for approval to the PGC and Science and Quality Council (SQC) and, subsequently, to the AUA Board of Directors for final approval.

In 2021, the draft Guideline inclusive of both medical and surgical management options was distributed to 91 peer reviewers of which 43 returned comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the Guideline was submitted for approval to the PGC and SQC and, subsequently, to the AUA Board of Directors for final approval.

Searches and Article Selection. For the surgical management of BPH, the Minnesota Evidence Review Team searched Ovid MEDLINE, the Cochrane Library, and the AHRQ database to identify randomized controlled trials (RCTs) and clinical controlled trials (CCTs) published and indexed between January 2007 and September 2017 for key questions relating to preoperative parameters that are necessary before surgical intervention and surgical management of BOO attributed to BPH. For the key question related to AUR, systematic reviews/meta-analyses and observational studies published and indexed between January 2007 and September 2017 were included in the systematic report. Following initial publication in 2018, this Guideline underwent an amendment in 2019 that included literature published through January 2019. An additional literature search was conducted through September 2019 and serves as the basis for a 2020 amendment. The Guideline underwent an additional amendment in 2021 to capture literature published since the 2020 amendment. For the 2021 amendment, AUA's consultant medical librarian

utilized the search strategy that was developed by the prior methodology team to identify new peer reviewed publications that have been indexed on PubMed, Embase and the Cochrane Controlled Register of Trials (CENTRAL) database from September 1, 2019 to September 2, 2020. A unique search strategy was used for each of the three topics. Systematic reviews and meta-analyses were searched to identify additional eligible studies.

For medical management of BPH, the Minnesota Evidence Review Team searched Ovid MEDLINE, Embase, the Cochrane Library, and the AHRQ databases to identify eligible studies published and indexed between January 2008 and April 2019. An additional search was conducted to obtain studies published from April 2019 to December 2020.

Search terms included Medical Subject Headings (MeSH) and keywords for pharmacological therapies, drug classes, and terms related to LUTS or BPH. Limits were used to restrict the search to English language publications. The review team also reviewed articles for inclusion identified by the Panel. Limits were used to restrict the search to English language publications.

Abstract review was completed independently by two investigators to determine if citations were eligible for full text review. Two investigators independently reviewed full text articles to identify studies that met inclusion criteria. Conflicts between investigators on inclusion status were resolved through discussion or by a third investigator when necessary. Note, additional studies published outside of search date ranges may have been included to inform background sections or provide historical context.

Risk of Bias (ROB) and Data Extraction. A bias is a systematic error in results or inferences that can lead to underestimation or overestimation of the true intervention effect. Differences in ROB can help explain heterogeneity in the results of studies included in a systematic review. ROB domains include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. The review team used the Cochrane Collaboration's tool for assessing ROB and assessed ROB[2] for the following outcomes: change in IPSS, percent responders based on IPSS (e.g., percentage achieving a minimally detectable difference [MDD] such as a 30-50% reduction in score from baseline or achieving an IPSS score of ≤7 points following treatment), change from baseline in quality of life (IPSS -QoL), perioperative adverse events, and other adverse events (e.g., symptom recurrence, need for reoperation). For blinding of outcome assessment and incomplete outcome data the review team assessed ROB for short-, intermediate-, and long-term follow-up. The overall ROB judgement for each outcome across domains was determined using an approach suggested in the Cochrane Handbook version 5.1.[3] ROB was assessed by a single reviewer and quality checked by a subject expert. Discrepancies were resolved by consensus.

Data Synthesis and Analysis. Reviewers assessed clinical and methodological heterogeneity to determine appropriateness of pooling data. Data were analyzed in RevMan[4] using DerSimonian-Laird random effects to calculate risk ratios (RR) with corresponding 95 percent confidence intervals (95%CI) for binary outcomes and weighted mean differences (WMD) with the corresponding 95%CIs for continuous outcomes. Statistical heterogeneity was assessed with the I^2 statistic. If substantial heterogeneity was present (i.e., I^2 ≥70%), reviewers stratified the results to assess treatment effects based on patient or study characteristics and/or explored sensitivity analyses. For IPSS and IPSS-QoL, reviewers determined the statistical significance of the effect of interventions versus control but defined clinical efficacy based on whether the mean or median effect between intervention and control exceeded thresholds for clinical significance (i.e., the MDD). For IPSS this is a difference of >3 points. For QoL reviewers defined this as >1 point.

Overall quality of evidence for the primary outcomes within each comparison was evaluated using GRADEpro[5] based on five assessed domains.[6,7] The quality of evidence levels range from high to very low. The five domains include the following: 1. Study limitations (ROB); 2. Directness (single, direct link between intervention and outcome); 3. Consistency (similarity of effect direction and size among studies); 4. Precision (degree of certainty around an estimate assessed in relationship to MDD); and 5. Reporting bias.

Determination of Evidence Strength. The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the Guideline. The

AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (**Table 1**). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/ burdens is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, and future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence is *likely to change confidence*. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A in support of a Conditional Recommendation, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, the Panel provides guidance in the form of ***Clinical Principles*** or ***Expert Opinions*** with consensus achieved using a modified Delphi technique if differences of opinion emerged. A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature.

BACKGROUND

BPH is a histologic diagnosis that refers to the proliferation of glandular epithelial tissue, smooth muscle, and connective tissue within the prostatic transition zone, hence the term "stromo-glandular hyperplasia."[8,9] While several hypotheses exist, BPH is likely the result of a multifactorial process, the exact etiology of which is unknown. What is clearly necessary for the development of BPH, however, is the presence of functioning testes. Eunuchs and men castrated before puberty have atrophic prostate glands and do not develop BPH. That said, testosterone does not act alone. The mechanism by which testosterone exerts many of its physiological effects on the prostate gland is through dihydrotestosterone (DHT). Androgens, including testosterone, are produced by the Leydig cells of the testes and the adrenal glands. After production, testosterone is circulated via the bloodstream to the prostate gland, and then enters into the cells by simple diffusion. Once intracytoplasmic, testosterone is converted to its active metabolite DHT by the enzyme 5α-reductase, type 2. DHT forms a complex with androgen receptors that is then transported to the nucleus. Within the nucleus, this complex exerts its effects on the transcription of DNA. These effects are

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

necessary for the normal development of the prostate gland as well as the normal growth and hyperplasia of the prostate.

BPH is nearly ubiquitous in the aging male with worldwide autopsy proven histological prevalence increases starting at age 40-45 years to reach 60% at age 60 and 80% at age 80.[10] While BPH, or histological hyperplasia, in and of itself does not require treatment and is not the target of therapeutic intervention, it can lead to an enlargement of the prostate called benign prostatic enlargement (BPE). The onset of the enlargement is highly variable as is the growth rate,[11] and not all men with BPH will develop any evidence of BPE. The prostate gland may eventually cause obstruction at the level of the bladder neck, which in turn is termed benign prostatic obstruction (BPO), assuming a non-cancerous anatomy. It is important to realize that not all men with BPE will develop obstruction or BPO, just as not all men with BPH will have BPE. To complicate matters further, obstruction may also be caused by other conditions referred to as BOO. Thus, BPO is a subset of BOO.

Parallel to these anatomical and functional processes, LUTS increase in frequency and severity with age and are divided into those associated with storage of urine, and/or with voiding or emptying. Male LUTS may be caused by a variety of conditions, which include BPE and BPO. The enlarged gland has been proposed to contribute to the male LUTS complex via at least two routes: 1. Direct BOO/BPO from enlarged tissue (static component); and 2. Increased smooth muscle tone and resistance within the enlarged gland (dynamic component). This complex of storage symptoms is often referred to as overactive bladder (OAB). In men, OAB may be the result of primary detrusor over activity (DO)/underactivity, or secondary to the obstruction induced by BPE and BPO.[12]

It is important to recognize that LUTS are non-specific, occur in men and women with similar frequency and may be caused by many conditions, including BPE and BPO. Histological BPH is common and may lead to BPE. BPE may cause BPO, but not all men with BPH will develop BPE, and not all BPE will cause BPO. Because BPH is nearly ubiquitous and because LUTS in men is commonly associated with and/or caused by BPE/BPO, a compromise terminology is often used referring to "LUTS most likely associated with BPE/BPO and BPH" or "LUTS secondary to BPH." In this Guideline, the Panel refers to "LUTS attributed to BPH" to indicate LUTS among older men for whom an alternative cause is not apparent after a basic evaluation. The Panel acknowledges that with a more extensive evaluation, some of these men will be found to have other conditions causing or contributing to their symptoms. As treatments being considered specifically for BPO become more invasive and risky, the importance of a more definitive diagnosis increases.

Supplements and Nutraceuticals

This Guideline does not offer an in-depth discussion of the utility of supplements, nutraceuticals, and herbal preparations. These agents are both widely available and utilized by men suffering from voiding symptoms that they believe may be attributable to an enlarged prostate and remedied by such compounds. There are many studies that have been published in favor of the most common ingredients such as saw palmetto, Pygeum africanum, stinging nettle, zinc, selenium, and others.[13] Many such studies suffer from multiple shortcomings (e.g., single center and/or single investigator, short duration, poorly chosen or defined placebo or lack of placebo, lack of placebo run-in period, lack of medication wash out period, unconventional endpoints, lack of intention to treat analysis, responder analysis only).

There are two independently-conducted double-blind, placebo controlled, parallel group trials that were done using a specific extract of the berries of the American dwarf palm tree (saw palmetto), which is the most commonly found ingredient of such supplements.[13,14] Both studies found no benefit over placebo in terms of symptoms, bother, QoL, flowrate recordings, serum PSA, or any other measurable parameter. These two trials, the STEP trial published in 2006[13] and the CAMUS trial published in 2011,[14] point to the of the lack of efficacy in the target population for this Guideline; however, it is noted that formal detailed review beyond these two publications was not conducted for this topic.

LUTS

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 AUA Symptom Index (AUA-SI) score of ≥7.[15] 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 AUR as a symptom of BPH progression, increasing from an incidence of 6.8 episodes per 1,000 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.[16] Although LUTS/BPH is not often a life-threatening condition, the impact of LUTS/BPH on QoL can be significant and should not be underestimated.[17] When the effect of BPH-associated LUTS on QoL was studied in a number of community-based populations, the most important motivations for many 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.[18]

IPSS versus AUA-SI

The IPSS is a validated, self-administered seven-question symptom frequency and severity assessment questionnaire that was originally developed by the AUA Measurement Committee under the leadership of Dr. Michael Barry and first called the AUA-Symptom Index (AUA-SI).[19] IPSS and AUA-SI are identical in terms of questions and answers, administration, and interpretation. This tool is widely available and culturally validated and translated into more than 40 languages. The IPSS is used with a single question on QoL Due to Urinary Symptoms, which is scored separately from the seven IPSS questions:

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?

0= Delighted

1= Pleased

2= Mostly satisfied

3= Mixed about equally satisfied and dissatisfied

4= Mostly dissatisfied

5= Unhappy

6= Terrible

Treatment Indications

To provide some reference to the clinical efficacy and side effect profile of the procedures discussed in this Guideline, clinical statements are made in comparison to what is generally accepted as the historical standard, that being TURP (monopolar and/or bipolar).

Traditionally, the primary goal of treatment has been to alleviate bothersome LUTS that result from BPO. More recently, treatment has also focused on the prevention of disease progression and complications such as AUR.[20] Pharmacologic classes of medications used to treat LUTS/BPH include alpha-adrenergic antagonists (alpha blockers), 5-ARIs, PDE5, and anticholinergics, which may be utilized alone or in combination to take advantage of their different mechanisms of action. An additional class of agent that may be considered in combination with alpha blockers is beta-3 agonists.

There also exist clinical scenarios in which conservative management—including lifestyle changes (e.g., fluid restriction, avoidance of substances with diuretic properties)—or pharmacological management are either inadequate or inappropriate. More recently, long-term use of medications for LUTS/BPH have been implicated in cognitive issues and depression.[21] These situations merit consideration of one of the many invasive procedures available for the treatment of LUTS/BPH. Indications for these procedures include a desire by the patient to avoid taking a daily medication, failure of medical therapy to sufficiently ameliorate bothersome LUTS, intolerable pharmaceutical side effects, and/or the following conditions resulting from BPH and for which medical therapy is insufficient: acute and/or chronic renal insufficiency, refractory urinary retention, recurrent UTIs, recurrent bladder stones, and recalcitrant gross hematuria. Acute and chronic adverse events are associated with each class of medical therapy and can include cardiovascular and sexual effects.

Surgical treatment of symptomatic BPH may be classified into three general types: 1. MIST; 2. Simple prostatectomy; and 3. Transurethral surgery. Transurethral surgery involves removal of the obstructing adenomatous tissue via the transurethral route, classically with monopolar electroconductive TURP. A variety of alternatives to the standard monopolar TURP have been developed, including bipolar TURP and various laser-based therapies, to achieve similar clinical efficacy while reducing the risks of perioperative bleeding and short- and long-term complications. In appropriate patients for whom the physical size of the prostate cannot be addressed due to the expertise of the surgeon via a safe or efficacious transurethral approach, simple prostatectomy (i.e., adenoma enucleation) may be considered using an open, laparoscopic or robotic-assisted approach. Finally, in select patients, recent innovations in MIST allow for office-based treatments that obviate the need for regional or general anesthesia, hospital stay, discontinuation of anticoagulation therapy, and surgery.

For this Guideline, the Panel evaluated the commonly used surgical procedures and MISTs to treat LUTS/BPH

when indicated based on evaluation by an appropriately trained clinician. These procedures include monopolar and bipolar TURP, robotic simple prostatectomy (retropubic, suprapubic, and laparoscopic), TUIP, bipolar TUVP, PVP, PUL, thermal ablation using TUMT, WVTT, TUNA, enucleation using HoLEP or ThuLEP, RWT, and PAE. Data utilized to generate these statements are based on the results from what the Panel felt were acceptably performed RCTs and CCTs comparing each technique to TURP or SHAM.

Index Patient

For this Guideline, the Index Patient is a male aged 45 or older who is consulting a qualified clinician 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.

Prostate Size and Choice of Surgical Procedure

The first LUTS Guidelines published by the Agency for Health Care Policy and Research in 1994 recommended against measuring prostate size to guide treatment. Knowledge gained over the past 25 years now allows surgeons to select treatments using a refined approach informed in large part by prostate size and morphology. The Panel recognizes and embraces these important developments and, where possible, provides specific size criteria in statements to inform treatment decisions based on higher-order evidence. Statements without size criteria are those modalities that the Panel concluded are efficacious and safe for a broad range of prostate sizes. In this sense, the Panel also recognizes that the availability of various surgical technologies will vary from one practice setting to another and sought to avoid overly restrictive size criteria.

The Panel also made the following observations with respect to prostate size:

1. Since the specific gravity of the prostate is 1.05 g/mL, the units gram and milliliter (cc) can be used interchangeably to denote size or volume.[22]

2. In the absence of standardized prostate size categories in the literature, the Panel recommends consideration of the following categorical size descriptions when planning treatment: small (< 30 g), average (30-80 g), large (>80 to 150 g), and very large (>150 g). These category suggestions are based on the assumption of surgical expertise with BPH and the Panel opinion; they do not necessarily imply that efficacy in prostates outside the recommended ranges does not exist. The Panel hopes that providers will choose the surgical technique that has the best benefit-to-risk ratio for a specific size range, and, that in cases where that technique is not readily available or where no expertise exist, the patient may be referred to another provider with access and expertise in that technique.

3. Randomized trials for some devices enrolled men with prostates within specific size ranges. As such, statements for those treatments contain the size ranges most commonly referenced in the currently available and reviewed RCT's included in these Guidelines, and/or as used for FDA approval. However, the Panel recognizes that these devices do not necessarily lack efficacy in prostates below or above the size ranges stipulated in the Statements.

Sexual Dysfunction and Surgical Therapy

Data on the sexual side effects of BPH surgery can be difficult to ascertain as many studies are not primarily designed to answer this question. As such, many studies evaluate sexual side effects by looking at reported adverse events only, rather than specifically assessing sexual function. In addition, in some studies, especially those evaluating surgical treatments, patients may not only be undergoing a surgical procedure but are also stopping the previous medical therapy, which can confound interpretation of postoperative sexual function.

Given the strong observed relationship between ED and LUTS/BPH, this group of men is at high risk for sexual dysfunction. Patients should be counselled about the sexual side effects of any surgical intervention and should be made aware that surgical treatment can cause EjD and may worsen ED. Interventions for LUTS/BPH have clear sexual side effects and tthese treatments have a significant rate of EjD. Libido does not appear to be affected significantly by surgical therapy, and some studies have even shown an improvement in erectile function (EF) after surgical treatment ((this improvement is controversial as other studies show a worsening of EF).[20] Most importantly, sexual side effects from surgical treatments are more likely to be permanent than those from medical treatments, which can often be reversed by stopping medical treatment or switching to an alternative treatment.

Shared Decision-Making

It is the hope that this clinical Guideline will provide a useful reference on the effective evidence-based management of male LUTS/BPH utilizing standard surgical techniques, MISTs using newer technologies,

and treatments the Panel feels are investigative. This Guideline also reviews a number of important aspects of the evaluation of LUTS, including available diagnostic tests to identify the underlying pathophysiology and to better assist in identifying appropriate candidates for invasive treatments. Certain treatment modalities recommended in the Guideline may be unavailable to some clinicians, for example due to lack of access to the necessary equipment/technology or a lack of expertise in the use of such modalities. In such instances, clinicians should discuss the key treatment classes with patients and engage in a shared decision-making approach to reach a treatment choice, which may necessitate a referral to another clinician for the chosen treatment. In all instances, patients should be provided with the risk/benefit profile for all treatment options in light of their circumstances to allow them to make informed decisions regarding their treatment plans.

GUIDELINE STATEMENTS

EVALUATION

Initial Evaluation

1. **In the initial evaluation of patients presenting with bothersome LUTS possibly attributed to BPH, clinicians should obtain a medical history, conduct a physical examination, utilize the International Prostate Symptom Score (IPSS), and perform a urinalysis. (Clinical Principle)**

Patients with bothersome LUTS may present to either a primary care provider or urologist. A complete medical history should be taken to assess patient symptoms, prior procedures that could explain presence of symptoms, sexual history, use of medications, and overall fitness and health. The IPSS, a validated self-administered questionnaire, can provide clinicians with information regarding the symptom burden patients are experiencing. Additionally, while a urinalysis cannot diagnose BPH, it can help clinicians to rule out other causes of LUTS not associated with BPH through the detection of bacteria, blood, white cells, glucose, or protein in the urine. When interpreting the results of the urinalysis, clinicians should focus on the presence or absence of glucosuria, proteinuria, hematuria, and infection.

Optional studies that may be used to confirm the diagnosis or evaluate the presence and severity of BPH include PVR, uroflowmetry, and pressure flow studies. A PVR can be useful in determining a baseline ability of the bladder to empty, detecting severe urinary retention that may not be amenable to medical therapy, and/or indicate detrusor dysfunction. There is no universally accepted definition of a clinically significant residual urine volume and following a trend over time is the best way to use this tool.

Uroflowmetry is a simple and risk-free, office-based procedure that can be an important adjunct in the evaluation of LUTS. Flow rates of <10 mL/s have shown a specificity of 70%, a positive predictive value of 70%, and a sensitivity of 47% for BOO. If the patient's condition is not sufficiently suggestive of obstruction (e.g., peak urinary flow [Qmax] >10 mL/sec), pressure flow studies should be considered 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 potentially higher failure rates of the procedure.

Following initial evaluation, clinicians and patients should utilize a shared decision-making approach to determine the need for and type of therapy. This decision will guide the need for further evaluation should the patient desire treatment.

2. **Patients should be counselled on options for intervention, which can include behavioral/ lifestyle modifications, medical therapy and/ or referral for discussion of procedural options. (Expert Opinion)**

Lifestyle and behavioral interventions are reasonable first-line treatments for all patients. Straightforward interventions include limiting intake of the following: fluids prior to bedtime or travel; mild diuretics, such as caffeine and alcohol; and bladder irritants, such as highly seasoned or irritative foods. Other interventions include avoiding constipation, increasing physical activity, weight loss, Kegel exercises at time of urinary urgency, timed voiding regimens, and double-voiding techniques.[25] Pelvic floor muscle training, including biofeedback, may be helpful for patients with urgency and storage symptoms.[26]

For those patients with bothersome LUTS in whom additional therapy is warranted, it is appropriate to discuss medical therapy. The potential benefits and harms of proceeding to a procedural intervention without trialing medications may also be discussed as part of the informed decision-making process. As primary care providers may not feel comfortable discussing procedural interventions, offering referral to a specialist without a trial of medication is reasonable.

Follow-up Evaluation

3. **Patients should be evaluated by their providers 4-12 weeks after initiating treatment (provided adverse events do not require earlier consultation) to assess response to therapy. Revaluation should include the IPSS. Further evaluation may include a post-void residual (PVR) and uroflowmetry. (Clinical Principle)**

Recommendations for follow-up after initiating medical therapy for bothersome LUTS/BPH remain undefined. Time intervals, tests to be conducted, and consequences of changes in parameters such as the IPSS, QoL score, flowrate recordings, or residual urine volume have not been systematically studied in the literature.

For shorter duration of onset drugs such as alpha blockers, beta-3 agonists, PDE5s and anticholinergics the first follow-up visit can be as early as four weeks. For longer acting drugs such as 5-ARIs, the first follow-up visit may be within three to six months if adverse events do not necessitate an earlier visit.

During the follow-up visits, patients should be queried regarding the occurrence of typical adverse events of the medication taken, the IPSS and QoL score should be re-administered, and uroflowmetry and residual urine determination is advised

There are no thresholds in the literature for monitoring changes in PVR to help guide therapy. However, increasing amounts of residual urine with worsening voiding efficiency over time may indicate the need for more frequent follow-up visits and prompt additional investigations such as pressure flow studies, cystoscopy and prostate volume assessment, and/or a change in therapy.

There are no thresholds in the literature for monitoring changes in Q_{max} to help guide therapy. On average, an improvement between 1 and 5 mL/s may be expected, while other patients may experience no changes or even a minor deterioration. Patients may not notice such subtle changes and they are not, in general, correlated to changes in the IPSS or the QoL score.

There are no thresholds in the literature for monitoring changes in the IPSS/QoL to help guide therapy. However, directional changes can be used as a springboard to a meaningful discussion of patients' expectations of symptom improvement, perceived response to treatment, and goals of treatment.

After some time on treatment, several studies asked patients Global Subjective Assessment (GSA) questions to assess subjective responses to therapy. The responses were then correlated to the changes in the IPSS score at the same follow-up visit and analyzed.[27,28]

How satisfied are you with the improvement in your urination symptom following the treatment?

- very satisfied/happy/pleased
- somewhat satisfied/pleased/happy
- neither satisfied/pleased/happy nor unsatisfied/ displeased/unhappy
- somewhat unsatisfied/displeased/unhappy
- very unsatisfied/displeased/unhappy

While substantial differences may exist among individual patients in terms of treatment expectations, perceptions of the overall IPSS, and treatment satisfaction, generalizable observations are as follows:

- There is a direct correlation between the direction of the IPSS and the GSA response (e.g., an improvement in one is typically matched with an improvement in the other).
- Large magnitude changes in the IPSS correspond to smaller magnitude changes in QoL (e.g., on average, a larger IPSS point improvement is required to achieve a relatively small improvement in QoL).
- The baseline IPSS score predicates the change in IPSS needed to achieve threshold improvements in IPSS and GSA: the greater the baseline IPSS score, the more of a drop is required to achieve improvements in GSA. This relationship between baseline IPSS and required drop in IPSS is linear and unique for each threshold of improvement elicited by the GSA question.

Barry et al. showed this relationship for the first time by correlating responses to a GSA at 13 weeks after treatment initiation in the VA Cooperative Study #405 that randomized 1,218 men to 4 different therapies (placebo, terazosin, finasteride, terazosin and finasteride combination) over 12 months.[27] Table 2 shows that, on average, a -3 point decrease is needed for a 'slight' improvement and a -5.1 and -8.8 point improvement for a 'moderate' or 'marked' improvement. However, depending on whether the patients were moderately or severely symptomatic at baseline, the decrease required to achieve the

threshold improvements differed substantially (**Table 2**).

Roehrborn et al. performed a similar analysis using a 7-point Likert scale centered around a neutral response

Table 2. VA Cooperative Study showing relationship between IPSS and GSA results

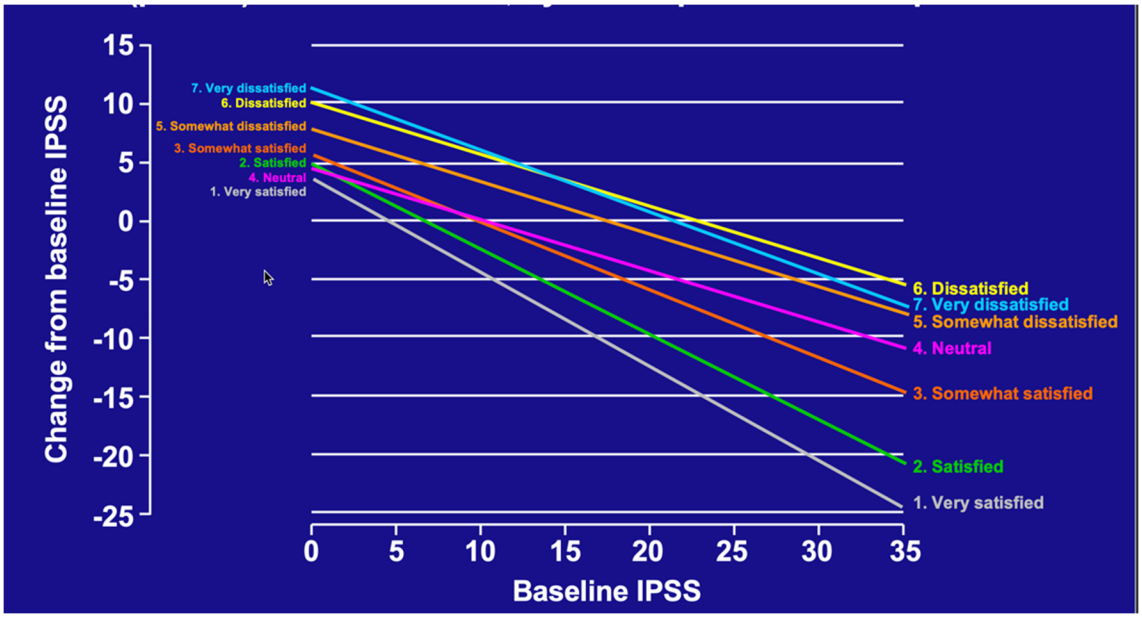
GSA question response regarding satisfaction with treatment	Mean predicted change in IPSS			
	Baseline IPSS =12	Baseline IPSS =16	Baseline IPSS =20	Baseline IPSS =30
1. Very satisfied	-6.13 (0.07)	-9.36 (0.07)	-12.59 (0.08)	-20.67 (0.17)
2. Satisfied	-3.96 (0.05)	-6.87 (0.04)	-9.79 (0.05)	-17.08 (0.10)
3. Somewhat satisfied	-1.41 (0.07)	-3.73 (0.05)	-6.05 (0.06)	-11.86 (0.12)
4. Neutral	-0.55 (0.09)	-2.32 (0.08)	-4.09 (0.09)	-8.51 (0.19)
5. Somewhat dissatisfied	+2.34 (0.21)	+0.56 (0.15)	-1.23 (0.15)	-5.70 (0.31)
6. Dissatisfied	+4.58 (0.34)	+2.80 (0.25)	+1.02 (0.24)	-3.43 (0.47)
7. Very dissatisfied	+4.90 (0.71)	+2.81 (0.52)	+0.72 (0.48)	-4.51 (1.00)

Table showing the relationship between the baseline IPSS, the change in IPSS after treatment (decreased = better, increased = worse or unchanged = zero, and the regression with the GSA question. It is evident that greater improvements in IPSS lead to greater satisfaction in terms of the GSA, and worsening in IPSS to dissatisfaction or less satisfaction. It is also evident that patients with higher baseline IPSS require greater changes to achieve similar levels of satisfaction.

Table 3. Correlation of Patient Perception of Study Medication (PPSM) responses to Question 11, "Overall how satisfied are you with the study medication and its effect on your urinary problems?" and IPSS:

PPSM Q11 response	Mean predicted change in IPSS (SE)			
	Baseline IPSS =12	Baseline IPSS =16	Baseline IPSS =20	Baseline IPSS =30
1. Very satisfied	-6.13 (0.07)	-9.36 (0.07)	-12.59 (0.08)	-20.67 (0.17)
2. Satisfied	-3.96 (0.05)	-6.87 (0.04)	-9.79 (0.05)	-17.08 (0.10)
3. Somewhat satisfied	-1.41 (0.07)	-3.73 (0.05)	-6.05 (0.06)	-11.86 (0.12)
4. Neutral	-0.55 (0.09)	-2.32 (0.08)	-4.09 (0.09)	-8.51 (0.19)
5. Somewhat dissatisfied	+2.34 (0.21)	+0.56 (0.15)	-1.23 (0.15)	-5.70 (0.31)
6. Dissatisfied	+4.58 (0.34)	+2.80 (0.25)	+1.02 (0.24)	-3.43 (0.47)
7. Very dissatisfied	+4.90 (0.71)	+2.81 (0.52)	+0.72 (0.48)	-4.51 (1.00)

Figure 1. Correlation of PPSM responses to Question 11, "Overall how satisfied are you with the study medication and its effect on your urinary problems?" and IPSS:



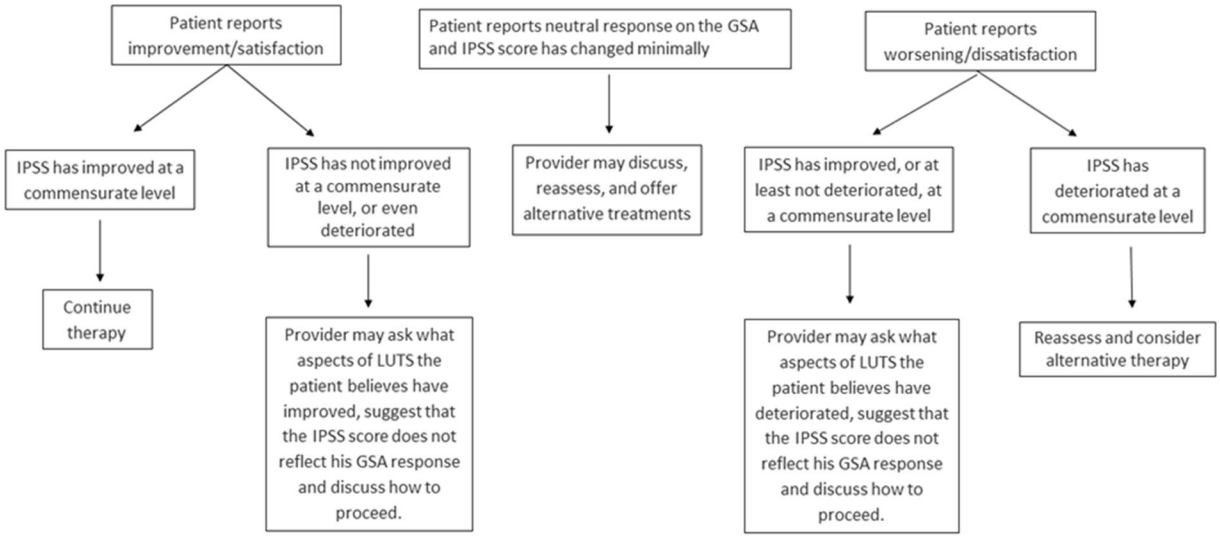
and stratified the patients treated with tamsulosin versus dutasteride versus tamsulosin and dutasteride by baseline symptom score in the CombAT study. The results are substantially similar to those from Barry et al. and are shown in Table 3 and Figure 1.[28]

The administration of the IPSS is recommended at each time point of follow-up as it enables a conversation about expectations and satisfaction and may lead to changes in treatment. Utilizing a GSA could be considered at follow-up evaluation and further direct conversation.

Uroflowmetry and residual urine measurement may offer warnings for deteriorating detrusor muscle or worsening urodynamic outlet obstruction, thus triggering appropriate further investigations.

At follow-up visits, providers may question patients as to their perception of treatment response and offer a similar Likert scale (from very satisfied to very dissatisfied) and contrast that response to the actual change in the IPSS score. This may lead to one of the following scenarios:

A perfect concordance between the IPSS and global



assessment should not be expected. If concordance is present, it is reassuring for the provider and patient to continue with therapy or jointly reassess and change to alternative strategies. If concordance is lacking, this offers the opportunity to revisit the patient's priorities and expectations and modify treatment strategies jointly, if indicated.

Therapy should not be continued if patients are neither satisfied nor show a decrease in IPSS.

4. **Patients with bothersome LUTS/BPH who elect initial medical management and do not have symptom improvement and/or experience intolerable side effects should undergo further evaluation and consideration of change in medical management or surgical intervention. (Expert Opinion)**

An initial trial of medical management over 4 weeks with an alpha blocker or PDE5, and over 6-12 months with a 5-ARI is reasonable in men with bothersome LUTS. Referral to a specialist who can offer additional workup and treatment options is recommended for men who either do not improve with medical management, or have symptomatic improvement but intolerable medication-related side effects.

When initial medical management does not lead to symptomatic improvement, the reason for medication failure and the etiology of LUTS should be considered by performance of studies, such as urodynamics, to confirm BOO versus DO. Understanding the contribution of DO versus BOO can aid in patient counseling and in the selection of additional medication options. In men with LUTS predominantly due to BPH, the reason for failure may be related to medication efficacy; as such, procedural or surgical options may be considered. In men with complicated LUTS (potentially not just related to BPH) with a combination of storage and voiding symptoms, failure may be due to the chosen medication effectively treating only a portion of their LUTS; as such, additional medication classes should be considered along with procedural options.

Preoperative Testing

5. **Clinicians should consider assessment of prostate size and shape via transrectal or abdominal ultrasound, cystoscopy, or cross-sectional imaging (i.e., magnetic resonance imaging [MRI]/ computed tomography [CT]) if such studies are available, prior to intervention for LUTS/BPH. (Clinical Principle)**

Since the publication of previous iterations of this Guideline, the approach to the differential diagnosis and the differentiated treatment of male LUTS/BPH has become substantially more sophisticated with prostate size and morphology playing important roles in the decision-making process. For example, intravesical protrusion (e.g., intravesical lobe, ball-valving middle lobe) has been recognized to predict poor outcomes from watchful waiting and most medical therapies.[29] Some of the available MISTs are indicated for prostates between specific sizes (i.e. 30 -80cc), and some very large prostates should be treated with laser transurethral, open, laparoscopic, or robotically-assisted laparoscopic enucleation. The weight of the prostate gland in grams without the seminal vesicles can be used as an alternative for prostate volume.[30]

Since DRE is unreliable in estimating prostate size and serum PSA is only a rough indicator, it appears reasonable to recommend prostate imaging, particularly prior to surgical interventions, given that prostate size may direct the clinician as to which intervention to consider.[31] Assessment of prostate size and morphology can be achieved by transrectal or abdominal ultrasonography, cystoscopy, or by cross-sectional imaging using CT or MRI. Many patients may have had such imaging as part of the workup for PSA elevation and/or prostate biopsy, or non-urologic conditions that include evaluation of pelvic anatomy; therefore, any such imaging obtained in the recent past preceding the planned surgical intervention may be utilized for size and shape assessment to verify suitability for the therapeutic alternatives under consideration. Imaging obtained within 12 months is preferred; however, given that prostate growth rates are 1.6% per year on average, older imaging can likely give a reasonably accurate estimate of current size if that is all that is available.[32] Imaging should provide cross-sectional and sagittal imaging of sufficient resolution to calculate prostate volume and assess presence or absence of an intravesical lobe.[33] Prostate size measurements by transrectal or transabdominal ultrasound, or by computerized tomography or other cross-sectional imaging should be done using the volume formula for an ellipsoid body: ellipsoid formula ([height× length× width]×∏/6) or ellipsoid formula ([height× length× width]×0.523). For ultrasound measurements it does not matter if the height is measured in the axial or midsagittal image.[34]

6. **Clinicians should perform a PVR assessment prior to intervention for LUTS/BPH. (Clinical Principle)**

While the evidence base is limited, multiple

organizations and their guidelines include PVR measurement as part of the basic evaluation of LUTS. A rising PVR can indicate medication failure and the need for surgical intervention, or further workup may be warranted. While there are no data to indicate the threshold at which an elevated PVR becomes "dangerous," a "large" PVR (>300 mL) is worth monitoring, at the very least. Patients with symptoms from an elevated PVR (i.e., overflow incontinence, bladder stones, UTI, upper tract deterioration), may need to proceed on to surgery or for further urodynamics testing. To fully determine the etiology of an elevated PVR, formal urodynamics testing with a pressure flow study would need to be performed. While a clinically useful test that may drive management choices, PVR does not seem to be a strong predictor of AUR.[35]

7. Clinicians should consider uroflowmetry prior to intervention for LUTS/BPH. (Clinical Principle)

The generally accepted minimum threshold voided volume for adequate interpretation is 150cc, and patients should be instructed not to Valsalva void. In addition to the flow rate, the shape of the curve and duration of voiding provide useful information as a screening tool for LUTS. These results can help to characterize the voiding dysfunction and are useful in counseling patients regarding surgical outcomes and expectations. Should surgical intervention ultimately occur, comparison of pre- and post-operative flow rates can be very useful in providing objective outcome measurements and determining the impact of therapy on improving obstruction.

8. Clinicians should consider pressure flow studies prior to intervention for LUTS/BPH when diagnostic uncertainty exists. (Expert Opinion)

Pressure flow studies are the most complete means to determine the presence of BOO.[36] Non-invasive tools provide useful information, but only pressure flow studies can document detrusor contractility, or lack thereof. Most men with BOO will void with low urinary flow (Q_{max} < 10 cc/s) at peak voiding pressures and a pressure flow study will confirm BOO if high voiding pressures accompany the low urinary flow.[36] Nomograms that combine voiding pressures and maximum urinary flow rate can also be used to better assess probability of the patient having BOO.[36] Patients with BOO may have an elevated PVR; however, the correlation between residual volume and degree of obstruction is weak.[37]

Most patients can be managed and treated surgically without pressure flow studies, as supported by a recent randomized trial comparing routine care to urodynamic testing for LUTS that found a similar rate for progression to surgery (38% versus 36%, total n = 820).[38] However, certain circumstances dictate a more complex evaluation. Pressure flow studies can help differentiate urinary retention related to detrusor underactivity, detrusor sphincter dyssynergia, or obstruction due to prostatic enlargement. Urodynamic studies can also categorize LUTS related to DO or low bladder compliance. Treating patients with these underlying conditions for BOO may not lead to meaningful improvement,[39] subject patients to unnecessary surgery, and carry increased risks for incontinence and exacerbated voiding symptoms after finishing treatment.

In patients with catheter-dependent urinary retention who may have underactive detrusor function, a pressure flow study is advised; however, clinicians should be aware that there are such patients (e.g., those with bladder diverticulum) in whom studies inaccurately indicate a lack of detrusor contractility.

9. Clinicians should inform patients of the possibility of treatment failure and the need for additional or secondary treatments when considering surgical and minimally-invasive treatments for LUTS/BPH. (Clinical Principle)

The Panel identified several core concepts of treatment failure and retreatment. The Panel recommends consideration of these issues when interpreting outcomes of trials comparing different therapeutic modalities or of trials of a single modality with different lengths of follow-up.

First, treatment failure and retreatment are influenced by the completeness of the procedure and success in addressing obstructive prostatic adenoma, while reported rates of retreatment are influenced by both the duration and the completeness of follow-up. For the methodological analyses of this Guideline, the Panel focused primarily on follow-up duration, a more objective and readily captured metric, and defined durations of post-treatment follow-up as short- (<6 months), intermediate- (6 to 12 months), or longer-term (>12 months). These time intervals were chosen by the Panel prior to the literature search based on the available literature at that time.

Second, the risks of objective (e.g., urinary retention, reduction of flowrate, increasing residual urine, infection) and subjective failure (e.g., worsening of

IPSS and/or QoL) increase with longer duration of follow-up.

Third, retreatment may take the form of medical therapy, a minimally invasive intervention, or a surgical procedure.

Fourth, thresholds for and types of retreatments will vary substantially by provider, patient, category of failure (i.e., objective, subjective, or both), and initial treatment modality.

Finally, in contrast to minimally-invasive and newer surgical therapies, (including but not limited to WVTT and PUL), older clinical trials do not consistently report retreatment with medical therapy as an outcome. The difficulty of accurately recording initiation and duration of medical therapy precludes routine assessment. This pattern may lead to underreporting of medical retreatment relative to minimally invasive and surgical retreatments, for which there are clearly definable timepoints at which retreatment takes place.

Indeed, definitions of retreatment or treatment failure have varied considerably across trials, and not all the mentioned categories are standard in BPH studies. The FDA has not issued a standardized definition of retreatment, or requires reporting of retreatment in clinical trials. As a result, individual trial designs employ different definitions. This lack of agreement may potentially lead to misinterpretation of data or bias in assessing retreatment outcomes between different trials and therapies.[40] The field of BPH clinical research would benefit from development of an evidence-based and universally employed classification system for retreatment, which would provide urologists and patients with critical and transparent evidence of retreatment risk before determining the best clinical approach.

Despite the variability and limitations stated above, the Panel attempted to provide some evidence of retreatment rates for the majority of the modalities included in this Guideline. The Panel recognizes that this is an area of development/interest to be included in a future amendment.

TUIP and TURP:

Taylor and Jaffe performed a review of past and contemporary data, including American and European guidelines, and summarized secondary interventions after TURP and TUIP.[41] Their review included a study by Lourenco et al. that reported on data from 795 randomized participants across 10 RCTs of moderate to poor quality. Need for a repeat procedure after TUIP was more common than after TURP at 18.4% versus 7.2%.[42] Taylor and Jaffe reviewed 29 RCTS that revealed after 8 years, nearly 15% of TURP patients required a secondary procedure.

A more recent RCT (n=86, data reported for 80 completers) conducted in Egypt with 4-year follow-up comparing TUIP to TURP in men with small prostates (≤30g) was identified since last publication.[43] Mean age of the participants was 65 years, and the baseline IPSS and prostate size were 19, and 28g, respectively. The long-term need for reoperation was similar between the groups.

Unfortunately, either return to or de novo use of medication is difficult to report and varies considerably by study.

TUVP:

There are limited studies available for review of long term retreatment. Six RCTs (n=601) compared effectiveness of TUVP and bipolar TURP, all with followup ≤1 year. [44-49] Mean age was 66 years (range 60 to 69), baseline IPSS was 21 (range 18 to 24), and mean prostate volume was 56mL (range 32 to 64). TUVP showed similar need for reoperation (RR: 1.5; 95%CI: 0.6, 3.9). Given the short follow up of these studies, and lack of reporting of medication retreatment in either arms, no conclusions can be made regarding long term efficacy and/or retreatment rates.

PVP:

The Greenlight laser has undergone several upgrades since its inception. Men who underwent treatment with the older 80W platform have been shown to have higher rates of retreatment for LUTS/BPH as compared to TURP (RR: 2.0; 95%CI: 1.01, 3.8). In modern surgery most surgeons, if not all, now use higher powered platforms. In the GOLIATH study,[50,51] an international multicenter RCT comparing the higher powered 180W PVP to TURP, 24-month data reported a similar overall need for reoperation (RR: 1.4; 95%CI: 0.6, 3.0) between the two modalities. The Kaplan Meier estimates for reoperation at 24 months were 9.0% for GL-XPS and 7.6% for TURP, which were not statistically different (p = 0.7, log rank test). The breakdown for time period included 19 retreatment surgeries in the first 12 months (10 for GL-XPS patients and 9 for TURP patients); 5 additional cases were identified in the second year - 4 for GL-XPS patients and 1 for TURP. Reasons for reoperation were prostate tissue regrowth/ insufficient removal, bladder neck contracture, and urethral stricture.

While the GOLIATH trial excluded patients with prostate volumes > 80g,[50] a newer RCT randomized men with prostate sizes of 80-150g (average 105g) to PVP versus TURP versus HOLEP. PVP had a retreatment rate of 26.7% at three years of follow up, which was similar to[52-54] that seen with TURP (27.4%). However, both TURP and PVP had statistically higher retreatment rates than men who underwent HoLEP (5%, p=0.03).

Finally, there are several studies utilizing the 80W and 120W lasers with a maximum follow-up of 3 to 5 years. In these studies, redo procedure rates vary from 6.8% to 11% at 3 years, and 8.9% at 5 years of follow-up. Reoperation rates for urethral or bladder neck contractures are reported in 7.4% and 8% in two studies with 3-yr follow-up,[52,53] and in 1.2% of cases in another series with 5-year follow-up.[54] Medical therapy with alpha-blockers was seen in 5/84 patients (5.9%), and with anticholinergics in 1/84 (1.2%) at a mean follow-up of 57 months (+/- 6.8 months and 82% of cohort still reporting).

PUL:

Based on the L.I.F.T. study, reoperation due to symptom recurrence at 5 years was reported for 19 of 140 participants with 6 receiving additional PUL implants and 13 undergoing TURP or laser procedures.[55] Removal of encrusted implants was required in 10 participants, while 3 non-encrusted implants exposed to the bladder were removed prophylactically. Additionally, 15 participants were taking an alpha blocker or 5-ARI at five years.

The prospective, multicenter, randomized, non-blinded BPH6 study provided data comparing 2-year results of PUL compared to TURP.[42] A total of 80 patients with LUTS/BPH were assessed for reoperation due to symptom recurrence and there was no significant difference between groups over the 2-year study period (RR: 2.4; 95%CI: 0.5, 11.1).[56] Six patients (13.6%) in the PUL arm and two in the TURP arm (5.7%) of the BPH6 Study underwent retreatment for LUTS during the 2-year follow up period. These treatments included additional PUL, intradetrusor botox, laser treatment of the prostate or TURP. Medication retreatment in either arm of the BPH6 study was not reported.

TUMT:

The Albala trial (n=190) compared 40-minute TUMT with SHAM. Mean IPSS at baseline was 22 in both groups. Mean changes in IPSS from baseline through 3 months was greater with TUMT compared with SHAM (-10 and -5.8 points, respectively).[57] Need for recatheterization for transitory urinary retention and gross hematuria was reported for 17% and 9% of the TUMT participants compared to none for the SHAM group.

The Brehmer trial (n=44) compared 30- or 60-minute TUMT to a SHAM procedure.[44] Over the 12-month study period, treatment failed and required retreatment in 7 participants in the SHAM group (50%), compared to 5 in the TUMT group (17%). Note the evidence for retreatment of TUMT compared to SHAM is of low quality. The SHAM participants were treated with TURP or TUMT, and the TUMT participants were treated with alpha blocker or TURP.[58] The medication retreatment in either arm of this study was not reported.

Four trials (n=499) compared TUMT to TURP or control.[59-66] Mean baseline IPSS was 21 (range 20 to 21), and mean prostate volume was 56mL (range 50 to 69mL). Follow-up periods ranged from six months to five years. Reoperation was significantly higher with TUMT (9.9%) compared to TURP (2.3%). The medication retreatment in either arm of this study was not reported.

WVTT:

One double-blind trial from McVary et al. compared WVTT (135 subjects) with SHAM/control (61 subjects). At the primary double-blind period of three months, only one participant in the thermal therapy group required a reoperation due to LUTS.[67-70] At 4 years follow up, the reported retreatment rate had increased to 9.6% (6 subjects underwent procedural interventions, while 7 were on medical therapy). This reported rate was calculated based on the original 135 subjects, however, attrition yielded only 90 available for assessment. Therefore, the reintervention rate may be higher.[71]

Laser Enucleation:

Recurrence of symptoms or need for reoperation were reported in 5 studies comparing HoLEP to TURP. One of these studies reported no events.[72] Pooled analysis with the 4 remaining studies resulted in no differences (RR: 0.42; 95%CI: 0.07, 2.48].[73,74] Other adverse events, including urethral stricture and bladder neck contracture, were similar for the HoLEP and TURP groups. Similarly, few patients required reoperation following ThuLEP and TURP. Pooled analysis from 3 studies found that the groups were similar (RR: 1.3; 95%CI: 0.2, 11.3).[75-77]

The Zhang diode laser study reported urethral stricture occurrence in 1 participant (1%) in the diode laser group and 2 participants (3%) in the TURP group.[78]

There were no reported cases of bladder neck contracture.

One trial reported need for retreatment at 3 years due to recurrence of BOO symptoms, where retreatment included the use of medications such as alpha blockers, or surgery.[54] This study reported significantly higher retreatment rates in the TURP group compared to HoLEP group, 27.4% versus 5% (P=0.03). Other adverse events, including urethral stricture and bladder neck contracture, are similar for the HoLEP and TURP groups in the studies in which this was reported.

In pooled data from 11 ThuLEP studies, few patients required reoperation. Pooled analysis from 3 studies found the thulium laser and TURP groups had similar reoperation rates (RR: 1.3; 95%CI: 0.2, 11.3). Stress incontinence, reported in 4 studies, was similar for the thulium and TURP groups (RR: 0.46; 95%CI: 0.14, 1.56). Other post-surgical complications (e.g., urethral stricture, urge incontinence, urinary retention, UTI) were similar between groups.

RWT:

The one-year outcome data from the Gilling study revealed one participant in the TURP group (2%) and 3 in the RWT group (3%) required surgical retreatment for BPH (RR: 1.68; 95%CI: 0.17, 15.83).[79] At 36 months, one participant in the TURP group (1.5%) and 5 in the RWT group (4.3%) required surgical retreatment for BPH (RR: 2.80; 95%CI: 0.33, 23.47). All re-operations were done within the first 20 months after initial surgery.[80] The authors reported the occurrence of medical failure at 36 months follow-up (defined as needing to start alpha blockers or 5-ARI anew) in 9% of participants after RWT, and 14% of participants after TURP.[52]

MEDICAL THERPAY

Alpha Blockers

10. **Clinicians should offer one of the following alpha blockers as a treatment option for patients with bothersome, moderate to severe LUTS/BPH: alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin. (Moderate Recommendation; Evidence Level: Grade A)**

Multiple phase III RCTs, Phase IV studies, systematic reviews, and meta-analyses have demonstrated the efficacy of alpha blockers for the treatment of LUTS and BPH since the first drugs in the class (terazosin and doxazosin) were introduced in the 1980 and 1990s, respectively, for this indication. There is nearly universal agreement that they are all relatively equally effective in terms of IPSS improvement, with an expected range of improvement of 5-8 points, compared to an expected effect of placebo from 2-4 points.[81,82] One of the most recent exhaustive network meta-analyses verifies this observation (Table 4).[81]

Table 4. Effectiveness of Drug Therapies in Improving IPSS.

	Pairwise Meta-analysis	Network Meta-analysis		
	Studies (Patients), MD (95% CI)	MD (95% CI)	Absolute Effects*, (95% CI)	Ranking (95% CI)
Doxazosin	3 (1639), −2.83 (−3.60 to −2.07)	−3.67 (−4.33 to −3.02)	−7.06 (−10.41 to −3.71)	1.75 (1.00 to 3.00)
Terazosin	2 (2489), −3.76 (−4.30 to −3.22)	−3.37 (−4.24 to −2.50)	−6.76 (−10.16 to −3.35)	2.42 (1.00 to 5.00)
Sildenafil	1 (336), −4.40 (−6.93 to −1.87)	−3.15 (−5.29 to −1.01)	−6.55 (−10.43 to −2.61)	3.70 (1.00 to 12.00)
Silodosin	2 (1479), −2.60 (−3.18 to −2.01)	−2.44 (−3.24 to −1.64)	−5.83 (−9.19 to −2.42)	5.03 (3.00 to 9.00)
Tamsulosin	9 (4161), −2.09 (−2.60 to −1.59)	−2.13 (−2.56 to −1.71)	−5.52 (−8.85 to −2.19)	6.50 (4.00 to 9.00)
Vardenafil	1 (214), −2.20 (−3.94 to −0.46)	−2.18 (−4.61 to 0.25)	−5.57 (−9.67 to −1.46)	6.81 (1.00 to 14.00)
Alfuzosin	5 (2627), −1.71 (−2.14 to −1.29)	−2.07 (−2.66 to −1.49)	−5.46 (−8.79 to −2.10)	6.92 (4.00 to 10.00)
Naftopidil	NA	−2.03 (−3.02 to −1.04)	−5.42 (−8.84 to −1.97)	7.27 (3.00 to 12.00)
Tadalafil	9 (6436), −2.09 (−2.40 to −1.78)	−1.87 (−2.44 to −1.29)	−5.26 (−8.61 to −1.91)	8.15 (4.00 to 11.00)
Dutasteride	4 (14,266), −1.93 (−2.17 to −1.68)	−1.82 (−2.51 to −1.12)	−5.21 (−8.58 to −1.80)	8.37 (4.00 to 12.00)
Finasteride	10 (10,672), −1.09 (−1.44 to −0.74)	−1.35 (−1.87 to −0.83)	−4.74 (−8.06 to −1.39)	10.75 (8.00 to 13.00)
Tolterodine	1 (419), −0.60 (−1.56 to 0.36)	−0.86 (−2.20 to 0.48)	−4.25 (−7.79 to −0.65)	11.61 (6.00 to 14.00)
Solifenacin	1 (215), −0.30 (−1.72 to 1.12)	−0.30 (−2.50 to 1.92)	−3.69 (−7.65 to 0.30)	12.27 (5.00 to 14.00)
Placebo	Reference	Reference	−3.39 (−6.68 to −0.10)	13.46 (12.00 to 14.00)

The drug therapies in the table were sorted on effectiveness with an order from large to small. CI = confidence interval, IPSS = International Prostate Symptom Score (Range: 0–35 points; 1–7: mild, 8–19: moderate, and 20–35: severe). MD = mean difference, NA = not available.
* Absolute effects indicate the mean changes from baseline to study end.

Studies have attempted to discern efficacy differences between different alpha blockers and to identify subgroups of patients who may respond better to one alpha blocker or another. These data, by and large, have demonstrated equal efficacy across all alpha blockers, with no particular subset of patients more or less suited for such treatment.[83] Due to the similar efficacy and efficiency, it is not recommended to switch between different alpha blockers if patients fail to have sufficient improvement with the first drug, using an appropriate dosage, as it will unlikely succeed in improving the response. Rather, providers are encouraged during follow-up to reassess and discuss alternative treatment strategies or to further investigate the phenotype of the patient (e.g., rule out overly large prostate or presence of intravesical/middle lobe).[81] However, changing from one alpha blocker to another on the basis of a side effect is worthwhile.

11. When prescribing an alpha blocker for the treatment of LUTS/BPH, the choice of alpha blocker should be based on patient age and comorbidities, and different adverse event profiles (e.g., ejaculatory dysfunction [EjD], changes in blood pressure). (Moderate Recommendation; Evidence Level: Grade A)

Given the similar efficacy of the approved alpha-1-adregergic antagonists, the choice of specific agent should consider the differing adverse events profiles of each.

The quinalozin derivatives, terazosin and doxazosin, are non-specific alpha-1 receptor blockers that are both approved for the treatment of hypertension, as well as BPH. Tamsulosin, alfuzosin, and silodosin have lower potential to cause orthostatic hypotension and syncope than either terazosin or doxazosin.[84-86] Tamsulosin may further have slightly less effect on blood pressure than alfuzosin.[82] These differential effects on blood pressure by different alpha-1-antagonists may be due to their differential blocking of alpha-1 adrenoceptor subtype selectivity.[87] The only two alpha blockers with selectivity for the alpha 1a versus the alpha 1b receptor are tamsulosin (10:1) and silodosin (161:1).

The hypotensive effects of terazosin and doxazosin can be potentiated by concomitant use of a PDE5, such as sildenafil or vardenafil. Tamsulosin at a dose of 0.4 mg/day, however, does not appear to significantly potentiate the hypotensive effects of sildenafil.[88] Regardless, patients utilizing both these medications should be counselled appropriately regarding the risk for drops in blood pressure and symptoms associated with this.

It has long been understood that alpha-adrenergic receptor blockade may induce EjD. This also appears to be a reflection of the selectivity, and those drugs more selective for the alpha 1a versus the alpha 1b receptor are more prone to induce EjD (i.e., tamsulosin, silodosin).

In a recent comprehensive meta-analysis, Gacci et al.[89] reported that EjD events were significantly more common with alpha blockers than with placebo (7.7% versus 1.1%; OR: 5.88; $P < 0.0001$). Stratifying according to the drug used, EjD was significantly more prevalent with tamsulosin (OR: 8.57; $P = 0.006$) or silodosin (OR: 32.5; $P < 0.0001$) than placebo, while doxazosin (OR: 0.80; $P = 0.14$) and terazosin (OR: 1.78; $P = 0.71$) were associated with a low risk of EjD, similar to placebo. Data for about 1,400 patients from 4 RCTs compared silodosin and tamsulosin. Overall, tamsulosin was associated with a significantly lower risk of EjD than silodosin (OR: 0.09; $P < 0.00001$). These findings are in line with the alpha 1a selectivity over the alpha 1b receptor of tamsulosin (10:1) and silodosin (161:1).

For many years, EjD was referred to as retrograde ejaculation (RE), which is commonly found after TURP and surgeries affecting the anatomy of the bladder neck and prostate. However, Hellstrom demonstrated that the EjD associated with selective alpha 1a blockers is correctly called "anejaculation" and found that tamsulosin resulted in significantly decreased ejaculate volume (-2.4 +/- 0.17 mL) compared to alfuzosin (+0.3 +/- 0.18 mL; $p < 0.0001$ versus tamsulosin) or placebo (+0.4 +/- 0.18 mL; $p < 0.0001$ versus tamsulosin; p = nonsignificant versus alfuzosin).[90] Despite the difference in ejaculate volume, no significant differences were observed in post-ejaculate urine sperm concentrations between tamsulosin, alfuzosin, and placebo groups (1.6 ± 0.87, 1.3 ± 0.87 and 0.9 ± 0.88 million/mL, respectively). These data demonstrate that the phenomenon is anejaculation due to paralysis of the smooth muscles in the wall of the prostatic ducts and ejaculatory ducts rather than RE.

Anejaculation is noted by patients and may lead to dissatisfaction and treatment discontinuation. In the phase III silodosin studies, it was noted that the number of men reporting EjD as an adverse event decreased from 46% to 11% for men in their 50s versus 70s, respectively, and the number of men discontinuing treatment due to the adverse events decreased from 4.7% to 0 %.[91,92]

Based on these examples, it is reasonable to select alpha blockers with equal efficacy based on expected

Table 5. Silodosin, Ejaculatory Dysfunction, and Medication Discontinuation by Age.[91,92]

Population	RE	Discontinued due to EjD
Placebo N =457	4 (0.9%)	0 (0%)
Silodosin < 60 years N= 150	69 (46.0%)	7 (4.7%)
Silodosin 60-70 years N = 191	48 (25.1%)	6 (3.1%)
Silodosin > 70 years N = 125	14 (11.2%)	0 (0%)

adverse events. Younger sexually active men are more likely to discontinue due to EjD; therefore, it would be prudent to select alpha blockers with a low incidence of EjD.

When treating patients on several antihypertensives, or with orthostatic hypotension, it is best to select an alpha blocker that exhibits minimal impact on blood pressure (e.g., the highly selective alpha 1a blocker silodosin).

Alpha Blockers and Intraoperative Floppy Iris Syndrome

12. **When initiating alpha blocker therapy, patients with planned cataract surgery should be informed of the associated risks and be advised to discuss these risks with their ophthalmologists. (Expert Opinion)**

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.[93] 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.[93,94] A meta-analysis revealed tamsulosin carried the highest risk for IFIS (40x that of alfusozin), but all alpha blockers increase the risk of IFIS to some degree.[95] One study revealed that for every 255 men receiving tamsulosin in the immediate preoperative cataract surgical period, one serious complication (e.g., retinal detachment, lost lens or lens fragment, endophthalmitis) would result.[96] Discontinuation of tamsulosin 4 to 7 days prior to cataract surgery is routine practice, but it does not completely eliminate IFIS risk.[97] Urologists initiating alpha blocker therapy should inquire about the presence of cataracts or plans for future cataract surgery. Urologists should inform identified patients with planned cataract surgery of IFIS risk and delay initiation of alpha blocker therapy until after the procedure. Increased awareness of IFIS has resulted in a year by year decreased complication rate.[98] In a shared decision-making model, the ideal scenario includes a patient, urologist, and ophthalmologist all well informed about IFIS and cataract surgery risk. Ultimately, ophthalmologists performing the cataract surgery are responsible for taking a detailed medication history and initiating a prevention and mitigation strategy for IFIS-related complications. In addition to alpha blockers, several other non-urologic drugs, including benzodiazepines, donepezil and duloxetine, have been associated with IFIS.[7] Even in verified high-risk IFIS patients, ophthalmologists can decrease complication rates to baseline through a variety of mitigation strategies.[99-101]

5α-Reductase inhibitor (5-ARI)

13. **For the purpose of symptom improvement, 5-ARI monotherapy should be used as a treatment option in patients with LUTS/BPH with prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a prostate specific antigen (PSA) > 1.5ng/dL, or**

palpable prostate enlargement on digital rectal exam (DRE). (Moderate Recommendation; Evidence Level: Grade B)

While there are several medical and surgical ways to reduce the influence of androgenic steroids on the growth of the prostate (e.g., medical or surgical castration), the only hormonal therapies with an acceptable benefit-to-RR are the 5-ARIs. Both testosterone and DHT bind to the androgen receptor, although DHT does so with greater affinity and is thus considered to be the more potent androgenic steroid hormone. This conversion is enabled by the enzyme 5AR, of which there are two isoenzymes, known as type I and type II.

The T/DHT-androgen receptor complex within the nucleus of the cells of the prostate initiates transcription and translation, thus promoting cellular growth. BPH develops due to an imbalance between growth and apoptosis (cellular death) in favor of growth, subsequently causing an increase in cellular mass.[102,103]

5-ARIs act via inhibition of 5AR, leading to less available DHT in the prostate. This, in turn, leads to a reduction in the overall androgenic growth stimulus in the prostate, an increase in apoptosis and atrophy, and ultimately a shrinkage of the organ ranging from 15-25% measured at six months. The atrophy is most pronounced in the glandular epithelial component of the prostate, which is the source of the production and release of serum PSA. It is for this reason that organ shrinkage is associated with a reduction in serum PSA by approximately 50% (and a concomitant decrease in serum free PSA by 50%, which means that the ratio of free/total PSA remains constant).[104,105] Therefore, when providers are monitoring men who are on 5-ARIs, the measured serum value of the PSA should be doubled to accurately gauge disease progression and prostate cancer screening.

As the indication for treatment with 5-ARIs and combination therapy hinges on prostate volume and PSA threshold, the treating physician should discuss the relationship between PSA and prostate size/volume with the patient. Overall, the larger the gland, the greater the reduction in prostate volume with 5ARI therapy.[106,130] While the accepted historic threshold for significant improvement with 5ARI therapy has been 40 cc[106] , several very large studies defined enrollment at >30 cc and achieved significant results, therefore reducing the threshold volume. Obtaining imaging with TRUS (or reviewing existing cross-sectional imaging) to assess prostate size more objectively is reasonable for overall management, and its role when considering procedures is further discussed in the Evaluation section of this Guideline. A palpably enlarged prostate on DRE may also qualify men for 5-ARI treatment, but providers should be aware of the frequent inaccuracy of size determination by DRE.[31] While serum PSA is helpful in assessing treatment options (primarily as a surrogate for prostate size), providers do not need to obtain a PSA solely for determination of 5-ARI response, however, a minimum threshold PSA .1.5ng/dL is advised when initiating 5ARI therapy. PSA screening should be undertaken in age-appropriate men as part of shared medical decision-making for prostate cancer screening. 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.[107-109] Finasteride exclusively inhibits 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 DHT by approximately 70% with finasteride, compared to approximately 95% with dutasteride.[108] However, in the prostate, and specifically in BPH tissue, type II 5-AR is far more common than type I.[102] Therefore, the reduction of DHT in prostate tissues relative to placebo is less pronounced and has been measured at approximately 80% (finasteride)[110] and approximately 94% (dutasteride).[111] 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.[112]

Due to the slow onset of action of this class of medications, other medication classes (principally alpha blockers) may lead to more immediate relief for men with voiding symptoms. Patients should be counseled on a slower improvement in symptoms if men are treated with 5-ARI alone.

Finasteride

Numerous robust analyses of randomized, placebo-controlled trials have shown an improvement in standardized symptom scores (e.g., IPSS) superior to placebo. Numerically, improvements of 3 to 4 points were observed and maintained for 6 to 10 years of follow-up.[113,114] The magnitude of improvement was similar when patients were stratified by prostate volume or serum PSA. However, the natural history of symptomatic disease progression is more accelerated in men with larger glands and higher serum PSA values; correspondingly, the outcomes between finasteride and

placebo groups become more accentuated in men with larger glands over time.[115-118]

Dutasteride

Dutasteride is the second 5-ARI approved by the U.S. Food and Drug Administration (FDA) for the use in men with LUTS and BPH.[119] Initial phase-3 randomized studies demonstrated the efficacy of dutasteride and were reviewed along with the 2 year CombAT trial data.[120-122] Roehrborn and colleagues (2002) randomized 4,325 men with BPH and moderate to severe symptoms to dutasteride 0.5 mg daily or to placebo and followed them for 24 months.[123] These data are pooled from three identical phase-three clinical trials, encompassing 400 sites in the United States and 19 other countries. AUA-SI improved significantly in both treatment groups ($p<0.001$), with significantly greater improvement with dutasteride (-4.5) compared with placebo (-2.3) ($p<0.001$).

During the last decade, additional data from REDUCE have become available, along with two new RCTs. REDUCE's primary endpoint was to look at biopsy proven prostate cancer in men on placebo or 5-ARI. While original study inclusion criteria were PSA 2.5-10ng/dL, prostate volume ≤80g and IPSS <25, the post hoc analysis looked at men with IPSS<8 and prostate volumes 40-80g with particular interest in clinical progression of men with enlarged prostates, but mild LUTS symptoms attributed to BOO. Clinical progression (as defined by increase in IPSS of ≥4, AUR, UTI, or BPH-related surgery) was less common in men on dutasteride compared to placebo (21% versus 36%; $p<0.001$). When assessing for absolute risk reduction for men on dutasteride compared to placebo, there were noticeable differences both with AUR (6% risk reduction) and BPH-related surgery (3.8%).[124]

Only one study has directly compared the outcomes of men randomized to either finasteride or dutasteride. Amongst men randomized to either medication over 12 months, no differences were noted with regards to prostate volume, AUA-SI and Q_{max}.[125] Indirect comparisons of efficacy between finasteride and dutasteride are limited in that only patients with baseline prostate volumes > 30 cc 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 when compared to finasteride trials with less selective populations.

5-ARIs and Prostate Cancer

The Panel agreed that it is important to share the following observations regarding the use of 5-ARIs and prostate cancer prevention, risk reduction, the risk of high-grade disease, and the danger of not paying attention to the expected 50% reduction in PSA under 5 -ARI treatment.

The PCPT trial randomized 18,000 men with a PSA <3 to finasteride versus placebo; biopsy was performed if PSA >4 or abnormal DRE, and an end of study per protocol biopsy was performed in all participants. There was a significant reduction in the period prevalence of prostate cancer resulting in a relative risk reduction of 25%, with 18.4 % of the finasteride group and 24.4 % of controls being diagnosed with cancer. High-grade cancer was more frequent in the finasteride group (6.4% versus 5.1%).[126]

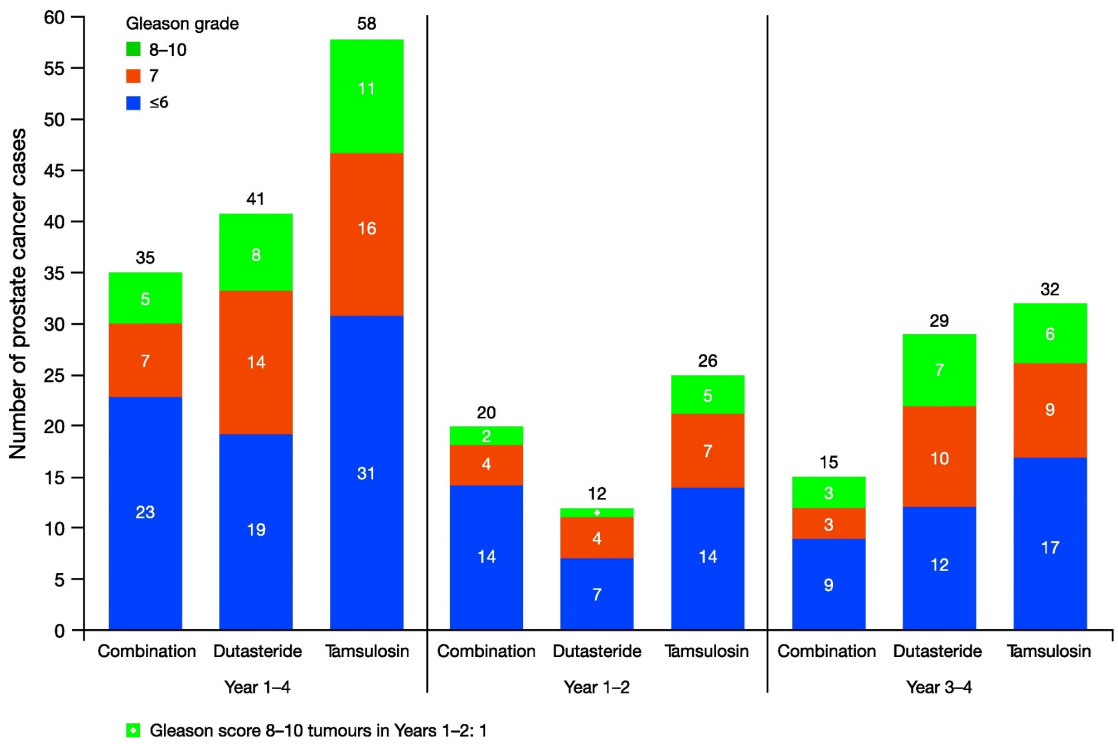
The REDUCE trial enrolled 8,000 men with a PSA 2.5-10, negative biopsy within 6 months of enrollment, and a planned per protocol biopsy at years 2 and 4. Relative risk reduction of the period prevalence of prostate cancer was 23%, with 25.1% in control group versus 19.9% in dutasteride group being diagnosed. High-grade cancer (Gleason score sum 8) was more common in the dutasteride group (0.36% versus 0.03%).[131]

CombAT was a 4-year randomized double-blind parallel group study in 4,844 men ≥50 years of age with clinically diagnosed moderate to severe BPH, IPSS ≥12, prostate volume ≥30 mL, and serum PSA 1.5-10 ng/mL. Participants underwent annual PSA measurement and DRE, and prostate biopsies were performed for cause, only. In this sense, the CombAT trial is the only study that followed BPH patients as would be done in routine practice without per protocol biopsies, instead performing only clinically indicated biopsies based on PSA and/or DRE findings. Dutasteride (alone or in combination with tamsulosin) was associated with a substantially greater relative risk rate for prostate cancer diagnosis of 44% compared with tamsulosin monotherapy (95%CI: 16%, 57%; $p = 0.002$), and a 40% reduction in the likelihood of biopsy. There were similar reductions in low- and high-grade Gleason score cancers. The biopsy rate in the groups receiving dutasteride trended toward a higher diagnostic yield (combination: 29%, dutasteride: 28%, tamsulosin: 24%). (Figure 2) [127]

Number of prostate cancer cases and Gleason score distribution by treatment group and time period. Numbers above bars indicate total number of cancers detected by treatment group; numbers within bars report occurrence by Gleason score.

Lastly, Sarkar et al.[128] published a population-based

Figure 2. Gleason score of prostate cancer diagnosed in the CombAT study.



cohort study linking the Veterans Affairs Informatics and Computing Infrastructure with the National Death Index to obtain patient records for 80,875 men with American Joint Committee on Cancer stage I-IV prostate cancer diagnosed from January 1, 2001, to December 31, 2015. The primary outcome was prostate cancer-specific mortality (PCSM). Secondary outcomes included time from first elevated PSA (defined as PSA≥4 ng/mL) to diagnostic prostate biopsy, cancer grade and stage at time of diagnosis, and all-cause mortality (ACM). PSA levels for 5-ARI users were adjusted by doubling the value, consistent with previous clinical trials. Median adjusted PSA at time of biopsy was significantly higher for 5-ARI users than 5-ARI non-users (13.5 ng/mL versus 6.4 ng/mL; P <.001). Patients treated with 5-ARIs were more likely to have Gleason grade 8 or higher (25.2% versus 17.0%; P <.001), clinical stage T3 or higher (4.7% versus 2.9%; P <.001), node-positive (3.0% versus 1.7%; P <.001), and metastatic (6.7% versus 2.9%; P <.001) disease than 5-ARI non-users. In a multivariable regression, patients who took 5-ARIs had higher prostate cancer-specific (subdistribution hazard ratio [SHR]: 1.39; 95%CI: 1.27, 1.52; P <.001) and all -cause (HR: 1.10; 95%CI: 1.05, 1.15; P <.001) mortality. This study demonstrates that prediagnostic use of 5-ARIs was associated with delayed diagnosis and worse cancer-specific outcomes in men with prostate cancer and highlights a continued need to raise awareness of 5-ARI-induced PSA suppression and appropriate correction (i.e., a multiplication of the PSA value under 5-ARIs x 2).

14. 5-ARIs alone or in combination with alpha blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery. (Strong Recommendation; Evidence Level: Grade A)

The Proscar Long-Term Efficacy and Safety Study (PLESS) trial was a large clinical study to investigate the effects of finasteride on the management of BPH.[129] In this multicenter, double-blind, placebo-controlled study conducted in the United States, more than 3,000 men with moderate to severe LUTS and an enlarged prostate on DRE were randomized to a finasteride group, 5 mg/day, or a placebo group. During the 4-year study period, 10% of the 1,516 men in the placebo group and 5% of the 1,524 men in the finasteride group underwent surgery for BPH (a 55% reduction in risk with the use of finasteride). AUR developed in

approximately 7% of the men in the placebo group and approximately 3% of the men in the finasteride group (a 57% reduction in risk with the use of finasteride). There was a significant ($p<0.001$) decrease in the mean IPSS, with a 3.3 fold reduction in the finasteride group and a 1.3 reduction in the placebo group. Treatment with finasteride improved urinary flow rates and significantly ($p<0.001$) reduced prostate volume.

LUTS/BPH can have a progressive natural history that is more profound in men with larger glands and/or higher PSA values. Men with these risk factors for progression who undergo conservative treatment (watchful waiting or placebo groups) face an increasingly worse prognosis due to a more rapid disease progression with unchecked continued prostate growth. The PLESS study suggests that long-term medical therapy could impact the natural history of BPH as manifested by AUR and surgery. As such, a 5-ARI could be utilized in appropriately enlarged prostates as prevention for BPH since it may alter the natural history thereof. Men with larger prostate glands and lower urinary flow rates appear to benefit most from treatment with finasteride. Amongst men randomized to 5-ARI instead of alpha blocker alone or placebo groups, there is a lower risk of AUR and BPH related surgery.[130]

15. **Before starting a 5-ARI, clinicians should inform patients of the risks of sexual side effects, certain uncommon physical side effects, and the low risk of prostate cancer. (Moderate Recommendation; Evidence Level: Grade C)**

Only three new long-term RTCs have examined the side effects of 5-ARIs since the 2010 Guideline, while a variety of observational and retrospective studies have also examined this topic in that timeframe.[124,131-134]

Sexual Dysfunction

As part of the Medical Therapy of Prostatic Symptoms (MTOPS) Trial, investigators prospectively measured sexual function, including erectile and ejaculatory function, as well as libido, utilizing questionnaire data.[135,185] Declines in overall sexual function were noted in all arms of the study, including men taking placebo. A small but statistically significant deterioration in ejaculatory function that was above the decline demonstrated in the placebo group was noted for men on finasteride and combination therapy. Men assigned to combination therapy also experienced significant worsening in EF and sexual problem assessment. There was no significant difference in changes in any of the ejaculatory domains among men assigned to doxazosin as compared to placebo.

Previous analyses of randomized, placebo-controlled trials utilizing adverse event reporting outcomes (not questionnaire data) have shown that in the first 6 to 12 months of treatment, patients on finasteride experience ED, libido disturbances, and ejaculatory problems at about twice the rate as the placebo control patients. Thereafter, the rates are often similar, suggesting that age-related deterioration in sexual and ejaculatory function is responsible (rather than direct drug effects) or that the age-related changes in the placebo group equilibrate drug effects. In the PLESS study, sexual adverse events were reported more frequently with finasteride (15%) than placebo (7%) during the first year of the study ($p<0.001$); however, no between-group difference was noted in the incidence of new sexual adverse events (7% in both groups) during years 2 through 4.[136] Study discontinuation due to sexual adverse events occurred in 4% of finasteride patients and 2% with placebo. Amongst men who do experience bothersome ED as an effect of 5-ARI therapy, cessation of drug may allow them to return to the baseline rates of ED.[137]

Sexually-related adverse events have been examined in a variety of randomized studies with dutasteride groups.[124,131-134] ED rates from the REDUCE trial were 9% versus 5.7% in the placebo group (ARD: 3.2%; 95%CI: 2.1, 4.4).[131] At 2-years, the CONDUCT trial reported that the incidence of ED was greater with dutasteride combined with tamsulosin compared with tamsulosin monotherapy at 8% versus 0% (ARD: 8%; 95%CI: 5, 10.7).

Decreased semen volume and decreased or absent libido were also higher in men on dutasteride compared to placebo.[124] Ejaculation failure was found to be higher in men on combination dutasteride and 0.2mg tamsulosin compared to 0.2mg tamsulosin, alone (2.6% versus 0.3%; ARD: 2.3%; 95%CI: 0.4, 4.2).[133]

Gynecomastia

The multinational 4-year REDUCE trial[131] found an increased incidence of gynecomastia (1.9% versus 1.0%; ARD: 0.8; 95%CI: 0.3, 1.3) with a larger between group difference in the post hoc analysis of a subset of 1,617 men (2.4% versus 0.7%; ARD: 1.7; 95%CI: 0.5, 2.9).[124] During the 2-year observational extension phase conducted in 2,751 participants, no new cases of gynecomastia were reported.[132] Conversely, a 2-year study conducted in Asia did not demonstrate any increased risk of gynecomastia in men on dutasteride.[133] One observational study reported a

greater incidence of gynecomastia in men who used finasteride or dutasteride, alone or with an alpha blocker, when compared to non-exposure to LUTS/BPH medications.[138] A meta-analysis looking at 14 studies found increased risks of gynecomastia and breast tenderness for men on 5-ARI when compared to placebo.[139]

Dementia

In observational studies, two studies reported on potential risk associated with 5-ARI use.[140,141] One study compared the use of finasteride or dutasteride to men not using either drug.[141] Dementia was greater in the finasteride and dutasteride groups as compared to the placebo group in analyses less than 27 months; however, rates were similar after 27 months.[141] In the second study, use of 5-ARI was compared to tamsulosin over 20 months with higher rates of dementia seen in the tamsulosin group with a dose-dependent risk noted.[124]

Depression

Two observational studies reported on risks of depression. Rates of depression in men on 5-ARI compared to a non-exposure group demonstrated slightly higher rates that were sustained after 3 years.[142] Hagberg et al. utilized both a cohort and case control analysis comparing use of finasteride or dutasteride, alone or with an alpha blocker, to alpha blocker.[143] These results contradicted the previous study as they largely demonstrated similar rates of treated depression independent of drug regimen. Other psychological effects, such as increased suicidality and psychological adverse events, have also been examined.[144]

Development of Diabetes

Two observation studies have examined the risk of diabetes to men on 5-ARI; however, these trials have yielded contradictory results.[145,146]

Post-Finasteride Syndrome (PFS)

PFS is a controversial and poorly-defined constellation of chronic 5-ARI-induced sexual, physical, and psychological symptoms that putatively persist after discontinuation of the 5-ARI.[147-150] Concerns regarding PFS prompted the FDA to amend the labels for 5-ARI with a warning of its risks. However, the robustness of the data justifying this change, which is based on anecdotal patient-reported outcomes rather than prospective trials, remains unclear. Dutasteride, which has activity at more 5-ARI receptors than finasteride, has largely not been implicated. In addition, dose response association with finasteride does not seem present as the 1mg dose has been more closely linked to PFS than the more potent 5mg dose.[151,152] The significant increases in reporting after the first published reports of PFS in 2012 (with no signal before 2012) points towards stimulated reporting.[21]

In general, current data on PFS draw primarily from case reports rather than prospective trials. It is the assessment of the Panel that much of these data are susceptible to bias. For example, many of the studies of male sexual dysfunction on which PFS is based lack baseline (i.e., pre-treatment) assessments of sexual function, a sufficient control population, considerations for perception of medication effects,[153] corrections for investigator bias (i.e., investigator awareness of PFS prior to assessment of symptoms), and use of validated sexual health questionnaires. Moreover, retrospective assessments of sexual function may be prone to recall bias.[154,155]

Overall, the existence of persistent sexual dysfunction following cessation of 5-ARI is currently not demonstrated by reliable scientific research. First, there are no properly designed studies (e.g., using appropriate controls and addressing the issues described above with respect to the study of sexual function) that report a significant association between discontinuation of finasteride and persistence of sexual dysfunction. Second, if the Bradford-Hill criteria,[156] which are used to assess causality, are applied, they do not support an inference of causality. There is neither a strong nor consistent association based upon well-designed, controlled epidemiological studies reported in the literature. The specificity of the outcome (the persistence or onset of new sexual dysfunction) is virtually non-existent given that sexual dysfunction occurs at background rates in all men and not just in men who use 5-ARI's.[135,157] As for biological gradient as one criteria of the Bradford-Hill criteria, it is difficult to understand how 1 mg of finasteride may cause persistence when the 5 mg dose of the same drug is much less likely.[151,152] Additionally, the more broadly acting dutasteride (activity at Type I and II receptors) has been less implicated than the more specific finasteride (activity at Type II receptors only). Finally, the proposed mechanisms for persistence have not been scientifically established and appear implausible in many circumstances as DHT levels return to normal within four weeks after cessation of finasteride use. This implies no persistent effect through a mechanism involving suppressed serum DHT levels.

Epidemiological studies are emerging that adhere to

fundamental scientific principles and fail to support the existence of PFS.[158,159] The results of RCT and well-designed, controlled epidemiological studies contain data that do not support the existence of an association between finasteride and persistent sexual dysfunction following drug discontinuation. These controlled studies used more rigorous methods compared to the anecdotal reports of persistence.

16. **Clinicians may consider 5-ARIs as a treatment option to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH. (Expert Opinion)**

Four randomized, placebo-controlled, well-executed studies,[160-163] two non-controlled studies,[164,165] and one randomized study with poorly defined methods of measuring blood loss[166] explored the ability of 5-ARIs prior to surgery to reduce blood loss associated with TURP. One of the randomized and the two non-randomized studies showed a reduction in blood loss or transfusion requirements. Other studies found no significant differences between the treatment group and placebo for blood loss during surgery, excessive or severe bleeding, or clot retention.[167] While surgical side effects may be mitigated by a short timeframe of use before surgery, the prescriber and patient should consider medication side effects prior to deciding to move forward with pre-surgical 5-ARI treatment.

Phosphodiesterase-5 Inhibitor (PDE5)

17. **For patients with LUTS/BPH irrespective of comorbid erectile dysfunction (ED), 5mg daily tadalafil should be discussed as a treatment option. (Moderate Recommendation; Evidence Level: Grade B)**

In 2002 Sairam first suggested that PDE5s could improve urinary symptom scores in men attending the andrology outpatient clinic for ED.[168] In 2006, Mulhall confirmed this pilot evidence in a population of men with comorbid ED and mild to moderate LUTS.[169] These studies were small, non-controlled cohorts. The following year, in an RCT of men with LUTS/BPH (with or without ED), McVary established the emerging role of PDE5s as an effective and well-tolerated treatment for LUTS.[170]

The majority of studies address the impact of PDE5s on LUTS/BPH used tadalafil. As such, the Panel is compelled to stress the well-documented impact of this agent on LUTS/BPH compared to other PDE5s in the overall summary. The mechanism of action of this PDE5 effect is only partially understood. Additionally, given the commonly co-morbid conditions of LUTS/BPH and ED, patients should be made aware that tadalafil improves EF in men with LUTS/BPH with and without co -morbid ED with LUTS/BPH.

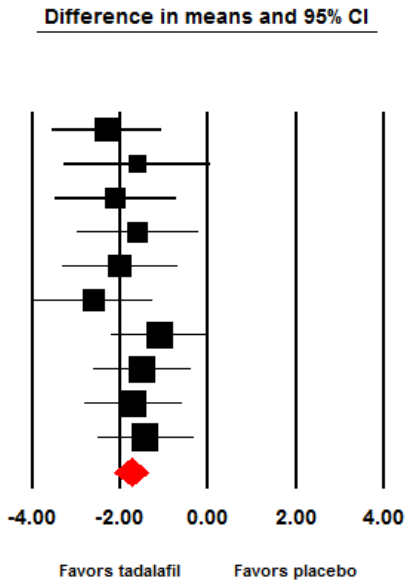
The evidence review identified 10 key reports from 10 trials that compared tadalafil 5 mg to placebo (n=5,129).[170-179] One study started with 5 mg and escalated the dose to 20 mg after 6-weeks.[170] All studies had a relatively short follow-up period of 12 weeks and were industry funded. Seven trials were conducted in multiple countries, one in Japan, one in Korea, and one in the US. Eight trials were rated as low ROB[171-177] and 2 as moderate.[170,179] All trials included men with an IPSS of 13 or more. The mean age was 63 years (61-66), and baseline IPSS was 16 points (16-22), indicating moderate symptom severity. Seven trials reported a mean BPH Impact Index score of 5.3 at baseline.[170-175,178] Four trials reported that 80% of participants had ED at baseline (range 59%-71%).[172,174,175,179] ED was reported in 66% of participants in one trial170 and 100% of participants in another.[179]

In one trial with a moderate ROB and 281 participants who were randomized to tadalafil or placebo after a 4-week placebo run-in period, participants randomized to tadalafil started at a dose of 5 mg daily and were escalated to a dose of 20 mg daily after 6 weeks.[170] At 3 months, participants in the tadalafil group on the 20 mg dose had a greater response to treatment, defined as a change from baseline of ≥3 points in IPSS, compared to placebo, 61% versus 43% ([RR: 1.43; 95%CI: 1.13, 1.80]; [ARD: 18%; 95%CI: 7, 30]; Number Needed to Treat [NNT]=6). On the 5 mg dose at 6 weeks, the proportion of participants on the 5 mg dose of tadalafil was also significantly greater than participants on placebo 49% versus 36%.

Conversely, tadalafil resulted in little to no difference compared to placebo in the IPSS change from baseline compared to placebo across the 10 trials, -5.4 points versus -3.6 points ([MD: -1.7 points; 95%CI: -2.14, -1.35]; high quality of evidence) (Figure 3), and IPSS-QoL ([MD: -0.3 points; 95%CI: -0.35, -0.17]; high quality of evidence) compared to placebo.[170-179] The minimal detectable difference of 3 points was not achieved for either measure. The tadalafil group had a greater mean change in the BPH Impact Index versus placebo, exceeding the minimal detectable difference of 0.4 points (MD: -0.6 points; 95%CI: -0.81, -0.37).[170-175,178] Four trials reported little to no difference between groups in frequency of nocturia (MD: -0.13

Figure 3. Mean Change from Baseline in IPSS in 10 RCTs:

Study name	Statistics for each study			Sample size	
	Difference in means	Lower limit	Upper limit	Tadalafil	Placebo
Egerdie 2013	-2.30	-3.55	-1.05	206	194
Kim 2011	-1.60	-3.27	0.07	51	51
Oelke 2012	-2.10	-3.49	-0.71	171	172
McVary 2007	-1.60	-2.99	-0.21	136	138
Porst 2011	-2.00	-3.30	-0.70	161	164
Roehrborn 2008	-2.60	-3.95	-1.25	212	210
Takeda 2012	-1.10	-2.20	0.00	140	139
Takeda 2014	-1.50	-2.61	-0.39	292	294
Yokoyama 2013	-1.70	-2.82	-0.58	154	154
Zhang 2019	-1.42	-2.51	-0.33	354	361
	-1.74	-2.14	-1.35		



Tadalafil=1,877; Placebo=1,877

I^2=0%

times per night; 95%CI: -0.26, 0.01).[170-174] It should be noted that nocturia is the one component of the IPSS least likely to improve with any medical treatment.

Graph displays the mean change from baseline in IPSS from the 10 RCT consisting of 3,754 participants. As noted, the mean change in the tadalafil arms was -5.4 points while the controls noted a mean change -3.6 points for a mean difference of **1.74** lower. This demonstrates that tadalafil results in little to no difference in mean change in IPSS compared to placebo. However, in data not shown, percentage of treatment responders, defined as ≥3 points in the IPSS scale decrease in 281 participants (1 RCT) showed a relative effect of **RR 1.43** (1.13 to 1.80) suggesting that tadalafil probably greatly increases response to the IPSS compared to placebo.

Overall withdrawals were reported in 8% of participants in the tadalafil group and in 9% in the placebo group ([RR: 0.94; 95%CI: 0.77, 1.16]; [ARD: -0.5%; 95%CI: -2.2, 1.3]). Compared with placebo, tadalafil resulted in little to no difference in withdrawals due to adverse events, 3% versus 2% ([RR: 1.64; 95%CI: 1.02, 2.62]; [1%; 95%CI: 0.3, 2.1]; moderate quality of evidence).[171-179] Tadalafil increased adverse events compared to placebo (26% versus 22%; [RR 1.22; 95%CI: 1.09, 1.37]; [ARD: 5%; 95%CI: 2, 8]; Number Needed to Harm [NNH]=20; high quality of evidence).[171-179] Headache, nasopharyngitis, and back pain were the most commonly reported adverse events and incidences were comparable between treatment groups.

Low-Dose Daily Tadalafil Versus Tamsulosin

The studies reviewed by the Panel noted that the impact of low-dose daily tadalafil on LUTS appears similar to that seen with tamsulosin. Although adverse events and treatment withdrawal profiles between the agents may differ qualitatively, there is little to no difference between these two classes.

In a single trial comparing tadalafil 5 mg daily to tamsulosin 0.4 mg daily, the proportion of participants with a 3-point improvement in IPSS was not reported.[173] At 3 months, this trial found little to no difference between groups in mean change in IPSS (-6.3 versus -5.7 points; [MD: -0.60 points; 95%CI: -1.99, 0.79]; high quality of evidence) and IPSS-QoL ([MD: -0.20 points; 95%CI: -0.48, 0.08]; high quality of evidence).[173] Mean change in BPH Impact Index (BII) or frequency of nocturia did not differ between groups (decrease of 0.5 times per night for both groups; [MD:

0 times per night; 95%CI: -0.28, 0.28]). There was more improvement in the International Index of Erectile Function (IIEF) with tadalafil compared to tamsulosin, 6 points versus 2 points ([MD: 4.3 points; 95%CI: 2.09, 6.51]; moderate quality of evidence).[173]

Tadalafil impact on Urodynamic Measures

While the impact of tadafil on LUTS/BPH symptoms has been described, the use of this drug does not appear to improve urodynamic profiles.[180] During a multicenter, randomized, double-blind, placebo controlled clinical trial comparing once daily tadalafil 20 mg versus placebo over 12 weeks in men with LUTS/BPH, investigators assessed change in detrusor pressure at maximum urinary flow rate. Urodynamic measures remained unchanged during the study with no statistically significant difference between tadalafil and placebo in change in any urodynamic parameter assessed including Qmax, maximum detrusor pressure, BOO index or bladder capacity (all measures p ≥0.13). While no improvement was seen, it is important to note that tadalafil also showed no negative impact on bladder function. The lack of improvement of urodynamic profile is clearly paradoxical and serves as a potential warning to clinicians that tadalafil has no established role in men with impaired bladder function, urinary retention, or those in the midst of a TWOC.

Treatment of LUTS/BPH with Sildenafil

Although tadalafil is the only PDE5 approved by the FDA for treatment of LUTS, there are limited data suggesting sildenafil may also be useful. One high-quality randomized trial conducted in the US with 369 subjects showed that at 12 weeks, sildenafil 50-100 mg improved the IPSS by 6.3 points compared to 1.9 for placebo.[181] IPSS change was also greater in the sildenafil group with severe and moderate LUTS. Furthermore, sildenafil resulted in significant improvement in IIEF-EF compared to placebo, 10 versus 3 points. Common adverse events with use of sildenafil included headache (11% versus 3% placebo) and flushing. The withdrawal rate due to adverse events was slightly higher (5% sildenafil to 3% placebo). Thus, sildenafil could be considered when tadalafil is not available and alpha blockers are not tolerated. Similar to statements in the AUA ED Clinical Guideline, sildenafil improves EF in men with LUTS/BPH with and without co-morbid ED.[182]

Combination Therapy

18. 5-ARI in combination with an alpha blocker should be offered as a treatment option only to patients with LUTS associated with demonstrable prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a PSA >1.5ng/dL, or palpable prostate enlargement on DRE. (Strong Recommendation; Evidence Level: Grade A)

In the 1990s, two studies of 12 months duration were conducted testing the hypothesis that combination medical therapy may be superior to monotherapy.[183,184] The VA CO-OP used placebo versus terazosin 10mg versus finasteride 5mg versus combination, and the European PREDICT trial used doxazosin instead of terazosin. Both studies concluded that combination therapy was not superior to alpha blocker monotherapy. They were criticized on account of the relatively short duration of only one year and the fact that patients were enrolled regardless of prostate size and serum PSA leading to a study population of, at, or below average sized prostates and serum PSA values. A meta-analysis has shown that finasteride was superior to placebo only in men with enlarged prostates and/or higher serum PSA values.[105,117]

The National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) also conducted a combination therapy study in the 1990s in which the primary outcome parameter was a composite progression endpoint:[20,185] MTOPS study enrolled over 3,000 men with at or below average sized prostates (similar to the VA COOP) and randomized them to placebo versus doxazosin 4 mg or 8 mg daily versus finasteride 5 mg daily versus combination of doxazosin and finasteride.

Men were treated and followed for up to 5.5 years. The risk of overall clinical progression, defined as an increase above base line of at least four points in the AUA-SI, AUR, urinary incontinence, renal insufficiency, or recurrent UTI, was significantly reduced by doxazosin (39% risk reduction; p<0.001) and finasteride (34% risk reduction; p=0.002), as compared with placebo. The reduction in risk associated with combination therapy (66% for the comparison with placebo; p<0.001) was significantly greater than that associated with doxazosin (p<0.001) or finasteride (p<0.001) alone. The risks of AUR and the need for invasive therapy were significantly reduced by combination therapy (p<0.001) and finasteride (p<0.001) but not by doxazosin. Doxazosin (p<0.001), finasteride (p=0.001), and combination therapy (p<0.001) each resulted in significant improvement in symptom scores, with combination therapy being superior to both doxazosin (p=0.006) and finasteride (p<0.001) alone. Although not a primary outcome,

symptom and flow rate improvement were superior in the combination therapy arm compared to both monotherapies.

The second major combination therapy study conducted was the CombAT trial in which 4,844 men were randomized to receive tamsulosin 0.4 mg versus dutasteride 0.5 mg versus combination therapy with both over four years (no placebo control group was used).[122] In contrast to prior studies, but in keeping with the study protocol of only enrolling patients with prostatic enlargement in LUTS/BPH trials with dutasteride, men had to have a prostate volume > 30 mL by TRUS and a serum PSA of >1.5 ng/mL. Combination therapy resulted in significantly greater improvements in symptoms versus dutasteride from month 3 and tamsulosin from month 9, and in BPH-related health status from months 3 and 12, respectively. A significantly greater improvement from baseline in Q_{max} for combination therapy versus dutasteride and tamsulosin monotherapies from month 6 was also noted. There was a significant increase in drug related adverse events with combination therapy versus monotherapies.

Four-year data from the CombAT trial was published in 2014.[28] Interestingly, dutasteride and combination therapy demonstrated similar improvements for men with a baseline prostate volume ≥60mL and PSA≥4ng/mL; however, combination therapy was superior if prostate volume and PSA were lower than these thresholds (but still above study inclusion criteria of prostate volume>30mL and PSA>1.5ng/mL). Q_{max} improvement was seen in combination therapy compared to placebo, but not dutasteride monotherapy. Q_{max} improvements were more profound with increasing prostate volume and PSA levels in combination therapy subjects.

In a study focused only on Asian men and using a 0.2 mg tamsulosin dose, men with characteristics often associated with disease progression obtained better symptomatic benefit from combination therapy compared to monotherapy with tamsulosin. In the 24-month study, improvements in Q_{max} and prostate volume reduction were more prominent in the combination therapy group. Reductions in the risk of AUR and BPH related surgery were also seen.

In a study looking at initiation of combination dutasteride and tamsulosin, or no medication, Roehrborn et al.[134] found that initial combination medication intervention improved QoL outcomes compared to later initiation of tamsulosin when men had disease progression.

Providers may start combination therapy with the intention of later discontinuing the alpha blocker (sometimes called "Withdrawal Therapy"). The rationale for this treatment is for men to initially gain the benefit of the alpha blocker and once the efficacy of the 5-ARI is fully developed at a later time, the alpha blocker may be removed. While this is a reasonable strategy, the concept has not been studied rigorously, and there are insufficient data to gauge the utility of this approach or the duration at which combination therapy should be continued before cessation of the alpha blocker.

As stated previously, providers do not need to obtain a PSA solely for determination of 5-ARI efficacy as part combination therapy, although knowledge of a pre-existing value may help guide treatment options.

19. Anticholinergic agents, alone or in combination with an alpha blocker, may be offered as a treatment option to patients with moderate to severe predominant storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)

Anticholinergics have been approved and used for OAB symptoms in men and women as detailed in the AUA/SUFU non-neurogenic OAB Guideline.[186] Although the exact cause may be varied, both storage LUTS and OAB have the same symptoms. While anticholinergics alone have been used for OAB symptoms in men and women, there has been some reluctance on the part of clinicians to use them alone in patients with LUTS/BPH due to the potential risk of worsening bladder residuals or retention. However, studies show the risk of urinary retention to be low in appropriately selected patients.

One large (n=222) low ROB, 12-week trial comparing solifenacin 6 and 9 mg to placebo in men with moderate-severe LUTS (IPSS≥13) showed no significant difference in IPSS (-6.3 placebo, -6.0 solifenacin 6 mg, -6.3 solifenacin 9 mg). Urinary retention occurred only in 1 of 43 subjects on solifenacin 9 mg and none in the other groups.[187] Withdrawals due to adverse events were very low in all groups.

Another large (n=425) US-based, 12-week trial compared tolterodine 4 mg to placebo in men with moderate to severe LUTS (IPSS≥12), resulting in IPSS changes of -6.7 for tolterodine compared to -6.2 for placebo. Post hoc analysis showed that in men with prostates <29 mL, IPSS change was -7.8 for tolterodine compared to -6.1 for placebo (p=0.06). There was no difference in the number of withdrawals due to adverse events or episodes of urinary retention between the

groups.[188-191]

A safety trial was conducted in patients with urodynamically-proven obstruction and over activity, comparing tolterodine 2 mg to placebo. The results showed mild increase in PVR (25 mL versus 0 mL) and mild decrease in bladder contractility index, with urinary retention occurring in only one patient, who was in the placebo group. The findings were felt to be clinically insignificant, and the authors concluded that tolterodine is safe to use in men with BOO.[192]

While anticholinergics have been used safely in men with storage LUTS, a PVR should be obtained and the usual precautions for the use of anticholinergic medications (e.g., gastric emptying/ GI motility issues, narrow angle glaucoma) should be followed. Furthermore, there have been recent publications suggesting an association between use of anticholinergic drugs and increased risk of dementia in patients over 55.[193,194] The side effects, especially in patients over 70, can be significant and the benefits and risks of treatment should be carefully weighed and discussed with the patient and family.

As for combination therapy of alpha blockers and anticholinergics, there have been numerous trials comparing combinations to placebo, or to alpha blocker alone. One low ROB trial (n=271) conducted in the Netherlands compared solifenacin 3 mg and tamsulosin 0.4 mg to placebo and showed clinically significant improvement in IPSS in the combined group compared to placebo at 12 weeks. Urinary retention occurred in 1% of the combined group; constipation and dry mouth were also more common in this group.[187]

Three other trials (n=1,674) compared solifenacin 6 or 9 mg and tamsulosin 0.4 mg to placebo. All were low ROB randomized controlled 12-week trials. Mean IPSS improvement in the combined tamsulosin/solifenacin arms were -7.34 and -6.58 compared to -5.73 for placebo. Overall IPSS improvement was not significant based on a high level of certainty, while adverse events in the combined group were higher (moderate certainty); there was no change in acute retention or withdrawals between the groups.[187,188,195]

One double-blind RCT lasting 12 weeks showed tolterodine 4 mg and tamsulosin 0.4 mg compared to placebo had statistically significant improvement in frequency, urgency, urge incontinence, and nocturia along with patient-reported benefit. IPSS change was -8.02 versus -6.19 for placebo (p=0.003).[196]

A total of 10 trials compared tamsulosin/solifenacin to tamsulosin alone. Doses of solifenacin ranged from 5 to 9 mg and tamsulosin from 0.2 to 0.4 mg. The mean difference in IPSS favored the combined group but only by 0.39-0.43 (-7.00 compared to -6.63). Thus, the difference in IPSS was not significant based on a high level of certainty, and while the adverse events increased slightly, the retention rate was similar (moderate certainty).

Trials comparing tolterodine 4 mg and alpha blocker to alpha blocker alone show significant improvement in the combined group in percentage of responders with > 3-point IPSS decrease. However, mean IPSS change showed little to no difference (-5.9 versus -5.6). Withdrawals due to adverse events in the combined group were slightly higher (low certainty).[197-199]

One large trial compared add on fesoterodine 4 or 8 mg and alpha blocker to placebo and alpha blocker over 12 weeks. This was a moderate ROB international trial in patients with moderate LUTS (baseline IPSS 19) and PVR<200 mL. IPSS change was -4.4 for both add on fesoterodine and placebo (moderate certainty), while adverse events related withdrawals were higher in the fesoterodine group (moderate certainty).[200]

An older 12-week double-blind RCT compared oxybutynin 10 mg and tamsulosin 0.4 mg to tamsulosin and placebo. Baseline IPSS was 20 and response to treatment defined as ≥3 point reduction in IPSS was greater (75%) in the combined drug group compared to placebo (65%). Mean IPSS change was -6.9 versus -5.2, and there was no difference in adverse events or withdrawals due to adverse events (moderate certainty).

Overall, it makes intuitive sense to use anticholinergics combined with alpha blockers in selected patients with storage predominant LUTS/BPH. However, the IPSS improvement in men with combined alpha blocker and anticholinergic compared to alpha blocker alone is variable. Since there are increased adverse events, it may make sense to initially start with alpha blocker alone and add anticholinergics in selected cases.

20. Beta-3-agonists in combination with an alpha blocker may be offered as a treatment option to patients with moderate to severe predominate storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)

Mirabegron Versus Placebo

Unlike the anticholinergic agents described in Statement 19, monotherapy with a beta-3-agonist has, thus far, not been shown to lead to significant differences in LUTS secondary to BPH. Nitti et al.[201]

compared mirabegron 50 mg and 100 mg to placebo (n=200) with a follow-up of 12 weeks. The mean age was 63 years, and the baseline BMI was 29 kg/m^2. The trial included men with a baseline IPSS of more than 8 with a mean of 20 points, indicating severe LUTS. Most participants were white (88%).

At short-term follow-up of 12 weeks, mirabegron 50 and 100 mg resulted in little to no difference in IPSS or adverse events. Mirabegron was safe at both dosages with no increased risk of hypertension as compared to placebo. IPSS scores were reduced in the mirabegron 50 mg, 100 mg, and placebo groups by 6.2, 4.8, and 5 points, respectively. Compared to placebo, mirabegron 50 mg or mirabegron 100 mg resulted in little to no difference in mean change in IPSS (low quality of evidence). Treatment response in IPSS, IPSS-QoL, and nocturia were not reported.

No adverse events related to sexual function were reported. Incidence of urinary retention did not differ between mirabegron 100 mg and placebo (2%). Overall withdrawal from participation was 7% in the mirabegron group and 3% in the placebo group (RR: 2.41; 95%CI: 0.54, 10.67). Study attrition due to adverse events did not differ between the groups, 3% versus 3% (RR: 0.96; 95%CI: 0.18, 5.12; low quality of evidence). Incidence of hypertension was 4% with mirabegron 50 mg, 3% with mirabegron 100 mg, and 3% with placebo.

Combined Mirabegron/Silodosin Versus Active Comparator

Matsukawa et al.[202] compared a combination of mirabegron 50 mg and silodosin 8 mg to a combination of fesoterodine 4 mg and silodosin 8 mg (n=120). This open-label study was conducted in Japanese men with persistent OAB symptoms and had a follow-up of 12 weeks. The trial included men with a baseline IPSS of more than 8. Mean age was 72 years and IPSS was 17 points, indicating moderate LUTS. Comorbidities at baseline included diabetes (24%), hypertension (57%), and hyperlipidemia (47%).[202]

At 12 weeks, combined mirabegron and silodosin resulted in little to no difference in IPSS (MD: 0.30; 95%CI: -1.27, 1.87; moderate quality of evidence) and IPSS-QoL (MD: 0.40; 95%CI: -0.40, 0.81; moderate quality of evidence) compared to combined fesoterodine and silodosin. Treatment response in IPSS and nocturia were not reported.[202] Side effects of dry mouth and constipation favored mirabegron over fesoterodine. Other side effects appear to be similar.

No adverse events related to sexual function or cases of urinary retention were reported in any group. Overall withdrawals were 13% with combined mirabegron and silodosin and 17% with combined fesoterodine and silodosin (RR: 0.80; 95%CI: 0.34, 1.89). Dry mouth and constipation occurred in 3% and 2% of participants in the mirabegron combination group compared to 12% and 5% in the fesoterodine combination group. Dizziness was also reported in 3% of participants in the combined mirabegron group compared to 2% in the combined fesoterodine group.

Combination therapy with a beta-3-agonist appears to be reasonably safe and tolerated and can lead to improvement in symptoms similar to those seen with anticholinergics. Therefore, in older patients where anticholinergic therapy is not recommended, a beta-3-agonist can be utilized. However, further studies are needed to determine whether combination therapy enhances the symptom response, or if the response is driven by the alpha blocker alone.

21. **Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C)**

Combination of Low-Dose Daily Tadalafil with Alpha Blockers

Clinicians are often asked if there is merit to the use of combination of low-dose daily tadalafil with alpha blockers. In the review of the related trials, the Panel was compelled to relate that the combination of low-dose daily tadalafil with alpha blockers offers no advantages in symptom improvement over alpha blockers or low-dose daily tadalafil alone.

In the review of the available data and as part of a systematic review, the Panel identified one trial that compared a combination of tadalafil 5 mg and various alpha blockers to a combination of a placebo and an alpha blocker (n=318).[203] The participants were receiving treatment with an alpha blocker therapy prior to randomization. Tamsulosin was the most commonly used alpha blocker (53%). This low ROB trial had a follow-up of 12 weeks, was conducted in the US, and was industry funded. Mean age was 67 years, and baseline IPSS was 14 points, indicating moderate symptom severity.

Similarly, the search found another trial that enrolled men with LUTS and ED that compared a combination of tadalafil 5 mg and tamsulosin 0.4 mg to tadalafil 5 mg

(n=340).[204] This low ROB trial had a follow-up of 12 weeks and was conducted in Korea. Mean age was 63 years and baseline IPSS was 21 points, indicating severe LUTS. Mean IIEF-EF score was 14.4, indicative of mild-moderate ED.

In the first trial, combined tadalafil and alpha blocker resulted in little to no difference in IPSS compared to alpha blocker alone at 12 weeks (-2.3 versus -1.5 points; MD: -0.79 points; 95%CI: -2.00, 0.42; moderate quality of evidence).[203] In the second trial, a combination of tadalafil 5 mg and tamsulosin 0.4 mg compared to tadalafil alone resulted in little to no difference in IPSS (-9.5 points versus -8.1 points; MD: -1.3 points; 95%CI: -2.54, -0.10; high quality of evidence) and IPSS-QoL (MD: -0.1 points; 95%CI: -0.39, 0.11; high quality of evidence).[14] There was little to no difference in change in IIEF (9.2 points versus 9.5 points; MD: -0.3 points; 95%CI: -1.47, 0.83; moderate quality of evidence).

In the first trial, outcomes related to sexual function were not reported.[203] Overall withdrawals were 11.4% in the combined tadalafil 5 mg and alpha blocker group and 12.5% in the alpha blocker group ([RR: 0.9; 95% CI: 0.50, 1.66]; [ARD: -1.1%; 95%CI: -8.2, 6]). Combined tadalafil and alpha blocker resulted in an increase in reported adverse events compared to alpha blocker alone ([RR: 1.26; 95%CI: 0.95, 1.68]; [ARD: 9%; 95%CI: -2, 19]; low quality of evidence). In the second trial, overall withdrawals were 18.3% with combination therapy and 10.5% with tadalafil monotherapy ([RR: 1.7; 95%CI: 1.01, 2.99]; [ARD: 7.8%; 95%CI: 0.4, 15]). Combined therapy increased adverse events compared to tadalafil alone ([RR: 1.4: 95%CI: 0.89, 2.33]; [ARD: 6% 95%CI: -2, 14]; low quality of evidence).

Combination of Low-Dose Daily Tadalafil with Finasteride

Clinicians are occasionally asked about the use of low-dose daily tadalafil with finasteride. The search identified one trial that compared a combination of tadalafil 5 mg and finasteride 5 mg to a combination of finasteride and placebo (n=696). This low ROB trial had a follow-up of 6 months. The trial was conducted in North America, South America, and Europe. Mean age was 64 years and baseline mean IPSS was 17 points. ED was reported in 65% of participants.

At 6 months, the combination tadalafil and finasteride group had little to no difference in response to treatment, defined as a change from baseline of ≥3 points in IPSS, compared to finasteride, 71% versus 70% ([RR: 1.02; 95%CI: 0.92, 1.12; [ARD:1%; 95% CI: -6, 8; moderate quality of evidence).[24] Response to treatment based on IPSS, defined as ≥25% improvement, was increased in the combined tadalafil and finasteride group ([RR: 1.06; 95%CI: 0.94, 1.20]; [ARD:4%; 95%CI: -4, 11]; moderate quality of evidence). A combination of tadalafil and finasteride resulted in little to no difference in mean change in IPSS, -5.5 versus -4.5 points (MD: 1.0 points; 95%CI: 1.83, 0.17; high quality of evidence) and IPSS-QoL (MD: 0.2 points; 95%CI: 0.48, 0.08; high quality of evidence) compared to finasteride. The minimal detectable difference was not achieved for either measure. There was also no difference between groups in frequency of nocturia based on IPSS (MD: 0 times per night; 95%CI: -0.28, 0.28). Combination tadalafil and finasteride resulted in improvement in IIEF-EF scores compared to finasteride alone in sexually active men (RR: 4.7; 95%CI: 3.04, 6.38).

Compared to finasteride alone, overall withdrawals were less in the combined tadalafil and finasteride group, 11.6% versus 18.3% (RR: 0.63; 95%CI: 0.44, 0.91). There was little to no difference between groups in withdrawals due to adverse events, 1.2% versus 2.9% (RR: 0.41; 95%CI: 0.13, 1.28; low quality of evidence). Combined tadalafil and finasteride resulted in an increase in adverse events compared to finasteride alone (31% versus 27%; RR: 0.41; 95%CI: 0.13, 1.28; low quality of evidence). The Panel consensus was that the impact of the combination of low-dose daily tadalafil with finasteride offers little or no advantages in symptom improvement over finasteride alone in the short term.

Other PDE5 and Alpha Blocker Combinations:

While not as extensively studied as tadalafil, both sildenafil and vardenafil have been combined with alpha blockers and results reported. In one study evaluating both IPSS and IIEF scores, sildenafil 25 mg with tamsulosin 0.4 mg resulted in significant changes in the IPSS. At 6 months, the IPSS mean change was -7.7 in the combined group compared to -4.3 in the tamsulosin only group. The IIEF improved by 9 points in the combined group compared to 2 points in the tamsulosin group, a highly significant difference. Thus, addition of sildenafil 25 mg daily may be considered in patients with LUTS/BPH who have an inadequate response to tamsulosin, especially if they desire concomitant therapy for ED.

Regarding the combination of vardenafil with, one tamsulosin, one small trial (n=60) conducted in Italy[205] compared vardenafil 10 mg plus tamsulosin 0.4 mg to

tamsulosin 0.4 mg alone. At baseline, IPSS was 20 with only a 2 point change at 12 weeks (was -5.8 in the combined group and -3.7 in the tamsulosin only group (MD -2.1). This study suggests that the addition of vardenafil is minimal and may offer no advantages in symptom improvement over tamsulosin alone.

There were more adverse events in the combined group but no change in overall withdrawals.

Acute Urinary Retention (AUR) Outcomes

22. **Physicians should prescribe an oral alpha blocker prior to a voiding trial to treat patients with AUR related to BPH. (Moderate Recommendation; Evidence Level: Grade B).**

23. **Patients newly treated for AUR with alpha blockers should complete at least three days of medical therapy prior to attempting trial without a catheter (TWOC). (Expert Opinion)**

24. **Clinicians should inform patients who pass a successful TWOC for AUR from BPH that they remain at increased risk for recurrent urinary retention. (Moderate Recommendation; Evidence Level: Grade C).**

Fourteen randomized clinical trials have investigated pharmacologic treatment of AUR in men.[206-220] The studies differ by definition of AUR (500- 1,500 mL), inclusion criteria, treatment length, and follow-up (1 day to 24 months). At baseline, mean age across the studies was 68 years (range 59-75 years). Mean IPSS was 16 at baseline (range 10-26) and reported in six trials.[206-220] The above guidelines were determined by assessment of successful TWOC at 1 month after the intervention (unless otherwise specified), urinary retention at 12 months, IPSS at 12 months, and QoL at 12 months.

Men prescribed alfuzosin (5mg twice daily and 10mg daily) or tamsulosin (0.4mg daily) demonstrated improvement in AUR signs and symptoms, as measured by TWOC. In the alfuzosin studies, follow-up ranged from 2 days to 2 years or time to surgery. Pooled results showed successful TWOC may be greatly increased with alfuzosin compared to placebo, 60% versus 39% (OR: 2.28; 95%CI: 1.55, 3.36). The tamsulosin studies had similar follow-up limitations (5 days to 6 months) but similarly showed efficacy. Pooled results for this medication showed that successful TWOC compared to placebo was 47% versus 29% (OR: 2.40; 95%CI: 1.29, 4.45). Doxazosin and silodosin have also been studied but have less data to support a recommendation either as monotherapy or combined with another alpha blocker.

Given the lack of standardized follow-up, it is challenging to determine long-term efficacy of alpha blocker therapy in treating AUR. All trials report a significant number of patients with subsequent urinary retention and LUTS after treatment occurring days to months later, who then require catheterization or surgical outlet procedures.

In addition to alpha blockers, 5-ARIs have been shown to prevent progression of AUR attributed to LUTS/BPH. MTOPS showed the risks of AUR and need for invasive therapy were significantly reduced by combination therapy of doxazosin and finasteride ($p<0.001$) and finasteride monotherapy, ($p<0.001$), but not by doxazosin, alone. As regards dutasteride, when assessing for absolute risk reduction for AUR as compared to placebo, there were noticeable differences both with AUR (6% risk reduction) and BPH-related surgery (3.8%) in the dutasteride group.[221] Further information regarding 5-ARIs and results can be found in statements 13, 15, and 18.

Practitioners should also consider delaying a voiding trial in patients with an active UTI until the infection has resolved.

SURGICAL THERAPY

25. **Surgery is recommended for patients who have renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross hematuria due to BPH, and/or with LUTS/BPH refractory to or unwilling to use other therapies. (Clinical Principle)**

The overwhelming majority of patients with LUTS/BPH who desire treatment will choose some form of medical therapy, either with a single agent or a combination of agents with different mechanisms of action, as the first approach. Since the advent of medical therapy for BPH, this has resulted in a steady reduction in surgical therapies for this condition. In fact, between 1999 and 2005, there was a 5% per year decrease in TURP.[222] When this study was updated, there was a further 19.8% decrease from 2005 to 2008.[223] As a result, patients who now undergo surgery for BPH are generally older[224] and have more medical comorbidities.[225] In addition, "failure of medical therapy" as an indication for surgery rose from essentially 0% in 1988 to 87% in 2008.[226]

Despite the more prevalent use of medical therapy for

men suffering from LUTS associated with BPH, there remain clinical scenarios where surgery is indicated as the initial intervention for LUTS/BPH and should be recommended, providing other medical comorbidities do not preclude this approach. Classically, these conditions include chronic renal insufficiency (defined as GFR < 60 for at least 3 months) secondary to BPH, refractory urinary retention secondary to BPH, recurrent UTIs, recurrent bladder stones or gross hematuria due to BPH, and/or with LUTS/BPH refractory to or desire to avoid other therapies.

Long standing BOO from BPH can progress to incomplete bladder emptying, bilateral hydroureteronephrosis, and, ultimately, acute and/or chronic renal insufficiency. Although transient urethral catheterization with concomitant medical therapy using an alpha-adrenergic antagonist can be considered, it is unlikely that the latter will adequately ameliorate the obstructive process to sufficiently prevent further upper urinary tract deterioration. In men with refractory urinary retention thought secondary to BPH, as opposed to that related to other etiologies (e.g., urethral stricture, neurogenic bladder), surgery should be the mainstay of therapy. Recurrent UTIs not due to other causes (e.g., bacterial prostatitis, renal calculi) and the presence of recurrent bladder calculi are generally thought to result from incomplete bladder emptying and a persistently elevated PVR. Surgical elimination of the obstruction when combined with the presence of adequate detrusor contractility should allow almost complete bladder emptying, thereby decreasing the risk of future infections.

Cystolithalopaxy can be performed concomitantly with the surgical procedure used to remove the obstructing prostate tissue and depending on the size and number of stones present, can influence the choice of surgical approach (e.g., transurethral, open, or laparoscopic). It has been shown that the use of a 5-ARI (i.e., finasteride, dutasteride) can be an effective treatment for gross hematuria secondary to BPH (see statement 42 for further discussion).[227] If, however, gross hematuria persists, surgical removal/ablation of the offending adenomatous tissue should be the next step unless precluded for other reasons. Finally, in patients with medically refractory LUTS associated with BPH or who choose not to pursue other minimally invasive therapies, surgery should be offered.

It is important to note that an elevated PVR should not be used as the only indication for bladder outlet surgery. The AUA Non-Neurogenic Chronic Urinary Retention White paper suggests that patients presenting with non-neurogenic chronic urinary retention should be evaluated for safety issues mentioned above (renal insufficiency, chronic UTI) and then for symptoms which impact urinary QoL (obstructive urinary symptoms, urinary frequency). Safety and QoL issues can be treated with bladder drainage such as intermittent catheterization while the patient is being evaluated for BOO. A patient with an incidentally discovered elevated PVR who does not have any safety issues related to retention or does not report any bothersome urinary symptoms can be followed with longitudinal safety and QoL assessments.[228]

26. Clinicians should not perform surgery solely for the presence of an asymptomatic bladder diverticulum; however, evaluation for the presence of bladder outlet obstruction (BOO) should be considered. (Clinical Principle)

Indications for surgical intervention include recurrent UTI, recurrent bladder stones, progressive bladder dysfunction (i.e., loss of low-pressure bladder storage function due to poor compliance), and renal insufficiency secondary to progressive bladder dysfunction. Prior to surgery for bladder diverticulum, clinicians should perform assessment for BOO and treat as clinically indicated.

Transurethral Resection of the Prostate (TURP)

27. TURP should be offered as a treatment option for patients with LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)

TURP remains the historical standard by which all other subsequent surgical approaches to treatment of BPH are compared and serves as the reference group for all other techniques in this Guideline. TURP helps to reduce urinary symptoms associated with BPH, including frequent/urgent need to urinate, difficulty initiating urination, prolonged urination, nocturia, non-continuous urination, a feeling of incomplete bladder emptying, and UTIs. Successful TURP can relieve symptoms quickly with most men experiencing significantly stronger urine flow within days of the procedure. TURP remains the most frequently taught and utilized procedure for the treatment of symptomatic BPH and the one with which nearly all urologists have experience and ability to perform.

28. Clinicians may use a monopolar or bipolar approach to TURP as a treatment option, depending on their expertise with these techniques. (Expert Opinion)

A large body of literature has been published in recent

years regarding certain modifications of the standard TURP using monopolar energy, most notably the use of bipolar energy transmission.

Contrary to monopolar TURP, bipolar energy does not travel through the body to reach a skin pad as the energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip. While monopolar TURP requires the use of either iso-osmolar solutions of sorbitol, mannitol, or glycine, bipolar TURP is performed in 0.9% NaCl solution. This reduces (if not eliminates) the risk for acute dilutional hyponatremia during prolonged resection, which may lead to the so-called TUR syndrome.

Regarding the comparative efficacy, effectiveness, and safety of monopolar versus bipolar TURP, there are five systematic reviews and meta-analyses published between 2009 and 2015 that compared bipolar TURP to monopolar TURP.[229-233] None of the authors found significant differences in terms of improvement in IPSS and peak urinary flow rates at 12 months, the main efficacy parameters of interest. However, there were differences regarding safety parameters. Time to catheter removal or catheterization time was evaluated in four pooled analyses. All four favored bipolar TURP; however, the differences in the effect estimate were highly variable as was the degree of heterogeneity. Length of stay and dilutional hyponatremia both favored bipolar TURP; however, there was close to 98% heterogeneity in each of the meta-analyses that evaluated these outcomes. Pooled data from Mamoulakis (2009), Burke (2010), Tang (2014), and Omar (2014) all supported that TUR syndrome occurred less frequently in the group that received bipolar TURP.[230-233]

Risk reduction for clot retention generally favored bipolar TURP. Bleeding and drops in hemoglobin seem to favor bipolar TURP but with a relatively high degree of heterogeneity in both meta-analyses. Need for blood transfusion post-operatively seems to favor bipolar TURP, although two out of six meta-analyses revealed no statistical significance.

The findings of the meta-analyses and systematic reviews allow the following conclusions:

- Since there are no differences in efficacy, it is reasonable to compare surgical interventions in this Guideline document with either monopolar or bipolar TURP series regarding efficacy measures.
- Since the main difference between monopolar and bipolar TURP is regarding TUR syndrome, which is unique to TURP and no other treatment, safety parameters other than TUR syndrome can also be compared between surgical interventions and monopolar and bipolar TURP.
- The reduced risk of hyponatremia and TUR syndrome allows for longer resection times; therefore, bipolar TURP may be used in larger glands compared to monopolar TURP.
- Since not all hospitals have bipolar TURP equipment available, it is left to the surgeon's discretion and level of experience as to which type of TURP energy is used.

For the remainder of this document the reader should assume that all efficacy comparisons between surgical interventions and TURP make no difference as to what type of energy was used for the TURP comparator arm (s).

Simple Prostatectomy

29. Open, laparoscopic, or robotic assisted prostatectomy should be considered as treatment options by clinicians, depending on their expertise with these techniques, only in patients with large to very large prostates. (Moderate Recommendation; Evidence Level: Grade C)

Landmark studies done in the 1990s showed that the risk of complications (e.g., bleeding, transfusion, hyponatremia, TURP syndrome, death) following monopolar TURP using sorbitol, mannitol, glycine, or a combination or mixture of such solutions, increase with increasing prostate size and increased duration of resection.[234] These studies lead to recommended resection time limits of 60 or 90 minutes, and alternate therapies were employed for prostates that could not be adequately resected within that time frame.

Bipolar TURP technology using 0.9% NaCl solution has substantially improved the safety of TURP by virtually eliminating hyponatremia and significantly reducing the risk for TURP syndrome, bleeding, and transfusions, as discussed in Guideline Statement 28. As a result, bipolar TURP allows the resection of larger glands over longer periods of time without increasing the risks of the feared TURP complications.[229] The experience and skill of the surgeon determines how large of a prostate can be addressed with this technology, and for many this includes glands up to 100cc, or even larger.

Before the introduction of bipolar TURP, large and/or very large adenomas were enucleated via open simple prostatectomy (OSP) using the transvesical or retropubic (Millin) approaches. Three RCTs (n=433)

compared OSP techniques to TURP.[235,236,252] Three trials used an open standard transvesical approach. Two trials reported significant differences in maximum urine flow at 12 months favoring OSP, while one trial found no difference between the groups. Need for blood transfusions were similar between groups (RR: 1.2; 95%CI: 0.4, 3.4). Need for reoperation as reported in 2 trials was lower in the OSP group compared to TURP (RR: 0.1; 95%CI: 0.01, 0.8). Long-term results for mean change in IPSS were not reported.

During widespread introduction of laparoscopic techniques into urologic surgery, approaches for laparoscopic simple prostatectomy/enucleation (LSP) were developed and favorable outcomes have been reported comparing LSP versus TURP[237] and LSP versus OSP.[238-243]

As with most other pure laparoscopic surgical techniques in urology, the LSP has nowadays been more or less replaced by robotic-assisted laparoscopic simple prostatectomy (RASP). A recent systematic review and meta-analysis of trials comparing minimally invasive simple prostatectomies versus OSP[244] found that RASP had similar efficacy in terms of symptom and flowrate improvement, but shorter catheterization time, length of stay, lower transfusion rates and lower complication rates overall.[245-247] Independent of specific technique, laparoscopic and robotic simple prostatectomy are effective and safe procedures for large to very large glands.[248]

Finally, the introduction of the single port I robot has prompted some to use this technology for simple prostatectomy as well. One study has shown that with this approach, efficacy is maintained, while postoperative narcotic use is reduced.[249]

Transurethral Incision of the Prostate (TUIP)

30. TUIP should be offered as an option for patients with prostates ≤30cc for the surgical treatment of LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)

TUIP has been used to treat small prostates, usually defined as ≤30g, for many decades. In past updates of the AUA and other guidelines, many prospective cohort trials were analyzed, and adequate results were reported in terms of IPSS and Q_{max} changes. A meta-analysis comparing TUIP with TURP after a minimum follow-up of 6 months identified a lower rate of RE (18.2% versus 65.4%) and need for blood transfusion (0.4% versus 8.6%) as the key advantages of TUIP versus TURP.[250]

For the search period of this Guideline, 1 RCT (n=86, data reported for 80 completers) conducted in Egypt with 4-year follow-up comparing TUIP to TURP in men with small prostates (≤30g) was identified.[251] Mean age of the participants was 65 years, baseline IPSS and prostate size were 19 and 28g, respectively. In these men, long-term mean change from baseline in IPSS was similar between the TUIP and TURP groups (WMD: 0.5; 9%CI: -0.2, 1.2), as was the need for reoperation and blood transfusion. In terms of sexual side effects, ED was reported for 8% of TUIP participants compared to 20% for TURP participations, though this difference was not significant (RR: 0.4; 95%CI: 0.1, 1.3). In contrast, there was a significant difference in reports of RE with a total of 30 participants experiencing RE (9 in the TUIP arm and 21 in the TURP arm).

Transurethral Vaporization of the Prostate (TUVP)

31. Bipolar TUVP may be offered as an option to patients for the treatment of LUTS/BPH. (Conditional Recommendation; Evidence Level: Grade B)

TUVP of the prostate is a technical electrosurgical modification of the standard TURP. TUVP can utilize a variety of energy delivery surfaces including a spherical rolling electrode (rollerball), grooved roller electrode (vaportrode), loop electrode, or hemi-spherical/oval mushroom electrode (button), amongst others. TUVP typically uses saline and is powered with a bipolar energy source. Compared to traditional resection loops, the various TUVP designs aspire to improve upon tissue visualization, blood loss, resection speed and patient morbidity.

Fourteen RCTs evaluating 1,828 participants compared bipolar TUVP with TURP.[252,253-271] Mean age among participants was 67 years (range 56 to 70). Mean baseline IPSS was 23 (range 18 to 27) and mean prostate volume was 51 mL (range 36 to 65 mL). Length of follow-up ranged from 3 months to 10.1 years. Overall, outcomes were similar in both groups for long-term response to treatment based on varying definitions using the IPSS; mean change in IPSS through 7 years; need for reoperation; and urinary incontinence. However, need for blood transfusion was lower for TUVP compared with TURP (<1% versus 4%; RR: 0.20; 95%CI: 0.08, 0.52).

Six RCTs (n=601) compared effectiveness of TUVP and bipolar TURP[272-277] Mean age was 66 years (range 60 to 69), baseline IPSS was 21 (range 18 to 24), and mean prostate volume was 56mL (range 32 to 64). Data were insufficient to compare IPSS changes. However, TUVP

showed similar need for reoperation (RR: 1.5; 95%CI: 0.6, 3.9) and incontinence rates (RR: 0.9; 95%CI: 0.4, 2.1) as well as need for blood transfusion (RR: 0.6; 95%CI: 0.3, 1.4).

There are several centers worldwide performing Transurethral Vapor Enucleation of the Prostate (TUEVP). Like any enucleation surgery, the skill set required to safely and adequately apply this approach is very different than either vaporization or vaporesection techniques. There is a paucity of literature that meets the criteria and comparison group for this Guideline; as such, to include this approach into recommendations for TUVP would be premature at this time.

Photoselective Vaporization of the Prostate (PVP)

32. PVP should be offered as an option using 120W or 180W platforms for the treatment of LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)

PVP is a transurethral form of treatment that utilizes a 600-micron side firing laser fiber in a noncontact mode. The laser wavelength is 532nm, which is preferentially absorbed by hemoglobin, resulting primarily in tissue ablation/vaporization with a thin layer of underlying coagulation that provides hemostasis. The procedure is generally performed with saline irrigation, eliminating the possibility of TUR syndrome that can occur with non-ionic irrigation. The goal of the procedure is to vaporize the prostate adenoma sequentially outwards until the surgical capsule is exposed and a defect is created within the prostate parenchyma through which the patient may void.

A substantial collection of data has been published on PVP since the last publication of this Guideline. As part of this review, RCTs of PVP versus TURP were identified and examined for the 80W,[278,287] 120W,[288-295] and 180W platforms.[50,51] However, given the lack of availability of the 80W platform and the superior outcomes encountered with the higher powered lasers, clinicians performing PVP should utilize either the 120W or 180W options.

The Panel noted that PVP may be less efficacious for larger volume prostates and that patient expectations should be aligned accordingly. While the GOLIATH trial excluded patients with prostate volumes > 80g,[280] a recent RCT randomized men with prostate sizes of 80-150g (average 105g) to PVP versus TURP versus HOLEP and found similar efficacy with regards to IPSS; however, PVP had a retreatment rate of 27% at three years of follow-up.[54,299,300] Additionally, the need for a blood transfusion was lower for PVP compared to TURP; as such, PVP may be preferential for medically complicated patients on anticoagulation. This is further detailed in the section on medically complicated patients.

While other laser technologies can be utilized for laser ablation/vaporization of the prostate, the Panel concluded that these were either still investigational or had results that were not considered sufficient or safe to recommend them for routine use. This includes Nd:YAG, which is preferentially absorbed by hemoglobin and has a depth of penetration of approximately 1 cm. This laser was used in the 1990's but fell out of favor secondary to side effects and high reoperation rates. It has recently had a resurgence, but data are lacking to support its routine use. Other lasers, such as various diode wavelengths, are also available on the market. Diode lasers are absorbed by hemoglobin and water. Like Nd:YAG, the depth of penetration is deeper than PVP. Clinicians should be aware that use of lasers for prostate surgery can lead to significant delivery of energy to the irrigating fluid, thereby increasing the temperature of the irrigant. High-powered and/or continuous lasers are at higher risk for temperature increases. Surgeons are advised to use continuous irrigation, occasionally test the temperature of the efflux, and consider whether a fluid warmer should be avoided. Overheated irrigant can cause thermal injury to any tissue that is subsequently exposed to the fluid and thermal injuries to the bladder have been reported after endoscopic prostate surgery.

Prostatic Urethral Lift (PUL)

33. PUL should be considered as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc and verified absence of an obstructive middle lobe. (Moderate Recommendation; Evidence Level: Grade C)

PUL alters prostate anatomy without ablating tissue via the placement of transprostatic suture implants. The implants pull the lumen of the prostatic urethra towards the capsule and widen the prostatic urethral lumen. The urethral side of the implant epithelializes within 12 months. Histopathologic analysis of tissue obtained after PUL demonstrates a benign response to the implant. No significant changes have been noted in PSA after implantation.

The L.I.F.T study compared PUL to SHAM[55] in 206 patients. It excluded patients with a prostate <30g, > 80g or an obstructive middle lobe. The primary outcome was urinary symptom score. The mean change from baseline IPSS (MD: -5.2; 95%CI: -7.45, -2.95)

and improvement in IPSS-QoL (MD: 1.2; 95%CI: 1.7, -0.7) favored PUL. The mean change in Q_{max} at 3 months was higher for those who underwent PUL (4.3mL/s) compared to SHAM (2.0mL/s), P=.005. Of the participants randomized to PUL, five-year follow-up data demonstrated slight decreases in mean IPSS and QoL scores; however, both remained significantly improved from baseline.

The BPH6 Study was a non-inferiority RCT of 80 patients comparing PUL to TURP. It assessed symptom improvement, sexual health, and other outcomes. A lower proportion of individuals in the PUL group responded to treatment at 12 months follow-up compared to TURP as measured by the IPSS reduction goal of ≥30% (73% versus 91%; P=.05).[56] At 24 months follow-up, the mean difference between PUL and TURP was 6.1 points (95%CI: 2.2, 10.0) favoring TURP; however, changes in IPSS-QoL were similar between groups at all follow-up intervals. Qmax was significantly lower in participants allocated to PUL at all follow-up intervals.

Clinicians should verify prostate morphology and volume as previously detailed in the Evaluation and Preoperative Testing section. The Panel limited this guideline statement to include patients with a prostate lacking an obstructive middle lobe, consistent with the L.I.F.T. study criteria. The Panel identified an observational cohort study (n=45 patients) observing improvements in urinary and sexual health outcomes from baseline in patients with an obstructive middle lobe following PUL. This study was excluded from formal efficacy analysis because it was a nonrandomized cohort study utilizing historic controls rather than an RCT.[301]

Since the last amendment, there have been retrospective chart reviews evaluating a small number of patients with prostate sizes between 81-100mL. The Panel recognizes that many devices do not necessarily lack efficacy in prostates below or above the size ranges stipulated in the Statements, but there is insufficient evidence to make formal recommendations beyond those sizes identified.

34. PUL may be offered as a treatment option to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

Compared to many other surgical interventions, PUL has a higher likelihood of preserving sexual function.[302] Woo et al. demonstrated that the sexual function of men with normal or moderate ED at baseline was unaffected, and those with severe ED reported modest improvement. There was no evidence of de novo EjD or ED over the course of the study. Ejaculatory bother improved by 40% at 1 year (p<0.001), while intensity of ejaculation and amount of ejaculate improved by 23% and 22%, respectively (p<0.001). This larger study verified the findings previously published in initial testing.[303]

In the BPH6 Study, no participants in the PUL group experienced adverse events related to sexual function. In comparison, ED and RE occurred in 9% and 20%, respectively, of the participants in the TURP group. While measures of EF using the Sexual Health Inventory for Men (SHIM) was similar between groups at all time points, ejaculatory function based on Male Sexual Health Questionnaire for EjD (MSHQ-EjD) score was better in the PUL group, with TURP participants experiencing declines from month one onward. MSHQ-EjD bother scores were similar throughout the 24-month follow-up. The L.I.F.T. study showed non-significant differences in sexual function between PUL and SHAM groups as measured via SHIM, IIEF-5, MSHQ -EjD function, and MSHQ-EjD bother. In men concerned about new onset of ED and/or EjD, PUL likely does not pose additional risk.

Transurethral Microwave Therapy (TUMT)

35. TUMT may be offered as a treatment option to patients with LUTS/BPH. (Conditional Recommendation; Evidence Level: Grade C)

TUMT was one of the earliest office-based MISTs available and several iterations have been modified since it was first described over 25 years ago. TUMT is a process whereby coagulation necrosis of the prostatic tissue is achieved by transferring energy into the tissue and creates heat. A specialized catheter with a cooling component is placed transurethrally into the prostatic fossa, as well as a rectal catheter that measures temperature, and a microwave antenna heats the prostatic tissue to a minimum 45°C. As the prostate shrinks over the ensuing weeks, the channel opens up.

Evidence regarding efficacy, symptom improvement, adverse events and urinary flow rates are inconsistent. Four trials (n=499) compared TUMT to TURP or control.[304-311] Mean baseline IPSS was 21 (range 20 to 21), and mean prostate volume was 56mL (range 50 to 69mL). Follow-up periods ranged from six months to five years. Response to treatment, defined as an IPSS ≤7 or >50% improvement from baseline, through 12 months was similar between the TUMT and TURP groups. Reoperation was significantly higher with TUMT

(9.9%) compared to TURP (2.3%). Incontinence through long-term follow-up was significantly lower with TUMT (0.7%) compared to TURP (3.9%). ED was similar for TUMT (6.3%) compared to TURP (11.5%).

Common to all approved TUMT devices is the exclusion of those men with obstructing median lobes enlarged out of proportion to the rest of the prostate and protruding significantly into the bladder, sometimes referred to as a "ball valve" median lobe.[312] For additional anatomic and clinical exclusions the urologists should consult the appropriate user manual.

Although the Panel concluded it remains reasonable to offer TUMT, the Panel also observed that the newer minimally-invasive technologies included in this Guideline will likely displace TUMT within the next several years.

Water Vapor Thermal Therapy (WVTT)

36. WVTT should be considered as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc. (Moderate Recommendation; Evidence Level: Grade C)

WVTT utilizes convective radiofrequency to create stored thermal energy in the form of steam, which is delivered transurethrally via a specialized device into the transition zone. The steam travels through the transition zone, denaturing tissue and thereby ablating the adenoma to create an opening. A double-blind RCT[67-69] (n=197) compared WVTT (also referred to as transurethral destruction of prostate tissue by radiofrequency generated water thermotherapy) with SHAM. Mean age of study participants was 63 years. Patients had a mean baseline IPSS of 22 and a mean prostate volume of 45 cm^3. The study excluded men with prostate volume < 30g and > 80g and did not exclude men with obstructing middle lobes or median bars.

Response to treatment through 3 months, based on an improvement in IPSS of ≥30% or ≥8 points, was significantly greater in the WVTT group (74%) compared to the SHAM group (31%) (RR: 2.4; 95%CI: 1.6, 3.5). Mean changes from baseline in IPSS and IPSS-QoL at 3 months were greater in the WVTT group compared to the SHAM group with a MDD of >3 points (MD: -6.9; 95%CI: -9.1, -4.8).

Three-year results showed sustained improvements for the IPSS IPSS-QoL, and Q_{max}, with scores remaining significantly improved from baseline;[70] Q_{max} improvement was > 50% from 3 to 24 months and 39% at 36 months.[13] At 36 months in the intent-to-treat population of the original 136 participants, mean change from baseline in IPSS was -11.0 points and the mean score was 10.4 points, representing a 50% improvement from baseline. Mean IPSS-QoL was improved from baseline by 49% at 3 years.

37. WVTT may be offered as a treatment option to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

Compared to many other surgical interventions, WVTT has a higher likelihood of preserving sexual function. In the RCT comparing WVTT to SHAM, the original 136 patients randomized to WVTT are expected to be followed for five years.[68] Few harms occurred in the WVTT group between months 3 and 12. A decrease in ejaculatory volume was reported by 2% of participants.[67-70] At 36 months, no de novo ED was reported, but dysuria was reported by 1% of participants.[67-70] At 48 months, there was a significant change in IIEF-EF scores compared to baseline (P=.03), but there was not a significant change at the other follow-up intervals.[71]

Function scores associated with ejaculation, assessed by the MSHQ-EjD, were significantly improved at 36 and 48 months following treatment (P=.005 and P=.003) but not at 12 and 24 months.[70] Bother scores associated with ejaculation, assessed by the MSHQ-EjD, were significantly improved at 12, 24, and 36 months but not at 48 months following treatment.[71]

Transurethral Needle Ablation (TUNA)

38. TUNA is not recommended for the treatment of LUTS/BPH. (Expert Opinion)

In 2010, the AUA BPH Clinical Guidelines Panel commented that since the development of the 2003 Guideline, little new information on effectiveness and safety had been published.[1,313,] At that time, the Panel concluded that a degree of uncertainty remained regarding TUNA because of a paucity of high-quality studies.

In the development of the current Guideline, the Panel again searched for studies meeting the updated inclusion criteria, yet none were identified. Based on the lack of peer-reviewed publication in the literature review timeframe and TUNA's substantially diminished clinical relevance, the Panel does not recommend TUNA.

Laser Enucleation

39. Holmium laser enucleation of the prostate

(HoLEP) or thulium laser enucleation of the prostate (ThuLEP) should be considered as an option, depending on the clinician's expertise with these techniques, as prostate size-independent options for the treatment of LUTS/BPH. (Moderate Recommendation; Evidence Level: Grade B)

Due to the chromophore of water and minimal tissue depth penetration with both holmium and thulium (0.4mm for holmium, 0.2 mm for thulium), these two lasers achieve rapid vaporization and coagulation of tissue without the disadvantage of deep tissue penetration. They have better coagulative properties in tissue than either monopolar or bipolar TURP, and combined with their superficial penetration, both thulium and holmium are appropriate for endoscopic enucleation.[314]

HoLEP and ThuLEP have similar outcomes when compared to TURP for the treatment of symptomatic BPH as measured by IPSS and IPSS-QoL outcomes. Based on 6 studies reporting long-term follow-up comparing HoLEP to TURP, ranging from 12 to 92 months, mean changes in IPSS (approximately -19) between groups favored HoLEP, but they did not meet the MDD of 3 points (WMD: -1.3; 95%CI: -2.3, -0.3). At the intermediate follow-up, the WMD was -1.3 (95% CI: -2.2, -0.3). Mean difference in IPSS at the short-term was different (favoring HoLEP), but the difference did not achieve the MDD of 3 points. Of the studies reporting QoL, mean differences between groups were similar at all follow-up points. Based on results from 3 long-term trials, the mean difference in QoL between HoLEP (-3.6) and TURP (-3.4) was -0.2 (95%CI: -0.7, 0.4).[54,73,74,315-320]

Q_{max} at last follow-up after HoLEP compared to TURP is generally similar. Of the 13 studies reporting Q_{max}, 9 found the HoLEP and TURP groups to be similar.[73,74,317-325] Three studies, however, found significantly higher Q_{max} in the HoLEP groups.[315,316,326]

Four studies reported IIEF scores following treatment with HoLEP.[54,74,315,320] 320One study reported that IIEF -5 scores were similar at 3, 12, and 24 months,[315] another reported similar scores at 6 months for the HoLEP and TURP groups,[320] and the last displayed similar scores at 4, 12, 24 and 36 months.[54] The other reported IIEF function and overall satisfaction scores were similar at 92 months.[74] An earlier article on this trial reported that HoLEP and TURP groups experienced similar levels of new onset ED (9% and 8%, respectively) and RE (75% and 61%) at 24 months.16 Three studies reported RE with one also reporting ED; no differences were noted between groups at follow-up to 24 months.

Three HoLEP trials that enrolled men with enlarged prostates (>60 g) met inclusion criteria.[54,315,316] The mean baseline prostate volume in the trial was 99 cm^3, and the mean baseline IPSS was 26. At long-term follow-up (24 months), IPSS between the resection and enucleation groups was similar (WMD:-1.87; 95%CI: -3.9, 0.2). IPSS-QoL was reported in two trials.[19,20] At 24 months, median QoL was 2 in both arms in one trial,[20] and mean IPSS-QoL was 0.9 and 1.4 in the other trial.[54] Comparable to the overall analysis, need for blood transfusion (peri- and post-operative) and incontinence were similar in the HoLEP and TURP groups.

Significant heterogeneity between most identified studies limits confidence of outcomes in pooled analysis of ThuLEP versus TURP. However, 11 studies were included with 3 trials[54,315,316,327-330] reporting long-term results in IPSS reduction (mean change approximately -15), ranging from 18 to 60 months (WMD: 0.4 points; 95%CI: -0.9, 1.6). There was no difference in mean reduction in IPSS within each group (- 15.1) or QoL outcomes (mean change approximately -2.0). At long-term follow-up, the mean difference was -0.3 (95%CI: -0.4, 0.9). Q_{max} after ThuLEP and TURP were similar at 3 months,[76,77,331-333] 12 months,[320,335,336] 18 months,[330] 48 months,[335] and 5-year follow-up.[329] Prostate volume was reported in one study with significantly lower prostate volume post-procedure in the ThuLEP group (mean 11.7g) compared to TURP (mean: 18.3g);[34] one study reported mean resected volumes of 51g in the ThuLEP group and 49g in the TURP group,31 and another study reported median resected volume of 7g in the ThuLEP group compared to 20g in the TURP group.[33]

Two studies reported IIEF scores were similar between the thulium laser and TURP groups at 18 months[28] and 12 months.[25] RE was reported in five studies with all reporting similar outcomes for the thulium laser and TURP groups.[20-23,34] One study reported higher incidence of ED after TURP (44%) compared to ThuLEP (17%).[32]

In reviewing the need for blood transfusion, either peri- or post-operatively, likelihood was significantly lower compared to TURP for both HoLEP (RR: 0.18; 95%CI: 0.08, 0.40) and ThuLEP (RR: 0.4; 95%CI: 0.2, 0.8).

In addition to HoLEP and ThuLEP, other laser modalities have been utilized for enucleation - namely diode and Greenlight. Diode lasers used in urology have variable

wavelengths and several have been utilized for enucleation, but only by a handful of surgeons with few studies. Diode lasers have absorption by both water and hemoglobin. Greenlight has gained in popularity and more studies have been published since it was first described. In addition to laser energy, electrosurgical, and even "cold" energy free, transurethral surgical tools have been utilized for enucleating. Published studies show promise with these modalities in the hands of surgeons comfortable with the technique of endoscopic enucleation. As of yet, the studies are too few to make guidelines recommendations. However, endoscopic enucleation, particularly with laser energy, has clearly become an accepted modality; as such, further applications and support in guidelines are likely in the future.

Robotic Waterjet Treatment (RWT)

40. Robotic waterjet treatment (RWT) may be offered as a treatment option to patients with LUTS/BPH provided prostate volume 30-80cc. (Conditional Recommendation; Evidence Level: Grade C)

RWT surgery utilizes a robotic handpiece, console, and conformal planning unit (CPU). The technique is not in the MIST category as patients must undergo general anesthesia. The resection of the prostate is performed using a water jet from a transurethrally placed robotic handpiece. Pre-treatment transrectal ultrasound is used to map out the specific region of the prostate to be resected with a particular focus on limiting resection in the area of the vermontanum. It is also used to monitor tissue resection in real time during the procedure. After completion of the resection, electro-cautery/thermal energy via a standard cystoscope/resectoscope, use of a tamponade balloon catheter, or traction from a 3-way catheter balloon is used to obtain hemostasis.

Several publications from a low ROB RCT (n = 181) assessing RWT were evaluable by the Panel.[80,337-340] Other recent publications evaluating RWT were excluded from analysis because of their cohort (not comparative) study design.[341] The trial utilized standard inclusion/exclusion criteria limiting participants to prostate sizes between 30-80g.[80,337-340] Treatment response through 12, 24, and 36 months, defined as at least a 5-point improvement in IPSS, was similar for RWT and TURP (quality of evidence was rated moderate for long-term treatment response for RWT compared to TURP). Mean improvement in LUTS based on the IPSS through 12, 24, and 36 months was similar for RWT and TURP (quality of evidence was rated moderate for IPSS mean-change from baseline for RWT compared to TURP). Mean improvement in QoL based on the IPSS-QoL through 12, 24, and 36 months was similar for RWT and TURP (quality of evidence was rated moderate for long-term mean improvement in QoL based on the IPSS-QoL for RWT compared to TURP).[80,337-340] At 12 months follow-up, Q_{max} increased similarly in the RWT group compared to TURP, 10.3 versus 10.6 mL/s (P=.86), respectively.[337-339] At 24 months, Q_{max} for RWT and TURP were 11.2 mL/s and 8.6 mL/s respectively (P=.19) and at 36 months, they remained similar (11.6 mL/s and 8.2 mL/s respectively (P=.09).[80,340]

At 3 months, RWT resulted in fewer harms classified as Clavien-Dindo grade ≥2 compared to TURP, 26% versus 42%, P=.015.[337,338] Also at 3 months, reduction in prostate volume was significantly less with RWT (31%) compared to TURP (44%) (P=.007).[337,338] Additionally, rates of RE were higher (P=.002) with TURP (23%) compared to RWT (6%).[337,338] At three years, post-operative anejaculation was noted less frequently in the RWT group (11%) compared to the TURP group (29%), P<.05. Other harms classified as Clavien-Dindo grades 1-4 occurred at similar rates in both groups, including bladder spasms, bleeding, dysuria, pain, and urethral damage. No deaths were reported. The authors reported the occurrence of medical failure at 36 months follow-up, defined as needing to start alpha blockers or 5-ARI anew, in 9% of participants after RWT and 14% of participants after TURP.[80]

Prostate Artery Embolization (PAE)

41. PAE for the routine treatment of LUTS/BPH is not supported by current data, and benefit over risk remains unclear; therefore, PAE is not recommended outside the context of clinical trials. (Expert Opinion)

Three RCTs (n=247) were identified comparing PAE to TURP.[342-344] One trial reported outcomes up to 2 years,[343] one up to 12 months,[342] and the other through 12 weeks.[344] There was substantial heterogeneity between trials; therefore, pooled results must be interpreted with caution. Definitions of and outcomes for subjective symptom response varied substantially between trials. One trial reported the proportion of responders, defined as achieving an IPSS score ≤8 points and/or a QoL ≤3 points, was similar between the PAE and TURP groups (RR: 0.9; 95%CI: 0.7, 1.1; low quality of evidence for IPSS score change for PAE compared to TURP).[342] Success through 12 months was reported for 87% of the PAE participants compared with 100% in the TURP group. Overall, results at intermediate term follow-up (>3 to ≤12 months) were

similar between groups (WMD: 4.8 points; 95%CI: -2.9, 12.5; very low quality of evidence for follow-up for PAE compared to TURP).3[42,343] The smallest trial (n=30) reported substantially greater improvement in symptoms with TURP compared with PAE (MD: 9 points; 95%CI: 4.6, 13.1),[342] and the other (n=107) reported no significant difference between the groups at 3 and 12 months.[343]

Results also differed between the trials regarding improvements in Q_{max}. Two trials reported lower flow rates with PAE compared with TURP,[342,344] and one trial reported similar flow rates between groups.[343] Mean prostate volumes were significantly higher in the PAE group compared with the TURP group at all follow-up time points.[342,343] Two studies found mean prostate size decreased among participants in the TURP group at short,[344] intermediate, and long-term follow-up.[343] Additionally, the 12-week trial reported PAE was not as effective in reducing BOO, indicated by change in detrusor pressure at Q_{max}, compared with TURP, -17.2 versus -41.1 cmH_2O (P=.002).[344] Postoperatively, 56% of PAE patients were considered less obstructed compared with 93% of TURP (P=.003).[344]

The need for reoperation was reported for 7 participants in the PAE group compared with 2 in the TURP group (RR: 2.9; CI: 0.7, 11.9; very low quality of evidence for reoperation for PAE compared to TURP). Two trials found incidences of sexual dysfunction to be higher with TURP compared with PAE. One trial reported all 15 TURP participants experienced RE while no cases were reported among PAE participants.[342] The short-term trial found incidence of EjD was lower with PAE (56%) compared with TURP (84%) after 12 weeks (RR: 0.67; 95%CI: 0.45, 0.98).[344] One trial reported a higher incidence of AUR requiring recatheterization in the PAE group (26%) versus the TURP group 6% (P=.004).[343] This trial also found adverse events were half as frequent after PAE (n=36) compared to TURP (n=70) (P=.003). Additionally, more cases of hematuria, urinary retention, UTI, and strictures were found after TURP,[342-,343,344] although postoperative incidences of clot retention and strictures were infrequent.[343,344] One incidence of TUR syndrome was reported.[343] No deaths were reported in any trial.

As with all of the interventions in this Guideline, the Panel carefully weighed the potential benefits and harms of PAE. The Panel concluded that substantial issues remain in recommending PAE for the routine treatment of bothersome LUTS attributable to BPH. What remains unclear is the role of PAE relative to other, more widely available minimally-invasive therapies for the routine treatment of LUTS. PAE is a technically demanding procedure, averaging fluoroscopy times of up to 50 minutes and procedure times up to 2 hours.[344] Attainment of proficiency involves a challenging learning curve for physicians who—while trained in the performance of endovascular interventions—may be less familiar with core concepts of BPH pathophysiology, diagnosis, treatment, and follow-up.[344] It is thus the opinion of the Panel that PAE should only be performed in the context of a clinical trial or registry study until additional evidence is available to indicate definitive clinical benefit and define specific indications. The Panel recommends trials involve multi-disciplinary teams of urologists and radiologists focused on further defining specific indications, including but not limited to gross hematuria recalcitrant to other therapies (see further discussion under Statement 42).

Hematuria

42. After exclusion of other causes of hematuria, 5-ARIs may be an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding. (Expert Opinion)

Refractory hematuria secondary to prostatic bleeding poses a challenging treatment dilemma for urologists and patients alike, particularly in the era of anticoagulation. Surgical interventions for symptomatic BPH are often used and have been described in the management approach. However, surgical intervention may not be desired depending on the ability to hold anticoagulation and/or the frailty of the patient.

One of the early intraprostatic effects of finasteride has been the suppression of vascular endothelial growth factor (VEGF).[20,346-348] Initially anecdotally,[349] and then in long-term follow-up studies[350-352,] it was noted that men with prostate-related bleeding (i.e., 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.[20] The role of short term use of finasteride to decrease perioperative bleeding in men undergoing TURP is less defined and is not considered to be a routine method of care.[353] As options are often limited in men with troublesome or refractory bleeding of prostatic origin, the use of 5-ARIs has benefits with regard to bleeding events; however, patients should still be counseled on potential side effects.

The potential role of PAE in the management of refractory hematuria is evolving. Many of the studies include a small number of patients with various etiologies of hematuria. Nevertheless, the ability to both decrease prostate volume and decrease vascular inflow makes PAE a potential adjunct in management of refractory hematuria.[354]

Medically Complicated Patients

43. HoLEP, PVP, and ThuLEP should be considered as treatment options in patients who are at higher risk of bleeding. (Expert Opinion)

Multiple studies have shown that the need for a blood transfusion (either peri- or post-operatively) was significantly less likely with HoLEP and ThuLEP as compared to TURP (RR: 0.20; 95%CI: 0.08, 0.47) and (RR 0.4; 95%CI: 0.1, 0.9), respectively.[73,273,318,355-357] In addition, studies of holmium laser prostate surgery in patients maintained on anticoagulation therapy at time of surgery have supported a relatively low transfusion rate. In a 2013 retrospective review on a series of 125 patients treated with HoLEP (52 patients were on antithrombotic therapy at the time of surgery, and 73 patients were not), only 4 men (7.7%) in the antithrombotic group required a blood transfusion compared to none in the control group.[358] A similar 2016 study compared 116 patients who required anticoagulation/antiplatelet therapy at the time of HoLEP to 1,558 patients who did not. Other than a slightly increased duration of bladder irrigation and hospital stay, the use of anticoagulation/antiplatelet therapy did not adversely affect outcomes.[359] Lastly, a 2017 meta-analysis of patients on therapeutic anticoagulation/antiplatelet therapy when undergoing HoLEP supported that this approach can be performed safely on these patients, but the analysis stressed that there are limited data surrounding the class of direct oral anticoagulants and safety.[362]

While there are differences between wavelengths as well as the chromophore in which laser energy is absorbed (i.e., water, hemoglobin, pigment), in general, lasers have favorable hemostatic properties that treat bleeding more effectively than monopolar energy. Most lasers used in urology (532 nm, holmium, thulium) have superficial penetration and thermal diffusion depths that lead to the concentration of high-density energy in a superficial layer, thereby "sealing" vessels and creating shallow coagulation zones. Holmium and thulium both have similar wavelengths (holmium 2,140nm, thulium 2,013nm) and are absorbed by water. The major difference is that holmium is a pulsed laser while thulium is continuous, which impacts how quickly the temperature rises in the tissue. The decreased penetration depth of holmium and thulium as compared to monopolar energy leads to a more superficial area of ischemia and can reduce risk for delayed bleeding, as eschar sloughs approximately 7-14 days post procedure. During this timeframe, any anticoagulant therapy that may have been discontinued will have resumed and be in effect, thereby making the reduction in eschar a significant benefit. [314,359-364]

The safety of thulium in anticoagulated patients has been reported in several publications. In one study of 56 patients (32 on aspirin, 8 on clopidogrel or clopidogrel plus aspirin, and 16 on phenprocoumon), 4 patients needed blood transfusions, and 4 patients required immediate reoperation. Given this high-risk group and despite the reported issues, the patients did well overall.[365] Two other studies have described the feasibility of thulium laser for prostate surgery in anticoagulated patients and those bridged with low molecular weight heparin (LMWH). A 2013 study of 76 patients compared those on anticoagulant/antiplatelet therapy during surgery to those who were bridged with LMWH. There were no statistically significant variations in hemoglobin between the two groups.[363]

A similar more recent 2017 study of 103 patients revealed the drop in hemoglobin levels in the pre- and post-operative periods were significantly higher in the LMWH bridged group than those who remained on anticoagulant/antiplatelet therapy during surgery. Given that no cardiopulmonary adverse events occurred and bleeding was not problematic, the authors recommend abandoning LMWH bridging and continuing anticoagulant/antiplatelet therapy during thulium laser surgery.[366]

PVP is performed using the lithium triborate laser, which has a wavelength of 532 nm and a chromophore of hemoglobin. The depth of penetration with PVP is 0.8 mm. Multiple studies have found that PVP is safe and effective for patients who continue their anticoagulant/ antiplatelet therapy, with negligible transfusion rates. However, surgeons should be aware that longer catheterization and irrigation with an increased rate of complications has been reported, and delayed bleeding is more pronounced in these patients.[367-370] A 2017 study confirmed these findings in 59 of 373 patients undergoing PVP. Overall, Greenlight PVP with the 180W laser unit on patients therapeutic on heparin, warfarin, clopidogrel, dipyridamole, or new oral anticoagulant drugs revealed good safety outcomes.[371] As expected, anticoagulated patients were older, had a higher American Society of Anesthesiologists (ASA) score than the control group and, although no patient required blood transfusion, there was a higher incidence of high-grade Clavien-Dindo events. Similar to other studies, the therapeutically anticoagulated group had a significantly longer length of hospital stay and duration of catheterization as compared to the controls. In support of the concept of 120W PVP use in

anticoagulated patients, recent publications report that the need for a blood transfusion was lower for PVP with 120W compared to TURP.[296,297]

For additional information on the use of anticoagulation and antiplatelet therapy in surgical patients, refer to the ICUD/AUA review on Anticoagulation and Antiplatelet Therapy in Urologic Practice.[372]

FUTURE DIRECTIONS

BPH and ensuing LUTS is a significant health issue affecting millions of men. There are enormous gaps in knowledge; therefore, there are also significant opportunities for discovery. Many unanswered questions exist, including but not limited to the role of inflammation, metabolic dysfunction, obesity, and environmental factors in etiology, as well as the role of behavior modification, self-management, and evolving therapeutic algorithms in both the prevention and progression of disease.

Disease Etiology

Currently, there are few animal and human tissue models for LUTS/BPH. This limits the ability and efforts to understand both pathogenesis and progression. More specifically, computational biology and genomic factors should be aimed toward understanding drivers of BPH and prostate growth and therapeutic targets.

LUTS are differentially bothersome. Moreover, qualitative rather than quantitative changes have not been well described. Enhanced metrics including bother, pain, and incontinence will need to be incorporated and evaluated.

Addressing Healthcare Disparities and Cultural Competency

In a seminal 2003 report, the Institute of Medicine (IOM) defined healthcare disparities as differences in the quality of healthcare not due to access-related factors, clinical needs, patient preferences, and appropriateness of intervention. There remains a paucity of data on racial and ethnic variations in LUTS/BPH prevalence and treatment, most notably in the Black and Latinx communities. Further study of this topic to address systemic biases in the LUTS/BPH care of these populations would substantially inform this Guideline and promote healthcare equity. So, too, would implementation and study of educational endeavors focused upon improving cultural competency among LUTS/BPH clinicians.

Management of Nocturia

The most prevalent and bothersome symptom of the LUTS is nocturia. The differential diagnosis of increased nighttime urination frequency/volumes and the role of sleep apnea is an area of great importance given that nocturia is also associated with increases in overall mortality. Due to the considerable burden of nocturia on QoL and a lack of effective management options, more funded research is needed. Nocturia is often multifactorial in origin and symptomatic of other medical problems, further complicating effective management. Nocturia, whether global, reduced bladder capacity, or mixed, is a unique symptom complex requiring special concern and judicious evaluation.

Urodynamic Evaluation and Imaging

The natural history and predictive ability of various urodynamic measures, such as flow rate and PVR, in regards to predicting patient reported outcomes (e.g., symptoms, QoL), and objective outcomes (e.g., peak flow, development of total retention, need for retreatment) is an area of great interest with substantial clinical and health care economic consequences.

Morphological aspects such as bladder wall thickness, degree of trabeculation, prostatic urethral angle, and intravesical prostatic protrusion can affect natural history, treatment response, and treatment options. Prostate imaging and other novel tests are areas of potentially beneficial and significant research.

Development of a Patient-Centered Approach to Improve Adherence and Compliance

While medications for LUTS attributed to BPH have become the mainstay of therapy, there is wide variability among prescribers with respect to treatment choice (i.e., class of drug, monotherapy versus combination therapy). In addition, appropriate and patient-centered therapeutic strategies continue to lag behind evidence-based medicine. In large part, this has led to poor adherence and compliance with various therapies. Several factors play a role including insurance coverage, type of medication, side effects of medication, race and availability of information technology. Finally, managing patient expectations is variable among prescribers. Use of technology, improved informatics, and coalescence of treatment strategies are opportunities to improve both short- and long-term safety and efficacy with medications. In addition, this could provide more uniform approaches to treatment success and failure and gateways to both minimally-invasive and surgical therapies.

New Therapeutic Options

There have been a number of new therapeutic options utilized for LUTS/BPH over the past few years. Despite the expansion of the treatment algorithm, the ceiling on medical therapy has not been well elucidated. The potential role of combination therapy and other routes of delivery are under investigation and remain to be defined. These include changes in dosing patterns (e.g., weekly, monthly). Moreover, many promising MISTs and surgical alternatives are in development. It is the hope of this Panel that further data will be available in the peer reviewed literature on these therapies to allow incorporation into future iterations of this Guideline. With so many MISTs being developed for LUTS/BPH, the Panel is compelled to consider the necessary attributes to qualify as reasonable MIST therapies, as well as which patient characteristics will likely confer successful outcomes with each individual MIST option. Future MISTs should strive to attain outcomes similar to standard technologies, with fewer side effects, as well as ability to perform them in an office setting under local anesthesia.

From the patient perspective, the hallmarks of a successful MIST might include: 1. Tolerability, 2. Rapid and durable relief of symptoms, 3. Short recovery time with rapid return to life activities, 4. Minimal adverse events, and 5. Affordability. From the urologist's perspective, successful attributes might include: 1. Capacity for performance in an ambulatory setting under reduced anesthesia, 2. A fast learning curve, 3. Generalizability from RCT, 4. Ease of performance and follow-up care, 5. Low risk, 6. Applicable to a wide variety of patients.

Traditionally, the primary goal of treatment has been to alleviate bothersome LUTS that result from BOO. While a MIST may not alleviate symptoms to the same degree or durability as more invasive surgical options, a more favorable risk profile and reduced anesthetic risk would make such a treatment attractive to many patients and providers. Since many men discontinue medical therapy, yet proportionately few seek surgery, there is a large clinical need for an effective treatment that is less invasive than surgery. With this treatment class, perhaps a significant portion of men with BOO who have stopped medical therapy can be treated prior to impending bladder dysfunction.

Treatment and Definition of Efficacy and Treatment Failure

Studies of comparative efficacy of behavioral and lifestyle intervention versus medical treatment; medical therapies versus MISTs; and surgical treatments compared to each other are lacking and would be of great benefit for all levels of providers and patients, and perhaps result in cost savings. Models could include population science, the development of registries, and analysis of electronic medical records and insurance databases. In addition, a better definition of potential long-term complications of medical therapy needs to be delineated in the quest for enhancing both prescriber and patient choice. The ability of providers to use a calculator with patient parameters to obtain a treatment algorithm, or set of appropriate options, could streamline approaches and care.

In addition, MIST and surgical therapies for BPH require a different regulatory process where only patients who remain in follow-up are seen. Many who recover and no longer have symptoms do not return to the urologist or seek care. With medical therapy, patients remain in the care of their providers as therapy is ongoing and prescription renewals are necessary. This variance in patient interaction can lead to different definitions and criteria for treatment failure and in tracking of rates of retreatment.

More data are needed, and a proposed evidence-based classification system for guiding patient care, reimbursement practices, and research outcomes assessment that is applicable across a variety of surgical treatments is of critical importance.

ABBREVIATIONS

5- Alpha Reductase Inhibitor	5-ARI
95 Percent Confidence Interval	95%CI
Acute Urinary Retention	AUR
American Urological Association	AUA
AUA-Symptom Index	AUA-SI
Benign Prostatic Enlargement	BPE
Benign Prostatic Hyperplasia	BPH
Benign Prostatic Obstruction	BPO
Bladder Outlet Obstruction	BOO
Clinical Controlled Trials	CCT
Computed Tomography	CT
Dihydrotestosterone	DHT
Ejaculatory Dysfunction	EjD
Erectile Dysfunction	ED
Erectile Function	EF
Global Subjective Assessment	GSA
Holmium Laser Enucleation of the Prostate	HoLEP
International Index of Erectile Function	IIEF
Intraoperative Floppy Iris Syndrome	IFIS
International Prostate Symptom Score	IPSS
Laparoscopic Simple Prostatectomy/Enucleation	LSP
Low Molecular Weight Heparin	LMWH
Lower Urinary Tract Symptoms	LUTS
Male Lower Urinary Tract Symptoms Secondary/ attributed to BPH	LUTS/BPH
Magnetic Resonance Imaging	MRI
Medical Therapy of Prostatic Symptoms	MTOPS
Minimally Detectable Difference	MDD
Minimally Invasive Surgical Therapies	MIST
Open Simple Prostatectomy	OSP
Overactive Bladder	OAB
Patient Perception of Study Medication	PPMS
Phosphodiesterase-5	PDE5
Phosphodiesterase-5 Inhibitor	PDE5
Photoselective Vaporization of the Prostate	PVP
Post-Void Residual	PVR
Prostate Artery Embolization	PAE
Prostate Specific Antigen	PSA
Prostatic Urethral Lift	PUL
Quality of Life	QoL
Randomized Controlled Trials	RCT
Retrograde Ejaculation	RE
Risk of Bias	ROB
Risk Ratio	RR
Robotic-Assisted Laparoscopic Simple Prostatec-tomy	RASP
Robotic Waterjet Treatment	RWT
Thulium Laser Enucleation of the Prostate	ThuLEP
Transurethral Incision of the Prostate	TUIP
Transurethral Needle Ablation	TUNA
Transurethral Resection of the Prostate	TURP
Transurethral Ultrasound	TRUS
Transurethral Vaporization of the Prostate	TUVP
Trial Without Catheter	TWOC
Urinary Tract Infection	UTI
Water Vapor Thermal Therapy	WVTT
Weighted Mean Difference	WMD

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All panel members completed COI disclosures. Disclosures listed include both topic– and non-topic-related relationships.

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