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AUA Guideline Article

Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia (BPH): AUA Guideline Amendment 2023

Jaspreet S. Sandhu,[1]* Brooke R. Bixler,[2] Philipp Dahm,[3] Ramy Goueli,[4] Erin Kirkby,[2] John T. Stoffel,[5] and Timothy J. Wilt[3]

[1]MSKCC, New York, New York
[2]American Urological Association, Linthicum, Maryland
[3]University of Minnesota
[4]UT Southwestern
[5]University of Michigan

Purpose: The purpose of this American Urological Association (AUA) Guideline amendment is to provide a useful reference on the effective evidence-based management of male lower urinary tract symptoms secondary/attributed to BPH (LUTS/BPH).

Materials and Methods: The Minnesota Evidence Review Team searched Ovid MEDLINE, the Cochrane Library, and the Agency for Healthcare Research and Quality (AHRQ) database to identify studies relevant to the management of BPH. The guideline was updated in 2023 to capture eligible literature published between September 2020 and October 2022. 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.

Results: The BPH amendment resulted in changes to statements/supporting text on combination therapy, photoselective vaporization of the prostate (PVP), water vapor thermal therapy (WVTT), laser enucleation, and prostate artery embolization (PAE). A new statement on temporary implanted prostatic devices (TIPD) was added. In addition, statements on transurethral needle ablation (TUNA) and transurethral microwave thermotherapy (TUMT) were removed and information regarding these legacy technologies was added to the background section. References and the accompanying treatment algorithms were updated to align with the updated text.

Conclusion: This guideline seeks to improve clinicians' ability to evaluate and treat patients with BPH/LUTS based on currently available evidence. Future studies will be essential to further support these statements to improve patient care.

Key Words: LUTS, BPH, alpha blocker, IPSS, anticholinergic, prostate, prostate surgery, TURP, HoLEP, ThuLEP, PVP, MIST, water vapor thermal therapy, laser enucleation

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* Correspondence: Memorial Sloan Kettering Cancer Center, New York, NY (telephone: email: sandhuj@mskcc.org).

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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 (eg, 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.

The Panel recognizes that there has been a dramatic evolution in the operative techniques available for LUTS/BPH. The Panel recognizes that there are some "legacy technologies" that have been historically used, and are currently FDA approved, but have very limited newly published data to be able to comment on their efficacy. The Panel has observed that with newer minimally invasive technologies these "legacy technologies" are largely being displaced. The Panel recognizes TUMT and TUNA as 2 of these legacy technologies; therefore, guideline statement referencing these "legacy technologies" have been removed.

In 2023, an update review assessing abstracts from new studies published since the initial release of the 2019 Guideline was completed utilizing the same search strategies employed in the original guideline with search dates updated through October 2022. Relevant literature was graded and incorporated into existing text to produce the 2023 amendment.

Dr Wilt and Dr Dahm served as members of the AUA funded Evidence Review Team and were not voting members of the AUA Guideline Panel Members or developers of the recommendation statements.

GUIDELINE STATEMENT UPDATES

The statements summarized herein constitute the 2023 amendment; however, users are encouraged to reference the unabridged guideline for a complete listing of guideline statements and more detailed discussion. A summary of procedures discussed in the guideline is also detailed in the accompanying algorithms (Figures 1-3).

Combination Therapy

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

Anticholinergics as Monotherapy. While anticholinergics have been used safely in men with storage LUTS, a post-void residual should be obtained and the usual precautions for the use of anticholinergic medications (eg, gastric emptying/GI motility issues, narrow angle glaucoma) should be followed. Furthermore, recent publications suggest an association between use of anticholinergic drugs and increased risk of dementia in patients over 55.[1,2] The side effects, especially in patients over 70, can be significant; as such, the benefits and risks of treatment should be carefully weighed and discussed with the patient and family.[3]

Anticholinergic Therapy in Combination with Alpha Blockers. Overall, it makes intuitive sense to use anticholinergics combined with α blockers in selected patients with storage-predominant LUTS/BPH. However, the International Prostate Symptom Score (IPSS) improvement in men with combined α blocker and anticholinergic compared to α blocker alone is variable. Since there are increased adverse events, 1 can consider initially starting with α blocker alone and adding anticholinergics in selected cases. However, further studies with larger sample sizes are needed to determine whether combination therapy enhances the symptom response or if the response is driven by the α blocker alone.

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

Combined Mirabegron and Doxazosin Versus Active Comparator. Elbaz et al[4] studied a combination of mirabegron 50 mg and doxazosin 2 mg with a combination of tolterodine 4 mg and doxazosin 4 mg in 55 men with LUTS/obstructive symptoms and Erectile dysfunction (ED). This single-blinded (patients) study was conducted over 12 weeks. The trial excluded men with a high post-void residual volume (>150 mL). Mean age in the study was 59.5 years and IPSS was 17 points, indicating moderate LUTS. Comorbidities at baseline included diabetes (21%) and hypertension (23%).

Combination therapy with a β-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 or others where anticholinergic therapy is not recommended, a

Basic Management of LUTS in Men

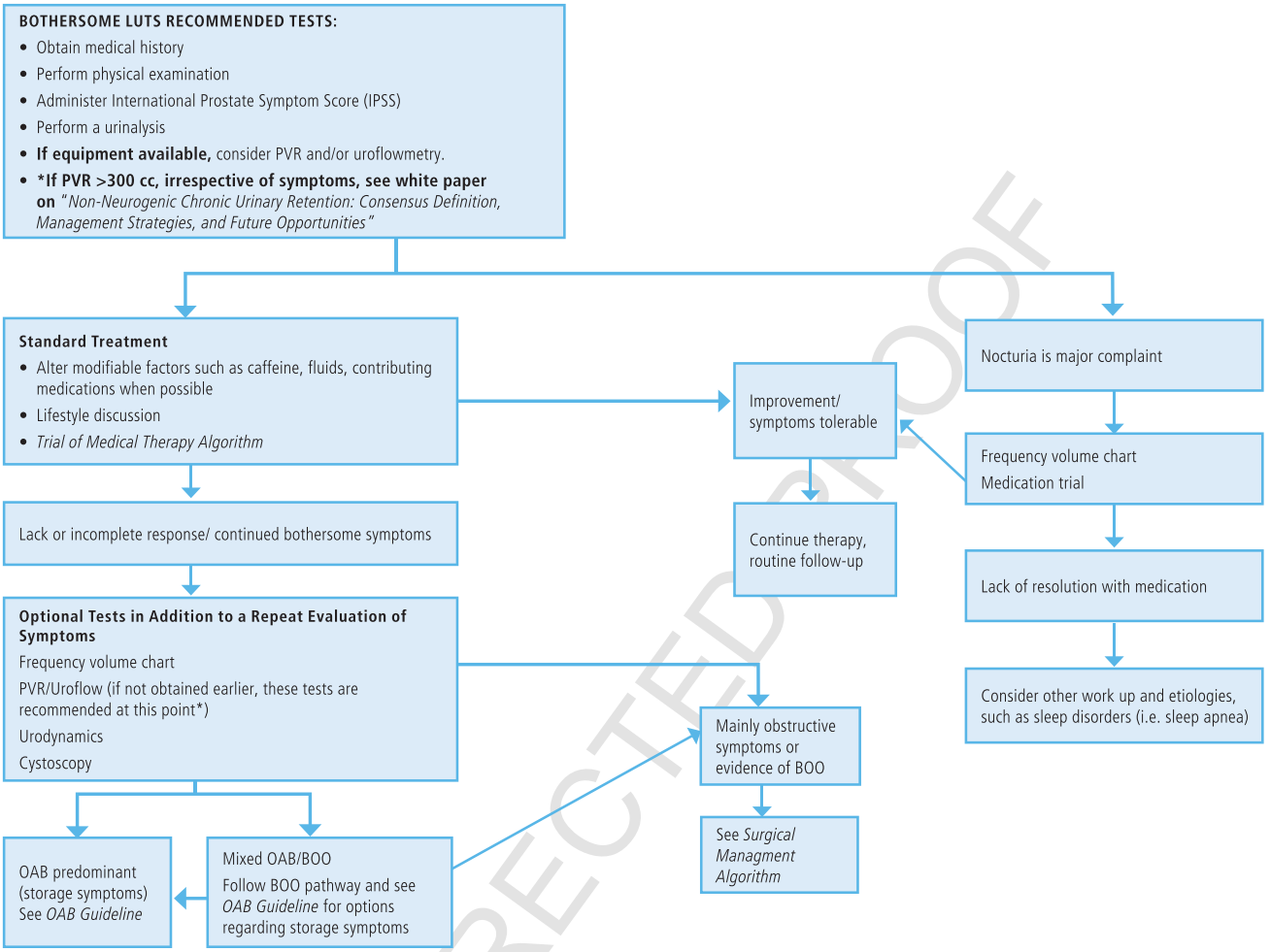

Figure 1.

β-3-agonist can be utilized. However, further studies with larger sample sizes are needed to determine whether combination therapy enhances the symptom response, or if the response is driven by the α blocker alone.

21. Clinicians may offer the combination of low-dose daily 5mg tadalafil with α blockers for the treatment of LUTS/BPH. (Conditional Recommendation; Evidence Level: Grade C)

Combination of Low-Dose Daily Tadalafil with Alpha Blockers. A trial compared a combination of tadalafil 5 mg and silodosin 8 mg with silodosin 8 mg alone.[5] Treatments were administered daily with follow-up after 3 months of treatment. Mean age of study participants was 63 years in both the combination and single medication groups. While there is signal that combination therapy is more efficacious, in this trial, there is likely little to no difference in mean change in IPSS scores between the combination and silodosin alone groups (-5.6 versus -4.1 points; mean difference [MD] 1.5 points [95% CI: 0.82 to 2.18]).[5] There is also little to no difference in mean change in International Index of Erectile Function (IIEF) scores (MD -0.40 points [95% CI: −1.00 to 0.20]).[5]

22. Clinicians may offer the combination of low dose daily tadalafil 5mg with finasteride for the treatment of LUTS/BPH. (Conditional Recommendation; Evidence Level: Grade C).

Clinicians are occasionally asked about the use of low-dose daily tadalafil with finasteride. Similar to combination therapy of α blockers and PDE-5 for LUTS/BUH, long-term follow up data are lacking.

Photoselective Vaporization of the Prostate (PVP)

33. 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 may be less efficacious for larger-volume prostates and patient expectations should be aligned accordingly. While the GOLIATH trial

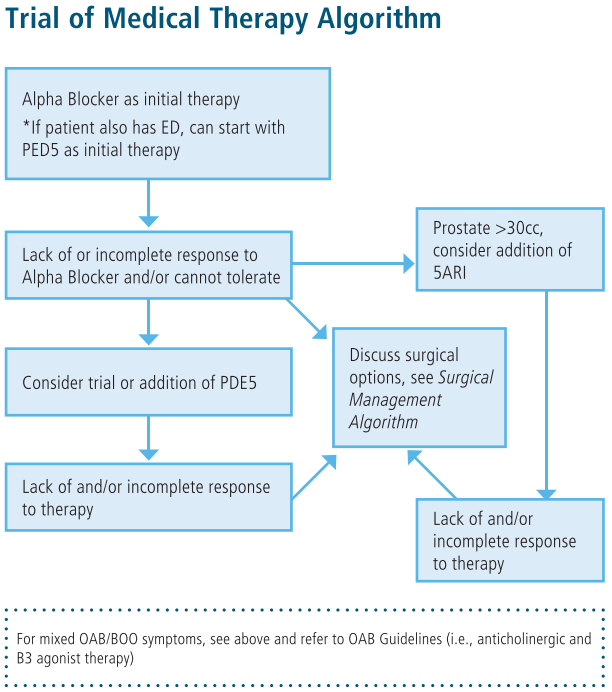

Figure 2.

excluded patients with prostate volumes >80g,[6] a recent randomized controlled trial (RCT) randomized men with prostate sizes of 80-150g (average 105g) to PVP versus transurethral resection of the prostate (TURP) versus holmium laser enucleation of the prostate (HoLEP) and found similar efficacy with regards to IPSS; however, PVP had a retreatment rate of 27% at 3 years of follow-up.[7-9] 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.

Laser vapo-enucleation, another hybrid technique, using a 180W 532 nm laser was compared to bipolar TURP in a study of 124 men with prostate size between 80 and 150g.[7] At 36-months postoperatively, there was no differences in IPSS or maximum flow rate between the 2 techniques. There was also no difference among arms in postoperative urinary tract infection, bladder neck contracture, or need for additional therapy at 36 months.

Water Vapor Thermal Therapy (WVTT)

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

Five-year results showed mean change in IPSS from baseline through 60 months was 15.1 points for the WVTT group compared with 13.2 points for the TURP group (MD 1.9 points [95% CI −1.41 to 5.21]).[10] At 60 months, improvements in the IPSS-Quality of Life (QoL) were similar with a mean score of 1.6 in both treatment arms. Maximum flow rates increased at 1 month after treatment in both groups and increases were maintained at 60 months.

Laser Enucleation

38. 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)

Five HoLEP studies enrolled men who had prostates of 75g or greater.[11-15] At follow-ups ranging from 12 to 36 months, HoLEP resulted in little or no difference in IPSS compared to TURP or another comparator (k=5; 2 studies showing an improvement with HoLEP and 3 showing no difference).[11-15] There was no difference in IPSS-QoL (k=4).[12-15]

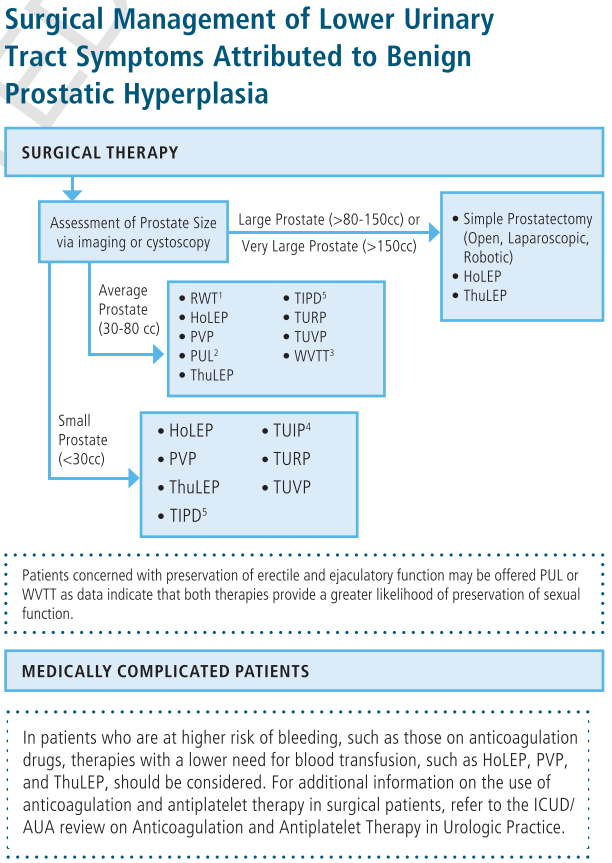

Figure 3.

In the 4 studies reporting need for blood transfusion, no significant differences between HoLEP and TURP or another comparator were reported although studies were likely underpowered to detect these infrequent events (a total of 0 events in the HoLEP group versus 9 in the TURP or other comparator group; total N=465).[11-13,15] Of the 4 studies reporting incontinence, none reported a significant difference in incidence between the HoLEP and TURP or other comparator groups. Significant heterogeneity between most identified studies limits confidence of outcomes in pooled analysis of ThuLEP versus TURP. However, 10 RCTs (n=1181),[16-26] 2 clinical controlled trials (n=159),[27,28] and 3 trials[7,11,15] reported long-term results in IPSS reduction (mean change approximately -15), ranging from 18 to 60 months (weighted mean difference [WMD]: 0.4 points; 95% CI: -0.9 to 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 MD was -0.3 (95%CI: -0.4 to 0.9). Q_{max} after ThuLEP and TURP were similar at 3 months,[17,18,23,24] 12 months,[27-29] 18 months,[22] 48 months,[27] and 5-year follow-up.[21] Prostate volume was reported in 1 study with significantly lower prostate volume post-procedure in the ThuLEP group (mean 11.7g) compared to TURP (mean: 18.3g)[30]; while another study reported mean resected volumes of 51g in the ThuLEP group and 49g in the TURP group.[31]

Two studies reported IIEF scores which were similar between the ThuLEP and TURP groups at 18 months[32] and 12 months.[33] Retrograde ejaculation was reported in 5 studies with all reporting similar outcomes for the ThuLEP and TURP groups.[30,34-37] One study reported higher incidence of ED after TURP (44%) compared to ThuLEP (17%).[38]

There have been 3 additional studies reporting other enucleating procedures.[39-41] One procedure on bipolar enucleation of the prostate and resection of the prostate (n=240),[39] plasma button transurethral vapor enucleation of the prostate (n=101),[40] and monopolar enucleation of the prostate (n-134).[41] All 3 studies showed improvement in IPSS and IPSS-QoL in both groups, but there was no significant difference between the individual enucleating procedure and their comparator. Maximum flow rates also improved in all the studies, with only 1 study showing bipolar enucleation to have slightly higher Q_{max} compared to TURP (24.9 versus 20.1, $P = 0.03$). When reported, there was no significant difference in the need for blood transfusions between enucleating and its comparator. There was no difference in ED or urinary incontinence between the individual enucleation technique and its comparator.

Prostate Artery Embolization (PAE)

40. PAE may be offered for the treatment of LUTS/BPH. PAE should be performed by clinicians trained in this interventional radiology procedure following a discussion of the potential risks and benefits. (Conditional Recommendation: Evidence level: Grade C)

One RCT (n=80) was identified comparing PAE to SHAM (PAE procedure with no embolization).[42] This was a single blind trial that reported outcomes at 6 months with no long-term data available. After 6 months, the patients randomized to the SHAM arm (n=38) were crossed over to receive PAE and followed for 6 months. Males over 45 years old were included in the study if they had severe LUTS defined as an IPSS $\geq$20 and a QoL score of $\geq$3 after a minimum of 6 months treatment with medical therapy. Patients were excluded if they had a computed tomography angiography showing the prostatic arteries were not amenable to PAE or if they had prior surgical or invasive treatment on their prostate. The PAE procedure was done with 300-500 μm microspheres. The procedure time was 71.3±18.1 min, fluoroscopy time 19.4±9.71 min, and a radiation dose 247.9±153.8 Gy.cm^2.

In this study, PAE may have improved IPSS scores compared to SHAM (MD -13.2 points [95% CI: -16.2 to -10.2]). Mean changes in IPSS-QoL also favored the PAE group (MD -2.0 points [95% CI: -2.5 to -1.5]). At 6 months, greater mean improvement in flow rates (Q_{max}) was achieved with PAE compared with SHAM (6.8 mL/s versus 2.8 mL/s). Mean prostate volumes were significantly reduced in the PAE group compared with the SHAM group (-17.6g versus -0.1g). Hematuria, ecchymosis, urethral pain and dysuria were the most common adverse events reported. No need for blood transfusion or reoperation was reported.

Five RCTs (n=352) were identified comparing PAE to TURP.[43-48] Two trials reported outcomes up to 2 years,[44,46] 2 up to 12[43,47] and 1 through 6 months.[48] 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 $\leq$8 points and/or a QoL $\leq$3 points, was similar between the PAE and TURP groups (RR: 0.9; 95%CI: 0.7 to 1.1 for IPSS score change for PAE compared to TURP).[43] Success through 12 months was reported for 87% of the PAE participants compared with 100% in the TURP group. Results from another trial found the mean change in IPSS from baseline through 2 years was similar between groups (MD 0.7 points [95% CI: -1.3 to 2.7][44] while results at year 2 from 1 trial favored TURP

compared to PAE (MD 2.9 points [95% CI: 0.04 to 5.72]).[46] Overall, while results at intermediate-term follow-up (>3 to≤12 months) were similar between groups, the Panel is very uncertain of the effect (WMD 2.3 points [95% CI: -3.2 to 7.8).[43,44,48] One of the trials (n=30) reported substantially greater improvement in symptoms with TURP compared with PAE (MD 9 points [95% CI: 4.6 to 13.1]),[43] and the other (n=107) reported no significant difference between the groups at 3 and 12 months.[44] Pooled results from 2 trials reporting data at 3 months showed no statistically significant difference between groups (WMD 3.4 points [95% CI: 0.0 to 6.8]; I^2=70%).

Mean changes in IPSS-QoL followed a similar pattern to the findings for mean change in IPSS scores. Long-term (24 months), 1 trial found mean change in QoL scores from baseline was similar between groups (MD 0.0 points [95% CI: -0.3 to 0.3][44] while the other long-term trial reported greater improvement with TURP MD 0.99 points [95% CI: 0.3 to 1.7]).[46]. Overall, results at intermediate-term follow-up were also similar between groups, though the Panel is very uncertain of the results (WMD 0.1 [95% CI: -0.8 to 1.1]).[43,44,48] There was substantial heterogeneity between trials (I^2=86%) with the smallest trial (n = 30) reporting greater improvement with TURP[43] and the other trials reporting no significant difference between the groups.

Results also differed between the trials regarding improvements in Q_{max}. Three trials, 2 intermediate-term and 1 short-term, reported lower flow rates with PAE compared with TURP.[43,46,48] In contrast, the other trial reported peak urine flow rates were similar between groups for the intermediate- (12 months) and long-term (24 months) follow-ups. Results from the other trial with long-term results reported much greater mean improvement in flow with TURP compared to PAE, 10.2 mL/s versus 3.9 mL/s, respectively ($P < .001$).[46] Mean prostate volumes were significantly higher in the PAE group compared with the TURP group at all follow-up time points.[43,44,47,48]

Additionally, for the portion of patient who underwent post-PAE urodynamics (39/82), the 12-week trial reported PAE was not as effective in reducing measures of bladder outlet obstruction (BOO), indicated by change in detrusor pressure at maximum flow rate, compared with TURP, -17.2 versus -41.1 cmH_2O ($P = 0.002$).[45] Post-operatively, 56% of PAE patients were considered less obstructed by these measures compared with 93% of TURP ($P = .003$).[45]

Overall need for a blood transfusion was infrequent; reported for 2 TURP participants and none receiving PAE (Peto OR 0.13 [95% CI: 0.01 to 2.15]).[43,44,48] Urinary incontinence was lower with PAE compared to TURP (risk ratio [RR] 0.13 [95% CI: 0.02, 0.70]).[43,44,47] Need for reoperation was greater in the PAE group (17 participants) compared with the TURP group (7 participants) (RR 2.4 [95% CI: 1.1 to 5.5]).[43,44] Two trials found incidences of sexual dysfunction to be higher with TURP compared with PAE. One trial reported all 15 TURP participants experienced retrograde ejaculation while no cases were reported among PAE participants.[43] One trial found incidence of ejaculatory dysfunction was lower with PAE (56%) compared with TURP (84%) after 12 weeks (RR 0.67 [95%CI: 0.45 to 0.98).[45,46] Another trial reported a higher incidence of acute urinary retention requiring re-catheterization in the PAE group (26%) versus the TURP group 6%, $P = .004$).[44] 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, urinary tract infection, and strictures were found after TURP.[43-45] Postoperative incidences of clot retention and strictures were infrequent.[44,45] One incidence of TUR syndrome was reported.[44]

The Panel was unable to find substantial evidence to recommend PAE over more widely available minimally invasive surgical therapies (MISTs) for the routine treatment of LUTS, but there is evidence showing a short-term benefit of PAE compared to observation in a very select patient population. PAE is a technically demanding procedure, averaging fluoroscopy times of up to 50 minutes and procedure times up to 2 hours.[45] 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, which is why the Panel recommends that these procedures are only performed by physicians specifically trained in this technique.[45] The Panel recommends continued investigation of PAE through 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.

Temporary Implanted Prostatic Devices (TIPD)

41. TIPD may be offered as a treatment option for patients with LUTS/BPH provided prostate volume is between 25 and 75 cc and lack of obstructive median lobe. (Expert Opinion)

One RCT conducted at 16 sites in the US and Canada, compared TIPD to SHAM. A total of 185 men with prostate volumes between 25 and 75 cc were randomized (128 to TIPD, 57 to SHAM). An improvement in the IPSS of at least 3 points at 3

months post-procedure was reported in 78.6% of the TIPD group and 60.0% of the SHAM group (RR 1.3 [95% CI: 1.1 to 1.7]; $P = .03$).[49] Mean change in IPSS at 3 months was 9.0 in the TIPD group and 6.6 in the SHAM group. This did not differ significantly between groups ($P = .06$) and the mean change in IPSS did not achieve the minimally importance difference of at least 3 points. There was a difference in the short-term mean change in the IPSS QoL score at 3 months with greater change in the TIPD group (MD 0.7 lower; 95%CI: 1.31 to 0.09).[49] The responder analysis (IPSS improvement of 7 or more points) was performed at 12 months and showed a responder rate of 72.6% compared to 50% in the SHAM arm ($P = .48$). Mean scores for the IIEF and the Sexual Health Inventory for Males (SHIM) did not differ significantly from the baseline at 3 months.[50] Mean peak flow rate at 3 and 12 months was significantly improved ($P < .0001$) from baseline in the TIPD group but was not reported for the SHAM group. There were few related serious adverse events but more overall adverse events within the first 30 days in the TIPD group than the SHAM group (38.1% versus 17.5%). Need for additional surgery or initiation of medication for BPH in the first 3 months was similar between groups.[49]

FUTURE DIRECTIONS

Recognizing the importance of equitable healthcare delivery, it is imperative to address the underrepresentation of diverse populations in research related to BPH. Therefore, the inclusion of diverse populations in BPH research studies should be encouraged, including individuals from different ethnic, racial, socioeconomic, and cultural backgrounds.

New Therapeutic Options

There have been 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 (eg, weekly, monthly). Moreover, many promising MISTs and surgical alternatives are in development, including prostatic stents, temporary implantable prostatic devices (TIPD), drug eluting catheters, balloon dilation devices, and transurethral prostatic split techniques to name a few. It is the hope of this Panel that further robust data will be available in the peer reviewed literature on these therapies to allow incorporation into future iterations of this guideline. To guarantee that newer technologies genuinely deliver enhanced improvements and outcomes for patients, it is crucial to maintain an ongoing benchmarking process that consistently compares new technologies to established technologies. 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.

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