AUA Guidelines

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Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I—Initial Work-up and Medical Management

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Abbreviations and Acronyms

5-ARI = 5-alpha reductase inhibitor
AUR = acute urinary retention
AUA = American Urological Association
BPE = benign prostatic enlargement
BPH = benign prostatic hyperplasia
BPO = benign prostatic obstruction
CT = computerized tomography
DO = detrusor overactivity
ED = erectile dysfunction
EF = erectile function
EjD = ejaculatory dysfunction
IFIS = intraoperative floppy iris syndrome
IPSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
LUTS/BPH = male lower urinary tract symptoms secondary/attributed to BPH
MRI = magnetic resonance imaging
PDE5 = phosphodiesterase-5
PDE5i = phosphodiesterase-5 inhibitor
PVR = post-void residual
PSA = prostate specific antigen
QoL = quality of life
TURP = transurethral resection of the prostate
TWOC = trial without catheter
UTI = urinary tract infection

Purpose: Benign prostatic hyperplasia (BPH) is a histologic diagnosis describing proliferation of smooth muscle and epithelial cells within the prostatic transition zone. The prevalence and severity of lower urinary tract symptoms (LUTS) in aging men are progressive and impact the health and welfare of society. This revised Guideline provides a useful reference on effective evidence-based management of male LUTS/BPH. See the accompanying algorithm for a summary of the procedures detailed in the Guideline (figures 1 and 2).

Materials and Methods: The Minnesota Evidence Review Team searched Ovid MEDLINE, Embase, Cochrane Library, and AHRQ databases to identify eligible English language studies published between January 2008 and April 2019, then updated through December 2020. Search terms included Medical Subject Headings (MeSH) and keywords for pharmacological therapies, drug classes, and terms related to LUTS or BPH. 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, information is provided as Clinical Principles and Expert Opinions (table 1).

Results: Nineteen guideline statements pertinent to evaluation, work-up, and medical management were developed. Appropriate levels of evidence and supporting text were created to direct both primary care and urologic providers towards streamlined and suitable practices.

Conclusions: The work up and medical management of BPH requires attention to individual patient characteristics, while also respecting common principles. Clinicians should adhere to recommendations and familiarize themselves with standards of BPH management.

Key Words: LUTS, BPH, alpha blocker, 5ARI, PDE5, IPSS, anticholinergic, beta 3 agonist, prostate

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Basic Management of LUTS in Men

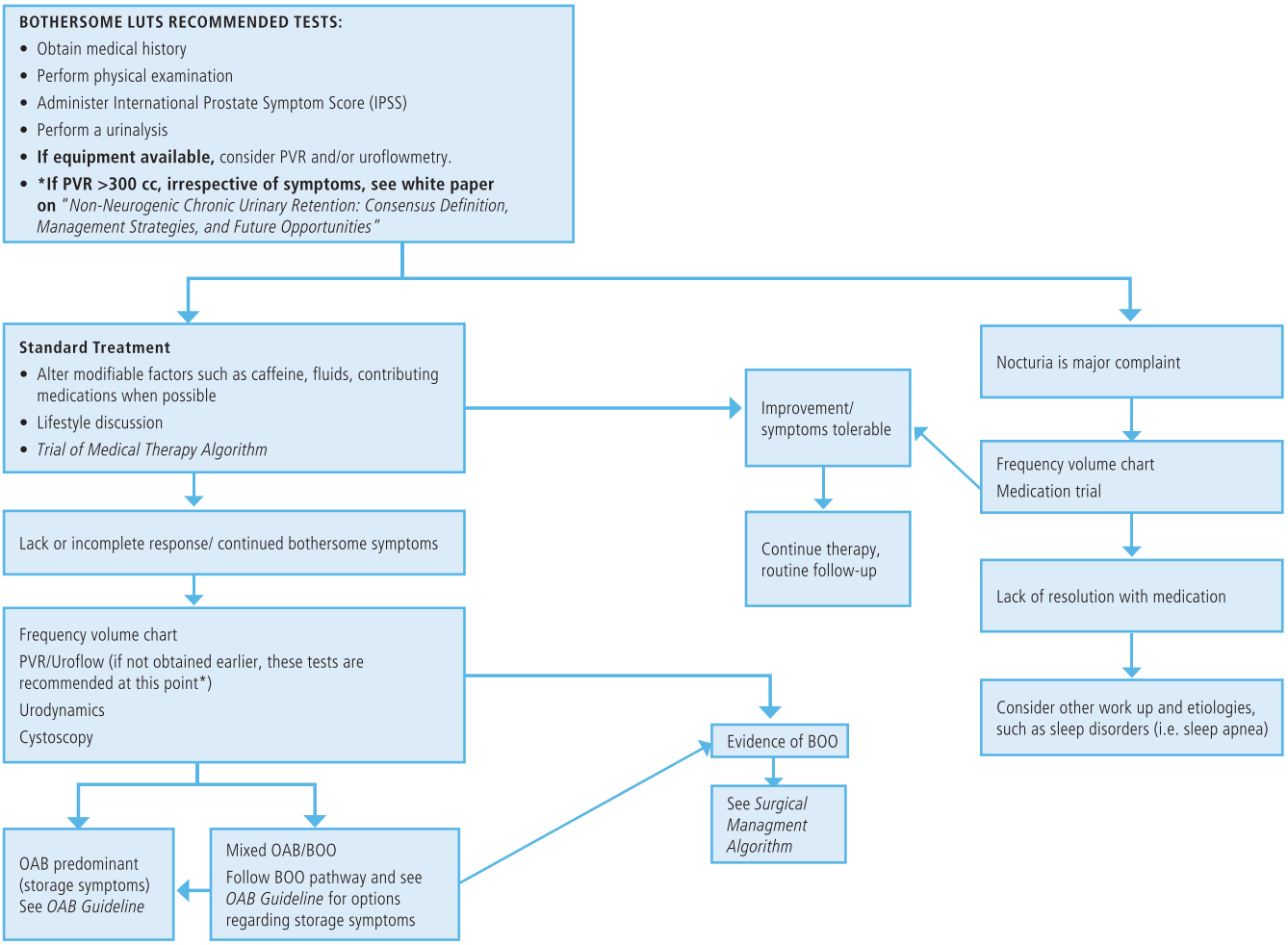

Figure 1. Basic Management of LUTS in Men Algorithm

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. BPH is likely a multifactorial process, the exact etiology of which is unknown, but requires testosterone. 5α-reductase (5AR), with its two isoenzymes - type I and type II, converts testosterone to its active metabolite, dihydrotestosterone (DHT). DHT, which has a higher affinity for the androgen receptor and is considered the more potent androgenic steroid hormone, forms a complex that is then transported to the nucleus.

The T/DHT-androgen receptor complex within the nucleus of the prostate cells initiates transcription of DNA and translation, with subsequent normal development, growth, and hyperplasia of the prostate. BPH develops due to an imbalance between growth and apoptosis (cellular death) in favor of growth, subsequently causing an increase in cellular mass.[1,2]

BPH is nearly ubiquitous in the aging male with increases starting at age 40-45 years, reaching 60% by age 60, and 80% by age 80. BPH can lead to benign prostatic enlargement (BPE), which can cause obstruction at the level of the bladder neck, termed benign prostatic obstruction (BPO).

Parallel to the development of BPH, lower urinary tract symptoms (LUTS) increase in frequency and severity with age and are divided into those associated with storage of urine, and/or voiding/emptying. Male LUTS may be caused by a variety of conditions, including BPE and BPO. BPE contributes to LUTS 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). In men, overactive bladder (OAB) storage symptoms may be the result of primary detrusor overactivity (DO), underactivity, or from obstruction induced by BPE and BPO.[3] It is important that healthcare providers recognize the complex dynamics of the bladder, bladder neck, prostate, and urethra.

BPH and LUTS in the aging male can be progressive, as seen in the Olmsted County Study. The prevalence of moderate-to-severe LUTS rose to

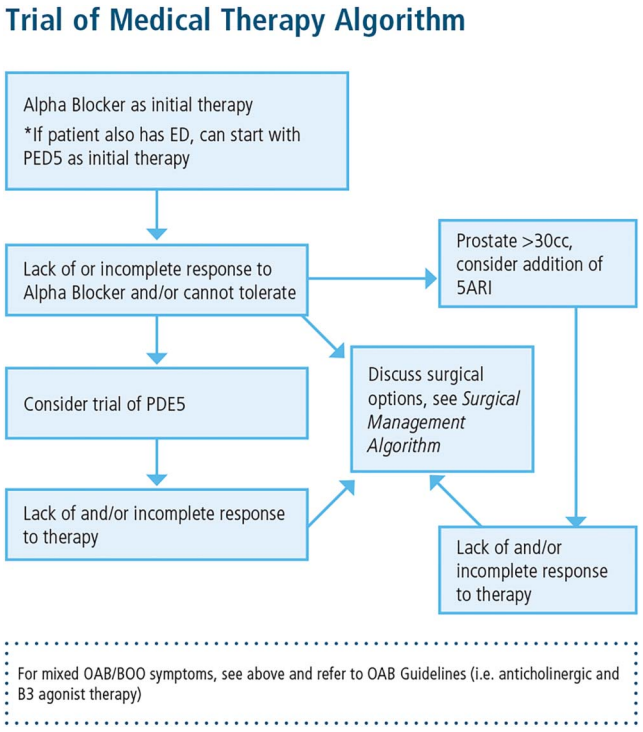

Figure 2. Trial of Medical Therapy Algorithm

nearly 50% by age 80, with the development of acute urinary retention (AUR) 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. Another study has estimated that 90% of men between 45 and 80 years of age suffer some type of LUTS. The most important motivations for men seeking treatment are severity and degree of bother associated with symptoms.[4] While LUTS/BPH is rarely life-threatening, the impact on QoL is significant and should not be underestimated.[5] The most prevalent and generally first line approach is behavioral and lifestyle modifications followed by medical therapy, including alpha-adrenergic antagonists (alpha blockers), 5-alpha reductase inhibitors (5ARIs), phosphodiesterase 5 selective inhibitors (PDE5s), anticholinergics, and beta-3 agonists - which may be utilized alone, or in combination to take advantage of their different mechanisms of action.

The following summary presents effective evidence-based supported recommendations for the initial work-up and medical management of male LUTS/BPH.

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)

Patients with bothersome LUTS may present to either primary care or urology. A complete medical history, including prior procedures that could explain presence of symptoms, sexual history, use of medications, overall fitness and health, IPSS and a urinalysis (attention to presence/absence of glucosuria, proteinuria, hematuria, and infection) should be performed.

Optional studies in initial management include post void residual (PVR) measurement and uroflowmetry. A PVR can help determine a baseline ability of the bladder to empty, identify severe urinary retention that may not be amenable to medical therapy, and/or indicate detrusor dysfunction. With no universally accepted definition of a clinically significant PVR, following a trend over time is suggested. Uroflowmetry is simple, risk-free, office-based, and can be an important adjunct. 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.[6] For more complex voiding scenarios with clinical uncertainty, urodynamics should be considered.

In general, first line management includes behavioral modification and/or medications. Advancing directly to a procedural intervention without trialing medications may also be discussed. Many supplements and nutraceuticals containing ingredients such as saw palmetto, Pygeum africanum, stinging nettle, zinc, selenium, and others are popular and have been marketed and studied.[7] Overall the results have been variable, as have study methods and quality, thus positive recommendations regarding their use are not warranted.

Shared decision making and understanding the patients' desires and risks for specific therapies can help guide treatment strategies.

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

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 Expert Opinion	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 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		

intolerable side effects should undergo further evaluation and consideration of change in medical management or surgical intervention. (Expert Opinion)

Recommendations for follow-up after initiating medical therapy remain undefined. Time intervals, tests to be conducted, and consequences of changes in parameters such as the IPSS, QoL score, flowrate recordings, or PVR have not been systematically studied in the literature. For faster onset drugs (alpha blockers, beta-3 agonists, PDE5s and anticholinergics), the first follow-up visit can be as early as four weeks. For longer onset drugs (5-ARIs), waiting 3-6 months is advised. At follow-up, important elements include adverse medication effects, IPSS, QoL, and when available, uroflowmetry/PVR. That said, there are no published thresholds for monitoring changes in PVR, Imax or IPSS/QOL to help guide therapy. Qmax changes after nonsurgical therapies may be subtle and not necessarily correlate with IPSS, but trends over time may encourage a change in treatment strategy. IPSS/QOL changes can be used to discuss patient expectations, perceived response, and goals of treatment. Increasing PVR may require additional investigations and/or a change in therapy. When medical management fails to address symptoms, or intolerable drug-related side effects occur, urologic referral for additional workup (eg, urodynamics, cystoscopy, prostate volume assessment) and/or alternate treatments is recommended (figure 3).

Preoperative Testing (Statements 5-9 are included and discussed in *Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART II — Surgical Evaluation and Treatment*)

Medical Therapy

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 (eg, ejaculatory dysfunction [EjD], changes in blood pressure). (Moderate Recommendation; Evidence Level: Grade A)

Multiple phase III randomized control trials, Phase IV studies, systematic reviews, and meta-analyses have demonstrated efficacy of alpha blockers for LUTS and BPH since the 1980's. They are all relatively equally effective in terms of IPSS

improvement, ranging from 4 -7 points as compared to placebo (2-4 points).[8] One of the most recent exhaustive network meta-analyses verifies this observation (table 2).[8] Attempts to identify subgroups of patients who may respond better to one alpha blocker or another have not shown differences in efficacy.[9] Given that medication type and patient characteristics do not impact effectiveness, it is not recommended to switch between various options for insufficient response.[10] However, changing from one alpha blocker to another on the basis of a side effect is worthwhile.

Terazosin and doxazosin are non-specific alpha-1 receptor blockers approved for hypertension, as well as BPH. Tamsulosin, alfuzosin, and silodosin have lower potential for orthostatic hypotension and syncope.[11-13] 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 (eg, the highly selective alpha 1a blocker silodosin).

Contrary to decreased hypotensive effects of the selective drugs, ejaculatory dysfunction (EjD), a long-understood side effect of alpha-blockers, is more common with activity at the alpha 1a (silodosin and tamsulosin) versus alpha 1b receptor. 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) or placebo.[14] 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 (alfuzosin).

Alpha Blockers and Intraoperative Floppy Iris Syndrome (IFIS).

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)

Urologists initiating alpha blocker therapy should inquire about plans for future cataract surgery and inform them of IFIS risk, with delay of medication initiation until after planned procedures. Fortunately, increased awareness of IFIS has resulted in a year by year decreased complication rate.[15]

5- Alpha 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,

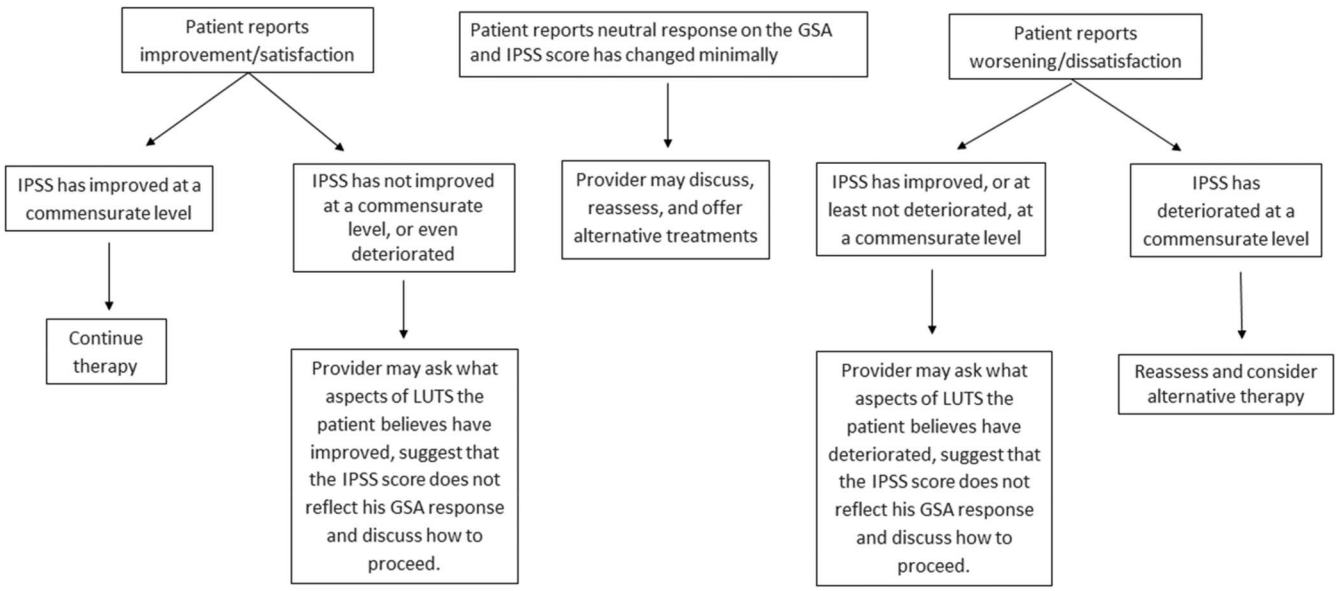

Figure 3. Algorithm for follow-up visits using IPSS and/or Global Subjective Assessment (GSA) question(s).

Table 2. *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.

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)

5-ARIs affect the influence of androgenic steroids on prostate growth via inhibition of 5AR, reducing DHT in the prostate. This leads to a reduction in androgenic growth and an increase in apoptosis and atrophy, shrinking the organ from 15-25% at six months. Atrophy is most pronounced in the glandular epithelial component of the prostate, the source of production and release of serum PSA, reducing levels by approximately 50% (and a concomitant decrease in free PSA by 50%, which means that the ratio of free/total PSA remains constant).[16,17] When providers are screening men for prostate cancer who are on 5-ARIs, patients should be informed of alterations in PSA due to the medication. After 1 year of 5-ARI therapy, the measured serum PSA value should be doubled to accurately gauge disease progression.[18]

Treatment with 5-ARIs and combination therapy hinges on prostate volume and PSA threshold therefore, obtaining imaging with TRUS (or reviewing existing cross-sectional imaging) to objectively assess prostate size is reasonable, with reservation of 5-ARIs for those with appropriately enlarged glands. A minimum prostate volume of >30cc or PSA >1.5ng/dL is necessary for a reliable 5-ARI response, but the larger the gland, the more pronounced the effects.[17]

Finasteride and dutasteride, the only approved medications, have two important pharmacological differences. Finasteride selectively inhibits the 5-AR type II isoenzyme, while dutasteride inhibits both types I and II. This difference in activity reduces serum levels of DHT by approximately 70% with finasteride, compared to 95% with dutasteride. However, in BPH tissue, type II 5AR is far more common than type I. Therefore, the reduction of DHT in prostate tissues has been measured at approximately 80% (finasteride) and 94% (dutasteride). Due to the slow onset of action of these medications as compared to alpha blockers, patients should be counseled on a slower symptom improvement if treated with 5-ARI alone.

Numerous robust analyses of randomized, placebo-controlled trials with finasteride have shown an improvement in standardized symptom scores (eg, IPSS) superior to placebo. Numerically, improvements of 3 to 4 points have been observed and maintained for 6 to 10 years of follow-up.[19,20] In the REDUCE trial, 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%; $p < 0.001$).[21] 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}.[22]

LUTS/BPH can have a progressive natural history that is more profound in men with larger glands and/or higher PSA values. The PLESS study suggested that 5-ARI therapy can be utilized in appropriately enlarged prostates as prevention for BPH as it alters the natural history thereof. Amongst men randomized to 5-ARI instead of alpha

blocker alone or placebo groups, a lower risk of AUR and BPH related surgery was seen.[23]

Gynecomastia and sexual side effects can occur with 5-ARI therapy. As part of MTOPS, investigators prospectively measured erectile and ejaculatory function, as well as libido, utilizing questionnaire data.[24] Declines in overall sexual function were more pronounced with finasteride. In addition, there has also been discussion regarding post-finasteride syndrome (PFS), a controversial and poorly-defined constellation of sexual, physical, and psychological symptoms that putatively persist after discontinuation of the drug.[25,26] 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.[27]

Finally, 5-ARI therapy and risk for prostate cancer has resulted in publication of numerous studies attempting to confirm or refute concerns. Sarkar et al.[28] used the Veterans Affairs Informatics and Computing Infrastructure and 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$\geq$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. 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). These patients 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. In a multivariable regression, patients who took 5-ARIs had higher prostate cancer-specific and all-cause mortality. The important outcome of this study was the delayed diagnosis, presumably related to lack of awareness and/or correction of PSA values (doubling of the PSA value), and worse cancer-specific outcomes.

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)

The majority of studies that address the impact of PDE5s on LUTS/BPH used tadalafil. The mechanism of action of this PDE5 effect is only partially understood. Ten key reports from 10 trials compared tadalafil 5 mg to placebo (n=5,129).[29-38] The mean change in tadalafil (-5.4 points) compared to controls (-3.6 points) was -1.74 (figure 4). Tadalafil resulted in little to no difference in IPSS as compared to placebo. However, the percentage of treatment responders, defined as $\geq$3 points change, showed a relative effect (1.13 to 1.80), suggesting that tadalafil probably increases response to the IPSS compared to placebo. Tadalafil is a reasonable option to trial in selected men, ideally those with concomitant erectile dysfunction.

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)

Combination therapy is a common approach to symptomatic LUTS, working on the premise that each medication targets a different site in the lower urinary tract. Together, they presumably maximize symptom control. Standard combinations include alpha blockers + 5-ARI; alpha-blocker + anticholinergic/antimuscarinic therapy, or alpha blockers + beta-3-agonists.

Two large studies evaluated alpha blocker and 5ARI combinations: Medical Therapy of Prostatic Symptoms (MTOPS) and Combination of Avodart and Tamsulosin (CombAT). Both studies showed statistically significant reductions in parameters of clinical progression with combination approaches over monotherapy.

MTOPS enrolled over 3,000 men with at or below average sized prostates and randomized them to placebo versus doxazosin versus finasteride versus

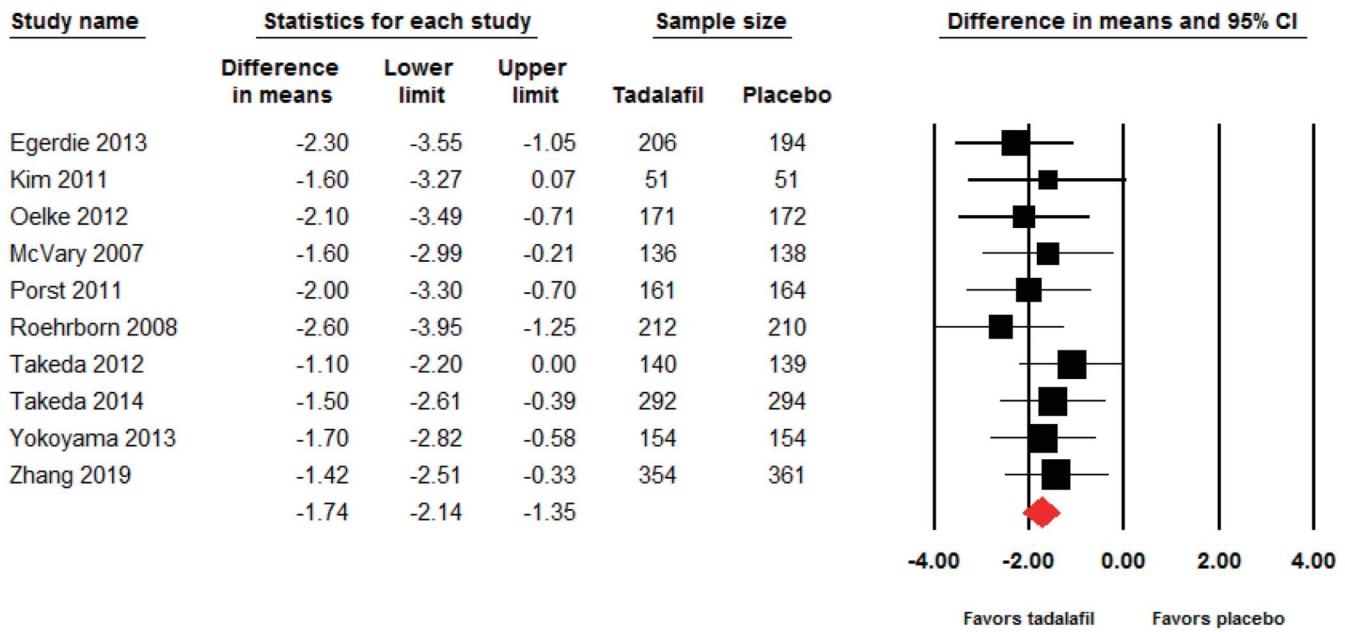

Figure 4. Mean Change from Baseline in IPSS in 10 RCTs

combination of doxazosin + finasteride. Men were treated and followed for up to 5.5 years. The risk of overall clinical progression, defined as an increase above baseline of at least 4 points in the IPSS, AUR, urinary incontinence, renal insufficiency, or recurrent UTI, was significantly greater with combination therapy than that associated with doxazosin or finasteride alone. The risks of AUR and need for invasive therapy were significantly reduced by combination therapy and finasteride, but not by doxazosin. Symptom and flow rate improvement were superior in the combination therapy arm compared to both monotherapies.

CombAT enrolled men with prostate volumes >30 mL by TRUS and PSA >1.5 ng/mL.[39] Q_{max} improvement was seen in combination therapy compared to placebo, but not dutasteride monotherapy. At 4 years, Q_{max} improvements were more profound with increasing prostate volume and PSA levels in combination subjects. Not surprisingly, however, these patients had more drug related adverse events over monotherapies.

Although the exact cause may be varied, both storage LUTS and OAB have similar symptoms, prompting use of anticholinergic, antimuscarinic, and beta-3-agonists therapy to help alleviate bother. A safety trial was conducted in patients with urodynamically-proven obstruction and overactivity, 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 no urinary retention in the treatment group.[40] Other studies have confirmed similar findings and as such, use in appropriately selected patients is reasonable. That said, a PVR should be obtained pre-treatment and monitored at follow-up.

Combination therapy with alpha blockers and anticholinergics makes intuitive sense in selected patients with storage predominant LUTS/BPH. Numerous studies of at least 5 anticholinergics have been conducted, but largely with short durations (ie 12 week endpoints). IPSS improvement in combination arms compared to alpha blockers alone is variable, making it challenging to derive conclusions regarding efficacy. With the increase of drug related adverse events, a reasonable approach is to start with alpha blockers alone and add anticholinergics in selected cases.

Unlike anticholinergic agents, monotherapy with a beta-3-agonist has, thus far, not been shown to lead to significant differences in LUTS secondary to BPH. While not yet extensively studied, combination therapy with an alpha blocker, however, may lead to improvement in symptoms similar to those seen with anticholinergics.

Finally, the combination of low-dose daily tadalafil with alpha blockers has not been shown to offer greater symptom improvement over alpha blockers

or low-dose daily tadalafil, alone. Therefore, this combination is not recommended, particularly given the higher side effect risk.

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).

Numerous clinical trials have investigated pharmacologic treatment of AUR in men.[41-49] The studies differ by definition of AUR (500- 1,500 mL), inclusion criteria, treatment length, and follow-up (1 day to 24 months). Men prescribed alfuzosin or tamsulosin 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 with alfuzosin compared to placebo, 60% versus 39%. The tamsulosin studies had similar follow-up limitations (5 days to 6 months) but similar efficacy (47% versus 29% for placebo).

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

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 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.

Areas of particular interest that could further define aspects of BPH/LUTS include, but are not limited to, the following:

- Investigating disease etiology using computational biology and genomic factors to understand drivers of BPH and prostate growth and target therapeutic agents.
- Further defining differentially bothersome LUTS and using enhanced metrics that include bother, pain, and incontinence.
- Addressing healthcare disparities and cultural competency to better deliver care across all members of society irrespective of race, ethnicity, socioeconomic and health status, and environment.
- The most prevalent and bothersome symptom of LUTS is nocturia, which is a unique symptom complex requiring special concern and judicious evaluation, including the role of sleep apnea. Nocturia is associated with increases in overall mortality and a lack of effective management options merits deeper understanding and investigation with more funded research.
- Determining predictive ability of various urodynamic measures, with the subsequent clinical and economic consequences of the findings, to impact overall outcomes and financial burden.
- Using imaging and tests to identify morphological aspects such as bladder wall thickness, trabeculation, prostatic urethral angle, and intravesical prostatic protrusion to learn how they affect natural history, treatment response, and treatment options.
- Creating studies that compare efficacy of behavioral and lifestyle intervention versus medication, and medication versus minimally invasive therapies, to determine ideal approaches and timing for individual patients.
- Development of registries and analysis of electronic medical records and insurance databases to better improve our understanding of the burden and cost of BPH/LUTS and identify areas for improvement and study.
- Development of a calculator with patient parameters to obtain a treatment algorithm, or set of appropriate options, to streamline and define care.

In summary, BPH and LUTS are rich with opportunities for research and development for those seeking to improve the lives of generations of men.

DISCLAIMER

This document was written by the Benign Prostatic Hyperplasia Panel of the American Urological Association Education and Research, Inc., which was created in 2016. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology and primary care with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis based or

consensus-based, depending on panel processes and available data, for optimal clinical practices in the treatment of early stage testicular cancer. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA, and the Panel Chair, with the support of AUA Guidelines staff and the PGC, reviews all disclosures and addresses any potential conflicts per AUA's Principles, Policies and Procedures for Managing Conflicts of Interest. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic– and non-topic-related relationships. Consultant/Advisor: Michael J. Barry, MD: US Preventive Services Task Force; Anurag Kumar Das, MD: Teledoc; Tobias S. Kohler, MD: Coloplast, American Medical Systems; Kevin T. McVary, MD: Merck, Olympus; Claus G. Roehrborn, MD: Glaxo Smith Kline, Neotract, Procept Biorobotics, Boston Scientific, ZenFlow, Teleflex; Charles Welliver, MD: Medscape. Scientific Study or Trial: Michael J. Barry, MD: Healthwise; Steven A. Kaplan, MD: Urotronics; Kevin T. McVary, MD: NIDDK, NxThera, Olympus, MedeonBio, Urotronic, Francis Medical; John T. Stoffel, MD: Department of Defense. Leadership Position: Anurag Kumar Das, MD: Indian American Urological Association; Kevin T. McVary, MD: UroNext; John T. Stoffel, MD: Journal of Urology, Neurogenic Bladder Research Group. Health Publishing: Kevin T. McVary, MD: SRS Medical Systems; Claus G. Roehrborn, MD: NIDDK; Charles Welliver, MD: Oakstone Publishing. Other: Anurag Kumar Das, MD: Novartis, Sanofi-Aventis, Astellas, Johnson and Johnson, Novo Nordisk, Schwabcare; Charles Welliver, MD: ALX Oncology

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