REVIEW

CME MOC

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Medical management of benign prostatic hyperplasia

ABSTRACT

Medical management of benign prostatic hyperplasia (BPH) has progressed gradually in recent years and remains the starting point for most symptomatic patients seeking treatment. Beyond well-known alpha-blockers and 5-alpha reductase inhibitors, there is growing evidence for the use of phosphodiesterase-5 inhibitors and beta-3 agonists in managing the condition, which may afford additional relief of "bothersome" symptoms in some patients. This review details contemporary medical management of BPH with an emphasis on the indications for certain classes of pharmacotherapy and their relative benefits and side effects. Surgical and procedural treatment of BPH is covered in a separate review.

KEY POINTS

- Medical management of BPH remains the starting point for most symptomatic patients seeking care.
- Treatment with phosphodiesterase-5 inhibitors helps maintain ejaculatory function and may provide additional relief of irritative symptoms, including urgency and frequency, compared with alpha-blockers and 5-alpha reductase inhibitors.
- The effectiveness of over-the-counter agents and herbal and natural supplements remains poorly characterized, and research on new pharmacologic agents like beta-3 agonists is ongoing.

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Benign prostatic hyperplasia (BPH), also known as benign prostate enlargement or obstruction, is a histologic diagnosis that describes the proliferation of glandular epithelial tissue and smooth muscle within the transition zone of the prostate.[1,2] The prostate gland has both intrinsic and extrinsic factors that likely play complex roles in its growth. These include the interaction between the stroma and epithelium, hormone and androgen exposure (specifically testosterone and, more importantly, dihydrotestosterone), dietary factors, micro-organisms, and genetic predisposition.[1,2]

Although the exact mechanism for the development of BPH is unknown, age-related changes causing metabolic disturbances, changes in hormone balance, and chronic inflammation appear to contribute.[3] Despite diminishing levels of testosterone as patients grow older, the amount of circulating dihydrotestosterone and prostatic androgen receptors remains high.[2] The average prostate is approximately 20 cc between the ages of 21 and 30. BPH can begin to develop in the early 40s in some men and is found in 50% of men ages 51 to 60.[3,4] The prevalence of BPH increases steadily with age, reaching 60% at age 60 and 80% at age 80.[5] An enlarged prostate gland, while not in itself pathologic, can result in lower urinary tract symptoms, either by directly obstructing the bladder outlet as enlargement changes the shape of the gland, or by increasing smooth muscle tone and resistance to flow within the enlarged gland.[2]

Lower urinary tract symptoms associated with BPH are characterized as disturbances in retention of urine, voiding, and postmicturition state.

These symptoms provide insight into the impact of BPH on patient quality of life.[6,7] The International Prostate Symptom Score is a validated 8-point questionnaire that numerically characterizes patient symptoms.[8–10] Three questions pertain to storage symptoms (frequency, nocturia, urgency), and 4 pertain to voiding (feelings of incomplete emptying, weak stream, intermittency, straining). The final question assesses self-reported impact of symptoms on patient quality of life.

The goal of treatment for lower urinary tract symptoms associated with BPH has long been to maximize quality of life and minimize "bothersome" symptoms. More recently, focus on preventing side effects or treatment complications has been growing. This review outlines the most common medical treatments for lower urinary tract symptoms associated with benign prostatic hyperplasia.

DIAGNOSTIC EVALUATION

Patients with bothersome lower urinary tract symptoms often first present to primary care for evaluation. It is recommended to obtain a detailed and complete medical history, including an assessment of fluid intake (volume and type), voiding patterns, and bowel habits, as well as prior surgical history, prostate-specific antigen (PSA), and International Prostate Symptom Score.[5,7] Additionally, evaluation of patient sexual history, medications (including supplements and complementary therapies), mental health, and physical activity levels can be helpful. A urinalysis should be obtained to rule out alternate causes for the lower urinary tract symptoms, focusing on the presence or absence of glucose, protein, inflammation, or blood (microhematuria: ≥ 3 red blood cells per high-power field on microscopic evaluation of a single specimen).[5,11]

CONSERVATIVE MANAGEMENT

Patients with symptoms considered mild by the International Prostate Symptom Score (0–7) can potentially opt for lifestyle modifications, depending on how bothersome their symptoms are.[5,7] Common lifestyle changes include losing weight, decreasing evening fluid intake, and decreasing total daily fluid intake or the quantity of substances with bladder-irritating or diuretic properties such as caffeinated beverages (coffee, tea, energy drinks, cola), sugary beverages (soft drinks, juices), alcoholic beverages, and fluids containing artificial sweeteners, artificial colorings, or artificial flavorings (often these substances exert diuretic and bladder-irritating effects).[7,12] Patients should also be advised to work on bladder management, if needed, including timed voiding (every 2–3 hours) and double-voiding. Doing pelvic floor stretches or relaxation exercises—not strengthening or Kegel exercises—and maintaining a regular bowel regimen to avoid constipation can also be quite impactful.[7,12]

Some men will experience spontaneous improvement in symptoms over time, without therapy.[12] The degree of changes in symptoms can vary, and monitoring and following these patients over time is important to avoid missing worsening symptoms.

For patients with moderate to severe lower urinary tract symptoms at baseline or symptoms refractory to conservative management, initiation of medical therapy and consideration of procedural treatment are options.[12] Medical therapy for BPH with lower urinary tract symptoms should be initiated after evaluation of the potential benefits and side effects of specific medications.

PHARMACOTHERAPY

Alpha-blockers

Alpha-blockers are a class of drugs first introduced in the late 1980s and early 1990s. They work by antagonizing alpha-1 receptors in the bladder neck and prostate, which results in the relaxation of smooth muscle in these areas,[12–17] and in turn, reduced constriction of the urinary channel and lower resistance to urinary flow.[14] Despite a plethora of medications within this class, all are relatively equally effective, with an expected International Prostate Symptom Score improvement from baseline of 3.7 to 7.1 points.[13]

The 5 main alpha-blocker medications include second-generation drugs (terazosin, doxazosin) and third-generation drugs (tamsulosin, alfuzosin, silodosin). The third-generation drugs are generally well tolerated, and tamsulosin is associated with fewer side effects.[12] The second-generation alpha-blocker medications require dose titration owing to their antihypertensive effects.[12]

The therapeutic effect of alpha-blockers starts within hours to days, although it generally takes 3 to 7 days to reach maximum effect.[13–15,18] Common side effects include lightheadedness, dizziness, headache, nasal congestion, erectile dysfunction, and ejaculatory dysfunction or anejaculation (formerly known as retrograde ejaculation). These side effects usually accompany the therapeutic effect of the medication, are generally dose-dependent, and resolve within a few days with medication discontinuation. Ejaculatory dysfunction results from relaxation of the smooth muscle within the prostatic and ejaculatory ducts with alpha

blockade.[19] This can be very distressing and bothersome for some and a relevant clinical concern for men who may want to father a child, as they may be unable to do so while using alpha-blockers.

Given similar efficacy across different alpha-blockers, it is generally not recommended to switch medications if a patient does not obtain a sufficient therapeutic response with the first drug. However, changing alpha-blockers to reduce side effects can be helpful.[20] Changing from a second- to a third-generation alpha-blocker can be beneficial to avoid orthostatic symptoms and hypotension. Changing among third-generation alpha-blockers can be beneficial owing to differences among these medications in the degree of sinus pressure, nasal congestion, or ejaculatory changes patients may experience when taking them. Anecdotally, there seems to be no identifiable pattern across medications regarding nasal symptoms, but many urologists favor alfuzosin to reduce ejaculatory symptoms.[15,18,20] The dose of many alpha-blockers can be titrated up to provide additional therapeutic benefit, but often at the risk of greater side effects that warrant close follow-up.

Patients taking alpha-blockers, specifically tamsulosin, who plan to undergo cataract surgery should be informed of the possible associated risk of intraoperative floppy iris syndrome. It is thought to occur due to local smooth muscle inhibition resulting in iris prolapse at the incision site during phacoemulsification in cataract surgery.[14,15,21] This risk should be discussed with patients when initiating alpha-blocker therapy. Fortunately, increased awareness of and communication about this syndrome have resulted in a decreased rate of complications in persons taking tamsulosin who undergo cataract surgery.[14]

5-alpha reductase inhibitors

Androgens are essential to prostatic growth.[16] The conversion of testosterone to dihydrotestosterone, a more potent ligand for the androgen receptor and arbiter of prostatic growth, is central to this process.[14–17,22] Inhibiting the conversion of testosterone to dihydrotestosterone with 5-alpha reductase inhibitors (5ARIs) can reduce prostate growth and tip the scales toward prostatic cellular apoptosis and atrophy. Atrophy is more pronounced in the glandular epithelium of the prostate where PSA is made, as opposed to the smooth muscle stromal component of the gland.[23] Thus, gland composition (more glandular vs more stromal) may impact medication efficacy. The impact of 5ARIs on the glandular cells results in a decrease in PSA of approximately 50% after 6 to 12 months of treatment.[16,22,23] Therefore, because PSA is a key predictor of treatment outcome, measurement of baseline PSA is recommended for all patients considering 5ARI therapy.

Owing to their mechanism of action and effect on gland size, 5ARIs should be reserved for patients with BPH and lower urinary tract symptoms who have prostate glands 30 cc or larger or palpable prostatic enlargement on digital rectal examination.[16,23] Finasteride and dutasteride are the most commonly used 5ARIs.[16,22,23] Finasteride inhibits the 5AR type II isoenzyme, while dutasteride inhibits type I and II isoenzymes.[22] Because type II 5AR is more commonly found in prostate tissue, the clinical effect of these medications does not differ. Notably, 5ARIs require about 3 months of use before noticeable improvements in urinary symptoms occur, and approximately 6 months to reach full effect in terms of prostate volume reduction.[16,22,23] It is critically important to explain to patients the expected time frame to ensure medication adherence.

5ARIs for prostate cancer prevention have been studied for some time, with the evidence showing these medications reduce overall prostate cancer rates, particularly low-grade cancers. This is likely because finasteride reduces prostate volume, resulting in improved detection of cancer on prostate biopsy, and because of its selective inhibition of low-grade cancers.[16,22] There is a black box warning regarding 5ARIs because they were thought to potentially increase the risk for higher-grade prostate cancers, but were later determined to be helpful in the process of detecting these cancers.[5,16,22] These medications are regularly used and thought to be safe.

Side effects of 5ARIs vary widely across research studies, but include bothersome symptoms related to testosterone deficiency including erectile dysfunction, ejaculatory dysfunction (reduced semen volume and thinned semen consistency), decreased libido, and possible fertility implications.[5,24] Although a causal link between 5ARIs and infertility has yet to be elucidated, 5-alpha reductase is physiologically active in human testes, with dihydrotestosterone promoting expression of tight junction protein in Sertoli cells.[24] Disruption of this process halts spermatogenesis.

Two prospective randomized controlled trials that compared 5ARIs (dutasteride, finasteride) with placebo found statistically significant ($P < .001$; $P < .005$) reductions in total sperm counts at 24 weeks, but not after 52 weeks, as well as mild sexual dysfunction.[24–26] Because both trials studied healthy male populations (excluding patients with prior infertility), the impact on men with preexisting subfertility remains unknown. Beyond these findings, patients should also be informed

of a small risk of gynecomastia and breast tenderness with 5ARI use.[5] Finally, there are limited data in the recent literature suggesting a possible increased rate of depression in men using 5ARIs.[24] Further study is needed to elucidate the mechanism behind these effects, as much of the data come from treatment with 5ARIs for androgenic alopecia where lower daily dosing of finasteride combats hair loss, making the results regarding depression unclear.[24]

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 (PDE5) inhibitors increase intracellular cyclic guanosine monophosphate, causing nitric oxide-mediated relaxation of smooth muscle throughout the prostate, detrusor muscle (bladder), and urethra.[27] It is thought that this is the beneficial mechanism of action of PDE5 inhibitors on patients with BPH and lower urinary tract symptoms. Tadalafil is the most-studied PDE5 inhibitor for patients with BPH and lower urinary tract symptoms, with an average improvement in International Prostate Symptom Score of 3 or more. Onset of effect is variable but usually within hours. Importantly, avanafil has the shortest onset of action (15–20 minutes) in this class but is not widely used for treatment of BPH.[5,28]

PDE5 inhibitors are not titrated up or down in dose. They offer an alternative therapy for patients who cannot tolerate or prefer not to use alpha-blockers or 5ARIs.[27] Additionally, a decrease in lower urinary tract symptoms, including overactive bladder symptoms such as urinary urgency and frequency, has been noted in patients taking PDE5 inhibitors.[14] Once rather expensive, many of these medications are now available generically at low prices, can be purchased without insurance through self-pay, and are available at smaller, local pharmacies.[29]

While the low daily dose of PDE5 inhibitors for BPH (such as US Food and Drug Administration-approved and guideline-based tadalafil 5 mg) can aid urinary symptoms, the benefit of such doses for erectile dysfunction is rather negligible.[14] However, some patients report improvement in erectile dysfunction.[30,31] For those without improvement, on-demand booster doses of PDE5 inhibitors can be administered with the low daily dose, although questions around precise timing, adjustments to daily dosing, and skipping of doses are debated and robust data for guidance are lacking. However, in general, the usual dose for medical management of erectile dysfunction can be administered in advance of sexual activity, as needed, for therapeutic effect and as tolerated according to side effects.

Side effects of PDE5 inhibitors include facial flushing, headache, back pain, dyspepsia, and the potential for blue-tinted vision; however, most of these side effects are minimal or absent at low daily doses for BPH. Well-known contraindications to PDE5 inhibitors include the use of nitrates.[5,14]

Beta-3 agonists and anticholinergics

Beta-3 agonists, including mirabegron and vibegron, work via the sympathetic pathway to cause relaxation of the detrusor muscle and increase bladder capacity.[5,14] They are indicated for patients with overactive bladder and can benefit patients with predominantly irritative lower urinary tract symptoms, including urgency, frequency, and incontinence. Onset of maximum effect is generally at around 3 weeks, an important factor to discuss with patients. While vibegron is only available in 1 dose, mirabegron is available in multiple doses and seems to provide similar therapeutic benefit.[32] Emerging research suggests this class of drugs may also benefit patients with BPH, but this remains an area of active investigation.[33]

Historically and prior to beta-3 agonist development, anticholinergic medications were used to treat bothersome symptoms. Currently, they are widely available, and many are generic. However, anticholinergic medications are associated with cognitive impairment and dementia, in addition to the well-known side effects of mental fogginess or confusion.[14] Studies have shown that trospium, a larger quaternary amine molecule, does not cross the blood-brain barrier and may be a safer option.[32]

However, all anticholinergics have undesired side effects, including dry mouth, dry eyes, constipation, and potential vision changes.[14] Anticholinergics exert therapeutic effect within hours to days, although this can vary between short- and long-acting formulations, as well as different doses (as anticholinergics can be titrated up for efficacy). Long-acting formulations tend to have less bothersome side effects, as these agents do not achieve the high peak serum levels responsible for unwanted effects.[5,14]

In contrast, beta-3 agonists have very favorable side-effect profiles and little to no risk for those with dementia or cognitive impairment.[32–34] The most common side effect of mirabegron is hypertension. Due to the risk for drug-drug interaction, concomitant use in patients on metoprolol must be done cautiously.[35] Overall, both mirabegron and vibegron are contraindicated in patients with poorly controlled hypertension, although vibegron has been found clinically to pose a negligible risk of blood pressure change. As a relatively

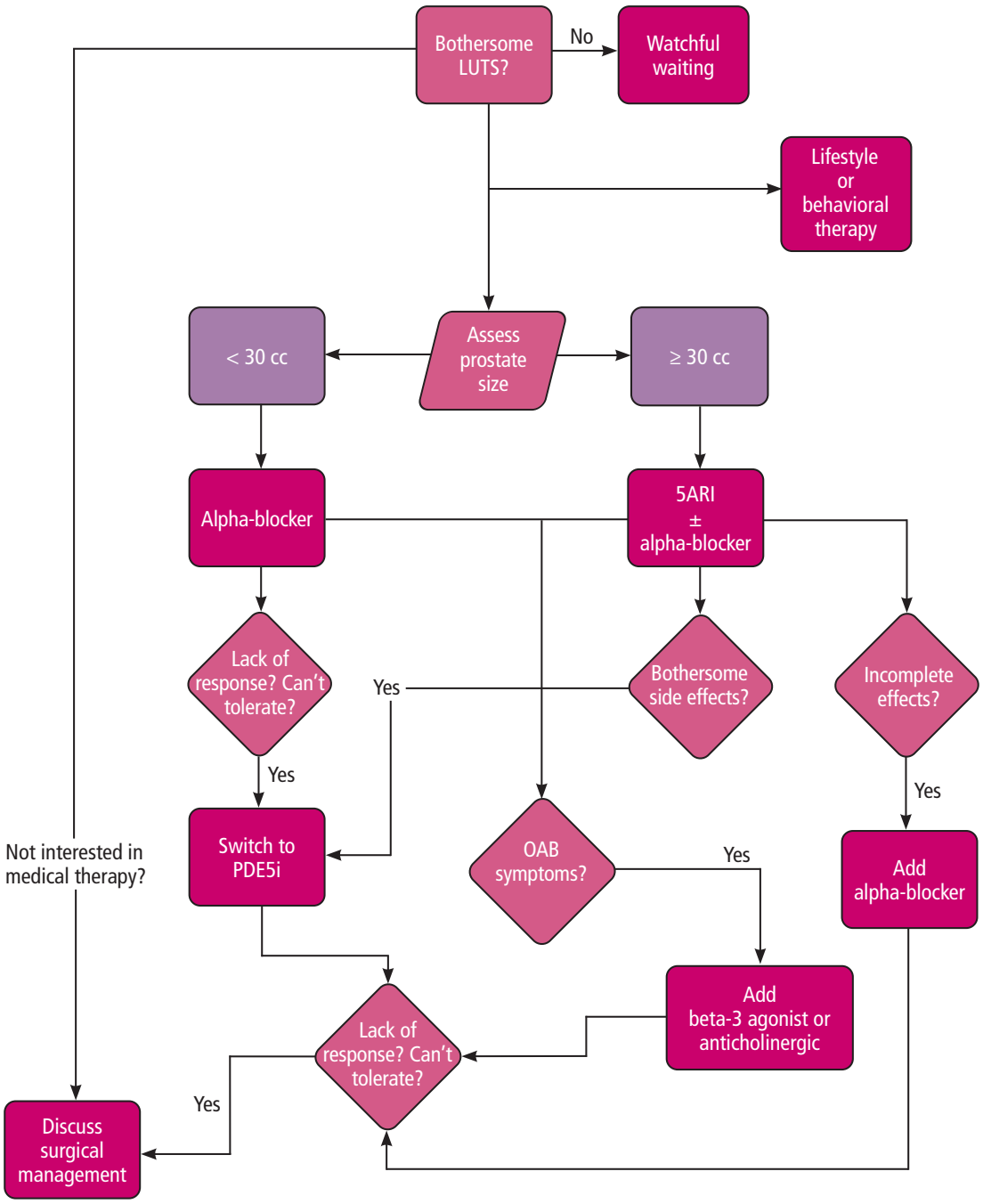

Figure 1. Algorithmic approach to medical management of benign prostatic hyperplasia.

5ARI = 5-alpha reductase inhibitors; LUTS = lower urinary tract symptoms; OAB = overactive bladder; PDE5i = phosphodiesterase-5 inhibitor

Adapted from the American Urological Association guidelines.[7]

newer therapeutic class, much remains to be learned about beta-3 agonists, but the initial clinical experience with them has been promising.[32–34] Additionally, beta-3 agonists can be combined with anticholinergics for the treatment of severe overactive bladder, as both agents target the bladder through 2 separate and synergistic molecular pathways.[5]

Combination therapy

Combination pharmacotherapy has been shown to be more effective than monotherapy or placebo, specifically in patients with larger prostates who meet criteria for 5ARIs and can be offered alpha-blockers simultaneously.[15,17,36] This follows findings from the 2003 MTOPS (Medical Therapy of Prostatic Symptoms) study of combination doxazosin and finasteride vs monotherapy or placebo that demonstrated decreased rates of symptom progression, urinary retention, and invasive BPH surgery or procedures with combination therapy.[15,37] Similarly, the 2010 CombAT (Combination of Avodart and Tamsulosin) trial found significant reduction in the relative risk of primary end points of acute urinary retention or prostatic hyperplasia-related surgery with combined tamsulosin and dutasteride compared with monotherapy ($P < .001$).[36] There is growing evidence that daily tadalafil and finasteride combination is also helpful, with the added benefit of avoiding alpha-blocker side effects.[13,38]

Historically, anticholinergic agents were offered in combination with an alpha-blocker for patients experiencing predominantly irritative lower urinary tract symptoms. However, studies have demonstrated variable improvements in the International Prostate Symptom Score for this combination compared with monotherapy.[5] As a result, and considering potential cognitive effects of anticholinergics, this warrants careful consideration. However, in this same population, combining alpha-blockers with beta-3 agonists presents a safer and well-tolerated alternative to improve symptoms with fewer side effects.[5] Lastly, while many drug interaction systems may warn against concomitant use of PDE5 inhibitors and alpha-blockers, this combination remains an option for some, albeit with close monitoring as it can lead to symptomatic orthostatic hypotension.[17,27]

MEDICINAL PLANTS

Medicinal plants and natural products derived from plants are becoming more common for treatment of BPH with lower urinary tract symptoms.[34,39,40] Knowing the common medicinal plants targeted for patients with lower urinary tract symptoms from BPH and how to counsel regarding them are essential. Pumpkin seed (*Cucurbita pepo*) or its extract is popular and contains a variety of biologically active compounds thought to inhibit 5-alpha reductase and decrease levels of circulating dihydrotestosterone.[22] However, pumpkin can cause gastrointestinal symptoms such as indigestion and diarrhea. Another common supplement is the fruit extract of the saw palmetto plant (*Serenoa repens*), which is sold over the counter. Postulated mechanisms of action for *Serenoa repens* include 5-alpha reductase inhibition and inhibition of dihydrotestosterone binding to androgen receptors.[22,24,25] However, there have been mixed results regarding the exact mechanism of action of each of these supplements, and the results vary further based on method of extraction and formulation.

Patients should be informed that many studies on supplements, nutraceuticals, and herbal preparations are limited by a lack of peer review, comparison with placebo control, and assessment using conventional end points.[5] The 2 independently conducted, placebo-controlled trials using specific extracts of saw palmetto found no benefit over placebo across multiple measurable parameters relevant to BPH and lower urinary tract symptoms.[41,42]

Additionally, as regulation and quality control of natural products derived from plants are not as stringent as those of the pharmaceutical industry, it is important to educate patients that the composition of certain supplements varies not only between retailers, but also between batches of supplements made by an individual manufacturer.[34] As a result, their effect, if any, can vary widely and be unpredictable. Additionally, manufacturers of natural products derived from plants often post claims regarding efficacy and effects that are not regulated or endorsed by the US Food and Drug Administration.

CONCLUSION

Several options exist for medical management of BPH, and choices are affected by indication, effectiveness, and side effects (**Figure 1**).[7] Research continues regarding newer agents and natural products derived from plants. While medication is a therapeutic option, it can provide diagnostic insight into the potential benefit of a procedure or surgery for patients with BPH. Furthermore, contemporary clinical management of BPH includes the consideration of surgeries or procedures as viable first-line options for properly selected, treatment-naïve patients, especially with the growing number of newer minimally invasive procedures with favorable side effects.

In line with this, some patients may wish to avoid the side effects of medications, taking a daily pill, or the cost burden of lifelong pharmacotherapy. Others may experience disease progression in spite of medical treatment. Beyond these reasons, as well as medication intolerance or allergy, the American Urological Association guidelines list the following indications for patients with BPH to undergo procedures or surgeries: urinary retention, recurrent urinary tract infections, bladder stones, obstructive uropathy, and prostate-related hematuria.[5] However, as noted earlier, contemporary approaches to management of BPH emphasize patient preference as a major factor for determining whether to pursue medical, procedural, or surgical treatment. The growing list of surgical and procedural treatment options for BPH is covered in another review.[43]

DISCLOSURES

Dr. Gill has disclosed consulting, work as advisor or review panel participant, and research as a co-investigator or site lead for Boston Scientific and Urovant Sciences. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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