



REVIEW ARTICLE

Benign Prostatic Hyperplasia: Personalizing Medical Management

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Abstract

Benign prostatic hyperplasia (BPH) is a prevalent condition among elderly men, impacting their quality of life. Traditional treatments primarily targeted bladder outlet obstruction (BOO) through alpha-blockers and 5-alpha reductase inhibitors. Recent additions, such as muscarinic receptor antagonists and phosphodiesterase-5 inhibitor (PDE-5i) tadalafil, provide more options. The 2021 American Urological Association (AUA) guidelines emphasize individualized management. Assessment involves physical exams, medical history, and tools like the International Prostate Symptom Score (IPSS), BPH Impact Index, prostate-specific antigen (PSA), and post-void residual (PVR) volume. This review provides primary care physicians with insights into assessing and tailoring BPH management, ensuring individualized care for patients with varying symptom presentations and comorbidities.

Keywords

BPH, LUTS, BOO

Introduction

Benign prostatic hyperplasia is a common disorder of elderly men that can significantly impact quality of life [1,2]. Per the Baltimore Longitudinal Study [3], 60% of male participants had clinically relevant BPH by age 60 and that figure increased by approximately 10% for each additional decade of life. Until recently, much of the associated lower urinary tract symptoms (LUTS) were attributed to bladder outlet obstruction (BOO) secondary to an enlarged gland. The mainstay of therapy has therefore been to relieve that

obstruction either through the use of alpha blocking agents (alfuzosin, tamsulosin, silodosin, doxazosin, terazosin) for immediate relief of symptoms or using 5-alpha reductase inhibitors (5-ARIs, finasteride and dutasteride) to reduce prostate size or a combination of agents from both classes [4-6]. 2010 guidelines by the American Urological Association (AUA) added the use of the muscarinic receptor antagonists (tolterodine, oxybutynin, solifenacin, fesoterodine, darifenacin, trospium) in patients with high post-void residual volumes [7]. Not included in these guidelines is the use of the phosphodiesterase-5 inhibitor (PDE-5i), tadalafil, which has more recently been approved for treatment of LUTS and BPH. 2021 AUA guidelines call for an individualized management approach to the treatment of BPH [8]. The purpose of this paper is to describe when and how the drug therapy management of BPH can be personalized to address individual patient's symptom presentation and comorbid conditions by the Family Physician.

Assessment

The assessment of BPH will include the physical exam, a careful medical history and a survey of the patient's recollection of symptoms. The International Prostate Symptom Score (IPSS) is a quick, 7-item survey plus a quality-of-life question that can be completed by the patient during an initial visit and following the initiation of therapy. Results can provide the clinician with valuable information to help assess the severity

of disease, guide the therapeutic decision process and monitor the impact of therapy. An IPSS of > 7 is indicative of at least moderate disease and a patient that may benefit from medical therapy. Responses to the IPSS can be subscored to help identify symptoms that are associated with either difficulty in voiding (IPSS-V, questions 1,3,5,6) or problems with storage (IPSS-S, questions 2, 4, 7). Liao reported that patients with a voiding to storage ratio more than 1 were likely to respond to therapies directed at voiding rather than storage [9]. Other useful assessment tools include the BPH Impact Index (Appendix 1, Appendix 2 and Appendix 3) prostate specific antigen (PSA) and a measured post void residual (PVR) volume using bladder ultrasound. Roehrborn, et al. in a study of over 4600 patients who were prostate cancer free demonstrated that the serum PSA could be used as a reliable predictor of prostate volume [10]. While the trans-rectal ultrasound of the prostate remains the gold standard for assessing prostate size, it is generally not readily available to most primary care physicians (PCPs). This could account for the finding reported by Miner that PCPs were 6-fold less likely to utilize a prostate ultrasound in evaluating men with BPH relative to urologists [11]. The digital rectal exam (DRE) certainly has a place in identifying irregularities in the prostate that may indicate a need for additional testing to rule out prostate cancer. However, as a tool to assess prostate size, it has been shown to be unreliable. Caballido, et al. found that a cohort of general practitioners was not able to accurately predict prostate size based upon findings from a DRE [12]. Measuring the serum PSA, in the absence of prostate cancer, clinicians can reliably identify a prostate volume of 30 mL or more when the PSA value exceeds 1.5 ng/mL [13]. Roehrborn in a later study of 1503 men randomized to a placebo arm a trial of finasteride found prostate volume and the PSA were the best predictors of patients who would develop acute urinary retention (AUR) as well as those requiring surgery [13]. An accurate assessment of prostate size can be useful in guiding and predicting response to drug therapy. Using a diagnostic algorithm of age, IPSS and PSA, Caballido, et al. demonstrated these 3 factors could identify BPH with a positive predictive value of 77.1% [12].

Treatment

Alpha blockers

The alpha receptor blockers with their rapid onset of action, have been the cornerstone of pharmacologic treatment of BPH for over 3 decades. Three alpha-1 receptors have been identified (1_{A} , 1_{B} , 1_{D}). Stimulation of the alpha- 1_{A} receptor is associated with prostate smooth muscle contractions, whereas the effects of alpha- 1_{B} and 1_{D} receptor stimulation within the prostate is less clear. The primary concerning side effect of this class has been orthostatic hypotension and area frequent cause of blood pressure related syncope particularly with the

first dose. This has been attributed to receptors other than 1_{A} . Consequently, manufacturers of this class intent on treating BPH have focused on developing agents specific to the 1_{A} receptor. Terazosin and doxazosin are nonspecific in their activity and received FDA-approval initially as anti-hypertensives. Consequently, upward dose titration is necessary to achieve maximal BPH benefit while minimizing the risk of hypotension (Table 1). Tamsulosin and silodosin have greater specificity for the 1_{A} receptor subtype than previously available agents. There remains potential for unwanted blood pressure changes but are less than either terazosin or doxazosin. The hypotensive effect of the alpha blockers, particularly with doxazosin and terazosin, can be exaggerated when combined with phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil, avanafil) and therefore caution is advised. An interaction crossover study of 18 healthy males found no difference in either diastolic or systolic standing blood pressure changes with the combination of tamsulosin plus tadalafil versus tamsulosin alone [14]. Alfuzosin, while not demonstrating specificity for alpha receptor subtypes, has an extended-release formulation that does not promote hypotension, nor does it require dose titration [15]. Giulliano failed to identify a statistical difference in supine systolic and diastolic blood pressures with the combined administration of alfuzosin ER and tadalafil [16]. Ejaculatory disorders, primarily retrograde ejaculation, is another relatively common side effect of the class [17]. All of the available α -blocking agents reportedly have the potential to produce this side effect. It has primary significance in males who desire to produce offspring and should be discussed with the patient. In addition, patients undergoing cataract surgery may experience floppy iris syndrome as an operative complication. The risk of this side effect should be discussed with patients who may be undergoing this procedure with an option of withholding these agents prior to the procedure. The primary benefit of agents within this class is their immediate impact on symptoms. Unlike the 5-alpha reductase inhibitors (discussed later), patients can see an improvement in symptoms with the first dose. Improvement in urine flow rates, IPSS scores and nocturia can be seen with maximal improvement generally occurring within 2-weeks of initiation. A review of 17, double-blind, placebo-controlled studies involving over 8100 patients, treated with the four available α -blocking agents generated symptom improvement between 5 and 31% with an improvement in peak flow rate of 9-24% versus placebo [18]. While there does not appear to be significant differences in terms of efficacy between agents in the class, differences in the side effect profile may guide the clinician to prefer one over another.

5-alpha reductase inhibitors

Two 5-alpha reductase inhibitors (5-ARIs) (finasteride,

Table 1: Agents for BPH.

Agent	Dose	Adverse Effects
First Generation α-blocking agents		
Doxazosin	1 mg daily PO initial, increase by 1 mg weekly to desired effect or max dose of 8 mg	Orthostatic hypotension, syncope, dizziness, IOFIS, retrograde ejaculation
Terazosin	1 mg daily, titrate to 2-10 mg to desired effect or maximum dose of 10 mg	See doxazosin
Second Generation α-alpha blocking agents		
Tamsulosin	0.4 mg PO daily initially 30 minutes after the same meal each day, increased to 0.8 mg in 2-4 weeks if inadequate response.	Retrograde ejaculation, asthenia, dizziness, IOFIS
Alfuzosin ER	10 mg PO daily with the same meal each day	Dizziness, lightheadedness, orthostatic hypotension, IOFIS
Silodosin	8 mg PO daily with the same meal each day, 4 mg PO daily with CrCl 30-50 ml/min, CI with CrCl < 30 ml/min	Retrograde ejaculation, orthostatic hypotension, IOFIS
5-α-Reductase Inhibitors		
Finasteride	5 mg PO once daily	Decreased libido, ejaculatory disorder, erectile dysfunction, breast tenderness and gynecomastia
Dutasteride	0.5 mg PO once daily	Decreased libido, ejaculatory disorder, erectile dysfunction
Phosphodiesterase Inhibitor		
Tadalafil	5 mg PO once daily decrease to 2.5 mg PO daily with CrCl 30-60 ml/min. Not recommended with hemodialysis	Non-arteritic anterior ischemic optic neuropathy
Antimuscarinics¹		
Oxybutynin ER	5-10 mg PO once daily	Constipation, xerostomia, blurred vision, dry eyes, confusion
Tolterodine	1-2 mg PO twice daily, 2-4 mg PO once daily extended relief. Not recommended with CrCl < 10 ml/min or Child-Pugh Class C	Constipation, xerostomia, angioedema
Solifenacin	5 mg PO once daily, may be increased to 10 mg daily if CrCl > 30 ml/min	See tolterodine, prolonged Qt
Trospium	20 mg PO twice daily at least 1 hour before meals, 60 mg PO daily extended relief at least 1 hour before a meal	Constipation, xerostomia, headache, hypertensive crisis, rhabdomyolysis
Darifenacin	7.5 mg PO once daily, may be increased to 15 mg after two weeks, Child-Pugh Class B or with a CYP3A4 inhibitor do not exceed 7.5 mg, not recommended with Class C	Constipation, xerostomia, headache, angioedema
B-3 Agonist¹		
Mirabegron	25 mg PO daily, may be increased to 50 mg after 4-8 weeks, not recommended with a eGFR < 15 ml/min/1.73 m ²	Hypertension, constipation, xerostomia, headache
Vibegron	75 mg PO daily, not recommended with a eGFR < 15 ml/min/1.73 m ²	Diarrhea, nausea, headache

¹Dosages given are from an indication for overactive bladder

IOFIS: Intraoperative Floppy Iris Syndrome, CrCl: Creatinine Clearance, eGFR: Estimated Glomerular Filtration Rate

dutasteride) are approved and generically available for the treatment of BPH. Type I and type II 5-alpha reductase enzymes are responsible for the conversion of testosterone to dihydrotestosterone (DHT). While type II 5-alpha reductase is the primary enzyme found in

prostatic tissue, type I is, to lesser extent also involved in the synthesis of DHT. DHT has been implicated as a stimulus for prostate tissue hyperplasia. Inhibition of DHT formation consequently leads to a decrease in prostate size over time and potentially a change in urine

flow. Finasteride targets the type II enzyme whereas dutasteride inhibits both. A double-blind, year-long study of daily administration of finasteride in over 1600 men found a 60% decrease in DHT levels without a significant change in testosterone [19]. Larger decreases in DHT are seen with dutasteride where a twenty-four-week study reported a 98% reduction. Maximum benefit has been shown in patients with prostate enlargement exceeding 30g corresponding to PSA of ≥ 1.5 ng/dl. Effectiveness of dutasteride was reported in a meta-analysis of 24 studies [20]. Compared to placebo, a statistically significant reduction in both IPSS and maximum urine flow (Q_{max}) was demonstrated. Multiple studies have looked at the combination of an α -blocking agent with that of a 5-ARI. Overall, in terms of efficacy, a modest impact in symptom control can be gained by the adding a 5-ARI to an α -blocker. There is however clear benefit in terms of progression, AUR and future need for invasive intervention [21]. The Medical Therapy of Prostate Symptoms (MTOPS) trial compared the combination of doxazosin and finasteride to placebo, finasteride or doxazosin alone [22]. The combination saw an 81% risk reduction of AUR compared to placebo, 13% greater than those taking finasteride alone. Furthermore, the risk for the need for an invasive intervention was reduced by 68% for the combination as compared to placebo or doxazosin alone. The most common side effect attributed to finasteride among MTOPS participants was sexual dysfunction (erectile dysfunction, decreased libido, abnormal ejaculation). Similar results were found in patients taking finasteride long term although the occurrence of each of these sexual side effects decreased as the duration of treatment increased [23]. The CombAT trial randomized men to either the combination of tamsulosin and dutasteride versus either drug alone [24]. Unlike MTOPS, the CombAT excluded men with a prostate size of < 30 cc as measured by trans rectal ultrasound or a PSA < 1.5 ng/ml and not > 10 ng/ml. A significantly greater increase in Q_{max} as well as symptom improvement was seen in the combination versus either drug alone. Because the 5-ARIs decrease prostate size over time, clinicians should also be aware of as much as a 50% reduction in the PSA from baseline [22,24]. While the reduction in PSA occurs early in treatment, symptom improvement may not be seen for up to 6 months. Patients should be advised of the anticipated delay lest they become disenchanting and prematurely stop taking their 5-ARI.

Phosphodiesterase inhibitors

First approved in 2003 for erectile dysfunction (ED), tadalafil gained FDA-approval for treatment of BPH in 2011 and thus far is the only phosphodiesterase inhibitor (PDEI) to do so. While both sildenafil and vardenafil have been studied for use in BPH their lack of FDA-approval places a discussion of their characteristics outside the scope of this manuscript.

The phosphodiesterase isoenzymes are distributed throughout the body and are responsible for the degradation of cyclic guanosine monophosphate (cGMP), necessary for relaxation of smooth muscle. Inhibition of these isoenzymes prolongs the activity of cGMP facilitating the persistence of smooth muscle relaxation. In addition, PDE-5 inhibitors positively affect concentrations of nitric oxide, improving urologic function via relaxation of smooth muscle along the bladder neck. Another mechanism proposed by Vignozzi, et al. postulated from experiments with *in-vitro* human BPH cells that tadalafil has an anti-inflammatory action on myofibroblast prostate cells primarily through an interaction with interleukin 8 [25]. Clinically, tadalafil has demonstrated subjective efficacy (change in IPSS and IPSS QOL) in BPH patients with and without erectile dysfunction. An effect that is similar in magnitude to the α -blockers. Less impressive is tadalafil's impact on objective measures (Q_{max} , average flow rate or voided volume). A study of escalating doses of tadalafil versus placebo was unable to demonstrate significant differences between the two treatment groups in any of these objective variables [26]. In a similar study of tadalafil improved IPSS storage and voiding scores versus placebo but again was not able to demonstrate a significant difference in Q_{max} or voided volume [27]. A Cochrane review of PDEI in combination with α -blockers and 5-AR found little difference of the combinations versus α -blockers or 5-AR alone [28]. The dose of tadalafil for treatment of BPH is 5 mg daily and escalating to doses often used for ED (10-30 mg) have not been beneficial in further relieving symptoms of BPH. Generic tadalafil is available at a modest price. More recently, a combination of tadalafil and finasteride has become available at a significantly higher cost to the patient than separate prescriptions for each. Finally, it is important to screen patients for potential drug interactions prior to prescribing tadalafil. Taken concomitantly with nitroglycerin products in any form are contraindicated since a precipitous drop in blood pressure may occur from an overabundance of available cGMP. Tadalafil alone can have a lowering effect on blood pressure and there is concern about prescribing it with hypertensive medications. Concomitant use with hypertensive medications was not however shown to have a significant impact on blood pressure according to a pooled analysis of over 15,000 patients in clinical trials [29].

Antimuscarinic agents

Treatment of LUTS has largely been aimed at controlling symptoms secondary to BOO. However, symptoms related to storage in men with LUTS are likely to play a role in 51.3% of patients [30]. Muscarinic receptors can be found in detrusor muscle cells and inhibition reduces detrusor muscle contractions. Once considered to be contraindicated in patients with BPH due to the concern for AUR and increased PVR, the

use of antimuscarinic agents has been advocated in patients with predominantly storage symptoms [8]. The TIMES trial compared the efficacy of tolterodine ER alone or in combination with tamsulosin to placebo and tamsulosin alone. Eight hundred and seventy-nine patients were randomized to 4 treatment groups. While all groups demonstrated benefit at 12 weeks compared to baseline, only tolterodine ER plus tamsulosin proved superior to placebo with respect to the primary endpoint, patient perception of treatment benefit [31]. Höfner, et al., reported the results of a prospective study of 741 patients treated with 4 mg of tolterodine ER with a mean IPSS of 17.2 without suspected BOO or receiving α -blocker therapy with inadequate relief of storage symptoms [32]. At twelve weeks the IPSS had decreased to a mean of 9.9 ($p < 0.0001$) without a significant increase in PVR. At the same time IPSS quality of life (QoL) scores improved from 3.9 to 1.9. Mechanisms other than decreasing DO may be involved. Sakilis, et al. reported a statistically significant decrease in prostate volume and prostate vascularity among patients treated with the combination of solifenacin and tamsulosin versus tamsulosin alone (-9.5% and 9.2%, respectively) [33]. These efficacy results differ somewhat by findings of the NEPTUNE trial. Investigators randomized 1334 patients to placebo, tamsulosin alone or a combination of tamsulosin to either 6 or 9 mg of solifenacin [34]. This trial found an improvement superior to placebo of the combination in terms of the primary efficacy endpoint, improvement in IPSS, but noninferior to tamsulosin alone. The combination did demonstrate superiority to tamsulosin alone in IPSS storage subscores as well as total urgency and frequency scores. Safety data from patients taking tamsulosin alone and the combination was similar. These findings persisted in a 52-week follow-on trial (NEPTUNE II) [35]. It appears clear that patients with predominant storage symptoms can benefit from a trial of an antimuscarinic agent either alone or in combination with an alpha blocker and is reflected in the 2021 AUA guidelines [8]. It must be noted that none of these agents have FDA-approval for treatment of BPH.

β -3 agonists

The β -3 agonists are a relatively new class of drugs with proven benefit in patients with OAB. β -3 agonism of receptors in the detrusor produces bladder relaxation during the storage phase and an increase in bladder capacity theoretically without a negative effect on PVR. Currently there are two FDA-approved agents (mirabegron, vibegron) for this condition. Kaplan, et al. randomized 676 men receiving tamsulosin to the addition of mirabegron or matching placebo [36]. After an initial 4-weeks of mirabegron 25 mg, the dose was increased to 50 mg for an additional 8-weeks (PLUS trial). Tamsulosin plus mirabegron (Tam+Mir) demonstrated superiority to tamsulosin plus placebo in

both number of micturitions and mean volume voided per micturition, but was not statistically different relative to IPSS either in total or subscores. Side effect rates were higher among the Tam+Mir treated patients (urinary retention). Rates of serious side effects were similar with only one patient requiring catheterization judged possibly related to Tam+Mir. In a later study of 92 men treated for 12-weeks with tamsulosin for BPH were randomized to the addition of either solifenacin or mirabegron for OAB symptoms [37]. IPSS, Quality of life index and MVV were significantly better in both groups. AUR necessitating catheterization occurred in one patient in the solifenacin group. PVR was higher among solifenacin treated patients, it was not deemed clinically significant. From available clinical trials it would appear mirabegron can offer some additional benefit in men with OAB complicating their treatment of BPH. Both the AUA and the European Urology Association suggest that β -3 agonists may be offered to BPH patients with a predominance of storage symptoms [8,38]. As of the time of this writing, β -3 agonists are approved only for treatment of OAB. The cost of mirabegron may be prohibitive to many patients as there is no available generic alternative.

Personalizing medical therapy

Primary care practitioners have many options when faced with a patient complaining of bothersome symptoms secondary to BPH. Alpha blockers remain after decades of use, the first choice for many as they have proven benefit in the majority of patients. There are conditions however, where an alternative may be considered. For patients with a PSA > 1.5 ng/ml, a 5-AR is a good option as their likelihood for progression to AUR and/or an invasive intervention is significant. Combining a 5-AR with an α -blocker can provide immediate relief while decreasing their risk for surgical intervention in the long term. There is equal efficacy among all the agents in the class, but differences in the side effect profile. Tamsulosin appears to carry the highest risk for ejaculatory disorders and may not be the best option for the patient who desires to have a child. At the same time, patients with boarder line low blood pressure, alfuzosin, tamsulosin or silodosin maybe the best option as these three have the least risk for hypotension. Tadalafil is another initial option as standalone treatment especially when erectile dysfunction is present provided the patient is not using a nitrate for coronary artery disease. The administration of an IPSS at the first visit with determination of subscores can also guide the clinician to additional options for initial treatment. For patients with a predominance of symptoms secondary to storage (frequency, nocturia, urgency) and little or no PVR, an antimuscarinic either alone or with an α -blocker can be beneficial. In these situation mirabegron with an α -blocker can also be considered but at a significant increase in cost.

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