

# Medical Treatment

---

## Editors:

Bilal Chughtai, MD

## Authors:

Dean Elterman, MD, MSC, FRCSC; Naeem Bhojani, MD; Kevin Zorn, MD; Bilal Chughtai, MD

## Last Updated:

Wednesday, June 14, 2023

## Keywords

Benign prostatic hyperplasia, Lower urinary tract symptoms, Bladder outlet obstruction,  $\alpha$ -adrenergic receptor blockers, 5 $\alpha$ -reductase inhibitors, Phosphodiesterase-5 inhibitors

## 1. Definition

**Benign prostatic hyperplasia (BPH)** refers to an increase in the number of prostatic stromal and epithelial cells, resulting in the formation of large, discrete nodules in the transition zone of the prostate.

## 2. Risk Factors and Pathophysiology

When sufficiently large, nodules of benign prostatic tissue result in **benign prostatic enlargement (BPE)**, causing urethral compression potentiating **bladder outlet obstruction (BOO)**. BOO can result in **lower urinary tract symptoms (LUTS)** which may be divided into storage, voiding, and post-micturition symptoms.<sup>1</sup> Obstruction of the bladder may lead to or coexist with detrusor overactivity (DO), which can also contribute to LUTS. BPH growth is influenced by multiple factors including androgen levels, estrogen levels, paracrine factors in the prostatic stroma and epithelium, growth factors (FGF-1,2,7,17; VEGF, IGF; TGF- $\beta$ ), cytokines (IL-2, 4, 7, 17; IFN- $\gamma$ ), sympathetic nerve signaling, and genetic inheritance.<sup>2</sup>

## 3. Epidemiology

The prevalence of BPH and LUTS increases with age. **BPH is estimated to affect 70% of US men aged 60-69 years, and 80% of those aged  $\geq 70$  years.**<sup>3</sup> The Boston Area Community Health (BACH) survey demonstrated that LUTS increased from 8% in men aged 30-39 years to 35% in men aged 60-69.<sup>4</sup> Similarly, the European and Korean UrEpik study reported that the prevalence of male LUTS increased 10% per decade from 40-79 years of age.<sup>5</sup>

## 4. Diagnosis and Evaluation

The evaluation of all patients presenting with LUTS suggestive of BOO should begin with a

**medical history and physical exam.** A physical examination, including both a digital rectal exam (**DRE**) and a focused neurologic examination, should be performed at initial visit and then regular intervals with PSA/DRE screening in accordance with **AUA guidelines for prostate cancer detection**.<sup>6</sup> A **urinalysis** should be performed at initial evaluation to screen for confounding or contributory diagnoses like hematuria and urinary tract infection.<sup>7</sup> While primarily used for prostate cancer screening, PSA has been investigated as means of estimating prostatic size, however is only reliable when significant cancer has been excluded. Studies have proposed age specific criteria for detecting glands >40ml with PSA cutoffs of 1.6ng/ml, 2.0 ng/dl and 2.3ng/dl in men in their 50s, 60s and 70s respectively.<sup>8,9</sup> As prostate size is predictive of disease progression and prostate related events, establishing prostate size at baseline has clinical value outside prostate cancer screening.<sup>10</sup> Subjective outcomes for LUTS due to BPH (LUTS/BPH) are measured by the **American Urologic Association Symptom Index (AUASI)** (**Figure 1**) and should be obtained at initial consultation and routinely thereafter to track bother and treatment success. **An AUASI of 0-7 is considered mildly symptomatic, 8-19 moderately symptomatic, and 20-35 severely symptomatic.** Objective measures include urinary **flow rate (Qmax)** and **post-void residual (PVR)** which can accompany the subjective outcomes reported by the AUASI and should generally be obtained before considering **surgical intervention**.<sup>7</sup> Providers may also see benefit in having patients identify their primary bothersome urinary symptom to help focus treatment.<sup>11</sup>

**Cystoscopy** and imaging focused on establishing prostate size and anatomy is not routinely recommended in otherwise healthy patients with an initial evaluation consistent with BOO. However, such testing may be helpful in determining both patients who may not respond to medications (due to presence of median lobe) or who are contemplating surgical or procedural intervention. **Urodynamic evaluation** (with pressure-flow study) is useful in definitively diagnosing BOO and/or further voiding function in the context of multiple or overlapping LUTS.<sup>12</sup> While uroflow may be suggestive of urinary obstruction, a flow rate of less than 10ml/sec has demonstrated only a 70% specificity, 70% positive predictive value and 47% sensitivity for BOO.<sup>13</sup>

The 2021 AUA guidelines for the management of lower urinary tract symptoms attributed to **benign prostatic hyperplasia** include the following key points for the initial work-up.<sup>14</sup> In addition to obtaining a medical history, physical examination, obtain an IPSS, and perform a urinalysis. Furthermore, permitting equipment availability, the urologist should also consider uroflowmetry and PVR. Patients should then be counselled on options for interventions. These can include behavioral/lifestyle modifications, medical therapy or discussion of procedural options.

## 5. Treatment

Behavioral modification may be beneficial in appropriate patients with strategies including double voiding, timed voiding, avoidance of caffeine (and other bladder irritants), alcohol and other diuretics, as well as night-time fluid restriction.

A recent study of both medical and surgical trends in LUTS/BPH treatment found medication usage increased from 2004 to 2013 with a corresponding decrease in surgical interventions. Medication use

increased with patient age, with the most pronounced increase amongst men 40 to 60 years of age.<sup>15</sup>

Patients who are started on any form of therapy, whether it's behavioral or medical should be re-evaluated by their providers 4-12 weeks after initiation of treatment. This is to assess response to therapy, adverse events, and re-evaluation with the IPSS. Optional additional tests could include a post-void residual (PVR) and uroflowmetry.<sup>16</sup>

## 5.1 Herbal Medications

Over 30 phytotherapeutic compounds have been described for the management of BPH. Given their classification as foods by the US Food and Drug Administration, there is minimal regulation of safety, production, and distribution of these supplements. Studies have demonstrated extreme variations in active compounds in products sold over the counter.<sup>17</sup> One of the most commonly utilized supplements, saw palmetto, is derived from *Serenoa repens*. However, in 2011, a randomized controlled trial examined 369 men with LUTS due to BPH treated with placebo vs. saw palmetto demonstrated no difference with active treatment.<sup>18</sup> In 2012, a Cochrane update of 32 trials including 5666 patients also reported no difference between treatment arms in terms of response and adverse effect.<sup>19</sup> Other examples include the use of beta-sitosterols from the *Hypoxis rooperi* plant<sup>20</sup> and pygeum from the *Prunus africana* plant.<sup>21</sup> There is no convincing evidence that pumpkin seed (*Cucurbita pepo*) or stinging nettle (*Urtica dioica*) are effective for BPH.<sup>22</sup>

## 5.2 Alpha-Adrenergic Antagonists

*Rationale:* Alpha ( $\alpha$ 1)-blockers relax smooth muscle at the bladder neck and prostate thereby helping to relieve bladder outlet obstruction. Alpha blockers represent the most common initial therapy for treating LUTS/BPH.<sup>15</sup>

*Outcomes:* The first generation agents, phenoxybenzamine (irreversible) and prazosin (frequent daily dosing) are no longer used.<sup>23,24</sup> Second generation agents, such as **terazosin** and **doxazosin**, allowed for once-daily dosing but needed to be titrated to effect.<sup>25,26,27,28,29</sup> Alpha 1a-selective blockers, such as **tamsulosin**,<sup>30,31</sup> **alfuzosin**,<sup>32</sup> and **silodosin**,<sup>33,34</sup> were developed to avoid the systemic side effects associated with  $\alpha$ -blockade. The improvements in Qmax with use of  $\alpha$ -blockers range from **0.59-4.8ml/s (Table 1)**. Symptom score reductions range from **1-4.2 points although pronounced changes are seen in both Qmax and AUASS with placebo in controlled trials**. Direct comparisons between different types of alpha blockers are limited; however in 2011, a large RCT involving 1228 patients compared tamsulosin, silodosin and placebo and found silodosin to be non-inferior to tamsulosin in improving storage and voiding LUTS while allowing for greater alpha 1a selectivity.<sup>35</sup>

*Adverse Effects:* **The most common side effects associated with alpha blockade include a decline in blood pressure that can result in dizziness (5 to 15% with  $\alpha$ 1 a-selective agents), retrograde ejaculation (6%), and rhinitis (12%).**<sup>30</sup> The cardiovascular effects are particularly seen when less selective drugs and higher doses of  $\alpha$ -blockade are used (tamsulosin 0.8mg daily). Silodosin is felt to be less likely to cause orthostasis given its high  $\alpha$ 1 a-selectivity and lack of activity

at other receptor types. In regard to ejaculatory dysfunction, alfuzosin is thought to pose a reduced risk when compared to other means of alpha blockade.<sup>36</sup> More recently, the use of alpha-blockers, in particular tamsulosin, has been associated with intra-operative floppy iris syndrome (IFIS) with an incidence of 0.9-3.7%.<sup>37,38,39</sup> This problem leads to higher rates of iris trauma and posterior capsule rupture during cataract surgery. Indeed, IFIS is associated with any prior use, not necessarily current use, of tamsulosin.

**Table 1. Selected Summary of  $\alpha$ -Blocker Efficacy**

Agent	Reference	N	Change in Qmax (ml/s)	Change in Boyarsky symptom score	Change in AUASI
Prazosin 2mg bid	Kirby, et al. <sup>23</sup>	55	+4.8*	N/A	N/A
Prazosin 2mg daily	Chapple, et al. <sup>24</sup>	75	+1.6	N/A	N/A
Terazosin up to 10mg daily	Lepor, et al. <sup>25</sup>	285	+1.9*	-2.3*	N/A
Doxazosin 4mg daily	Chapple, et al. <sup>26</sup>	135	+1.5*	N/A	N/A
Doxazosin up to 8mg daily	Fawzy, et al. <sup>28</sup>	100	+2.2*	N/A	-3.2*
Doxazosin up to 12mg daily	Gillenwater, et al. <sup>29</sup>	248	+3.5*	-2.1*	N/A
Tamsulosin 0.4mg daily	Lepor, et al. <sup>30</sup>	756	+1.23*	-1.6*	-2.8*
Tamsulosin 0.4mg daily	Narayan, et al. <sup>31</sup>	735	+0.59*	-1.08*	-3.84*
Tamsulosin 0.4mg daily	Chapple, et al. <sup>35</sup>	384	3.53*	N/A	-6.7*

Alfuzosin 10mg daily	Roehrborn, et al. <sup>32</sup>	955	+1.2*	N/A	-2.2*
Silodosin 8mg daily	Marks, et al. <sup>33</sup>	661	+2.8*	N/A	-4.2*
Silodosin 8mg daily	Chapple, et al. <sup>35</sup>	381	+3.77*	N/A	-7.0*

\* denotes p<0.05

[View Image.](#)

### 5.3 5- $\alpha$ -Reductase Inhibitors

*Rationale:* 5-ARIs block the conversion of testosterone to dihydrotestosterone (DHT). DHT has a more potent effect on the prostate and suppression with 5-ARIs leads to a reduction in prostate volume/PSA and decrease in symptoms associated with BOO. Contrary to alpha-blockers, these drugs have a slow onset of action and a clinical benefit does not manifest before 3-6 months of therapy in most patients.<sup>40</sup>

*Outcomes:* The two agents currently in use are **finasteride**<sup>41,42,43,44,45</sup> and **dutasteride**,<sup>46,47</sup> the former competitively inhibits 5 $\alpha$ -reductase type 2 and the latter inhibits both subtypes. Despite differing pharmacologic properties, there have been no demonstrable clinical differences between finasteride and dutasteride. In a head to head trial both Qmax and change in prostate volume were similar.<sup>48</sup>

The prototypical study highlighting the efficacy of finasteride was the Proscar Long-term Efficacy and Safety Study (PLESS).<sup>45</sup> At the end of the four-year study period, **patients on finasteride experienced a 57% risk reduction in urinary retention as well as a 55% risk reduction in the need for BPH related surgery**. Urinary flow rates increased by 0.2ml/s in the placebo group vs. 1.9ml/s in the finasteride arm (p<0.001). Mean decrease in symptom score was 1.3 in the placebo group vs. 3.3 in the finasteride group (p<0.001). Overall, mean increase in Qmax for the 5ARIs range from 1.5-2.2ml/s with corresponding reduction in symptom scores ranging from 0.8-4.5 (**Table 2**). 5ARIs reduced prostate volume 15-32%. Additionally, in a post-hoc analysis of the Reduction by Dutasteride of Prostate Cancer Events study (REDUCE) trial, it was observed that dutasteride in asymptomatic or mildly symptomatic men decreased the risk of LUTS/BPH-related symptoms, episodes of urinary retention and need for BPH-related surgery.<sup>49</sup>

**Table 2. Selected Summary of 5 $\alpha$ -Reductase Inhibitor Efficacy**

Agent	Reference	N	Change in Qmax (ml/s)	Change in AUASI	Change in prostate volume
Finasteride Up to 5 mg daily	Gormley, et al. <sup>41</sup>	895	+1.6*	-0.8*	-13cm <sup>3</sup> * <sup>3</sup>
Finasteride 5 mg daily	Andersen, et al. <sup>42</sup>	707	+1.5*	-2.0*	-19.2%*
Finasteride 5 mg daily	Marberger, et al. <sup>43</sup>	3,270	+1.5*	-3.2*	-15.3%*
Finasteride 5 mg daily	Stoner, et al. <sup>44</sup>	1,645	+2.3*	-3.6*	-27%*
Finasteride 5 mg daily	McConnell, et al. <sup>45</sup>	3,040	+1.7*	-2.0*	-32%*
Dutasteride 0.5mg daily	Roehrborn, et al. <sup>46</sup>	4,325	+2.2*	-4.5*	-25.7%*
Dutasteride 0.5mg daily	Roehrborn, et al. <sup>47</sup>	2,340	N/A	-1.9*	N/A

\* denotes p<0.05

[View Image.](#)

*Adverse Effects:* The most common side effects associated with the use of 5ARIs include **decreased libido (6.4%), erectile dysfunction (8.1%), ejaculatory disorder (0.8%), gynecomastia (0.5%), breast tenderness (0.4%), and rash (0.5%)** in the first year of treatment.<sup>45</sup> While age related declines in sexual function were noted in the placebo group, data from the Medical Therapy of Prostatic Symptoms (**MTOPS**) trial demonstrated more pronounced declines in ejaculatory function with long term finasteride use.<sup>50</sup> Other queried sexual domains (erectile function, sexual drive, overall sexual satisfaction) did not exceed placebo related declines in either the finasteride or doxazosin groups.

## 5.4 Combination Therapy

(See **Table 3**)

Alpha-blockers and 5-ARIs may be used in combination to compound therapeutic effect. Finasteride and terazosin have been examined in combination in the VA Cooperative Study and the Prospective European Doxazosin and Combination Therapy (**PREDICT**) Trial.<sup>51,52</sup> Finasteride and alfuzosin have also been studied in combination.<sup>53</sup> Finasteride and doxazosin have been studied in the largest combination therapy trial, MTOPS.<sup>54</sup> **Combination therapy demonstrated the greatest risk reduction (66%) in clinical progression of LUTS/BPH (as defined by an increase in AUASI score of  $\geq 4$  over baseline,) acute urinary retention, renal insufficiency, recurrent urinary tract infection, and urinary incontinence.** Combination therapy also reduced the risk of AUASI score increase of  $\geq 4$  by 64%, compared to doxazosin alone (45%) or finasteride alone (30%). These results were confirmed in the **CombAT** study, where combination of dutasteride (0.5mg) and tamsulosin (0.4mg) was studied.<sup>55</sup> Overall, the use of 5-ARIs has led to the ability to effectively reduce prostate volume, lower the number of episodes of acute urinary retention, and delay both BPH progression and the need for surgical treatments. **Current guidelines published by the AUA and EAU recommend combination therapy with alpha-blockers and 5ARIs and is most beneficial for patients with moderate-severe symptoms, prostates larger than 40cc and higher PSA values ( $> 1.3 - 1.5\text{ng/dL}$ ).**<sup>12,56</sup>

**Table 3. Selected Summary of Combination Therapy Efficacy**

Agent	Reference	N	Change in Qmax (ml/s)	Change in AUASI	Change in prostate volume
Finasteride 5mg + terazosin up to 10mg daily	Lepor, et al <sup>45</sup>	1,229	+3.2*	-4.4*	-7.5cm <sup>3</sup> *
Finasteride 5mg + doxazosin up to 8mg daily	Kirby, et al <sup>46</sup>	1,007	+3.8*	-8.5*	N/A
Finasteride 5mg + 5mg alfuzosin twice daily	Debruyne, et al <sup>47</sup>	1,051	+2.3	-6.3*	-4.9
Finasteride 5mg + doxazosin up to 8mg daily	McConnell, et al <sup>57</sup>	3,047	+5.1*	-7.4*	-19%*
Dutasteride 0.5mg + tamsulosin 0.4mg daily	Roehrborn, et al <sup>58</sup>	4,844	+2.4*	-6.3*	-27.3%*

\* denotes p<0.05

[View Image.](#)

## 5.5 Anticholinergics

*Rationale:* Anticholinergics have been used to minimize LUTS in men from detrusor overactivity occurring with (from obstruction), or independently, of BPH.<sup>59</sup> Anticholinergics block the acetylcholine signal at the neuromuscular junctions of the detrusor muscle, thus leading to inhibition of detrusor contractions.

*Outcomes:* The most definitive data for the use of anticholinergics in men comes from the Tolterodine and Tamsulosin for Treatment of Men with Lower Urinary Tract Symptoms and Overactive Bladder (**TIMES**) trial. This was a randomized, double blind, placebo-controlled study designed to evaluate the efficacy and safety of using an antimuscarinic agent (tolterodine ER) alone or in conjunction with a  $\alpha$ -blocker (tamsulosin) in the treatment of LUTS with OAB symptoms.<sup>60</sup> Combination therapy resulted in improved number of nocturia episodes, daytime frequency, and urgency episodes. There was no significant difference in Qmax or PVR between the four arms.

A meta-analysis of trials that studied the effects of anticholinergics on men with BPH was conducted, pooling data from 5 randomized controlled trials and 15 observational studies.<sup>61</sup> Although total AUASI scores did not change with anti-cholinergic therapy, AUASI storage sub-scores, which account for the majority of subjective bother, were improved. Anticholinergic use was found to be safe, with a low acute urinary retention rate of **0.3%** at 12 weeks of follow-up. Overall, the addition of anticholinergics to therapy for BPH improved symptom scores by 6-8.5 with mixed effects on Qmax and PVR (**Table 4**).

**Table 4. Selected Summary of Anti-Cholinergic Efficacy**

Agent	Reference	N	Change in Qmax (ml/s)	Change in Boyarsky symptom score	Change in AUASI
Tolterodine ER 4mg daily	Kaplan, et al. <sup>59</sup>	43	+1.9*	N/A	-6.1*
Tolterodine ER 4mg	Kaplan, et al. <sup>60</sup>	217	-0.6	N/A	-7*
Tolterodine ER 4mg + tamsulosin 0.4mg daily	Kaplan, et al. <sup>62</sup>	225	+0.07	N/A	-8*
Solifenacin 3mg	Van Kerrebroeck <sup>63</sup>	42	Not Reported	N/A	-7.4*
Solifenacin 6mg	Van Kerrebroeck <sup>63</sup>	42	Not Reported	N/A	-6.0*
Solifenacin 9mg	Van Kerrebroeck <sup>63</sup>	42	Not Reported	N/A	-6.3*
Solifenacin 3mg + Tamsulosin 0.4mg	Van Kerrebroeck <sup>63</sup>	179	Not reported	N/A	-7.8*

Solifenacin 6mg + Tamsulosin 0.4mg	Van Kerrebroeck <sup>63</sup>	176	Not reported	N/A	-7.7*
Solifenacin 9mg + Tamsulosin 0.4mg	Van Kerrebroeck <sup>63</sup>	173	Not reported	N/A	-6.6*
* denotes p<0.05					
<a href="#">View Image.</a>					

*Adverse Effects:* The most common side effects associated with the use of anticholinergics include dry mouth (up to 71%), constipation (up to 21%), and blurry vision (5%). In addition, recent data has demonstrated that most of these molecules can cross the blood brain barrier which can lead to cognitive impairment and even dementia especially in the elderly population. As Tropicium chloride is a quaternary molecule, it is the only anticholinergic that does not cross the blood brain barrier and therefore can be used in the elderly and other patient populations that may be at risk of cognitive decline.

## 5.6 Phosphodiesterase type 5 Inhibitors (PDE5i)

*Rationale:* PDE5i function by blocking the breakdown of cGMP to GMP by phosphodiesterase, thus leading to vasodilation. There are 11 PDE subtypes and the prostate contains several, most abundantly 4, 5 and 11. All PDE5i have significant cross-reactivity on PDE enzymes other than the target PDE5. They have classically been utilized for the treatment of erectile dysfunction (ED); however, improvements in LUTS have been observed in patients using **sildenafil**,<sup>64,65,62,66</sup> **tadalafil**,<sup>67,68,69</sup> and **vardenafil**.<sup>70</sup>

*Outcomes:* The largest study was reported by Roehrborn et al. who examined the use of daily 2.5, 5, 10, or 20 mg tadalafil vs. placebo in 1,058 men with LUTS/BPH.<sup>68</sup> Significant improvement was seen in AUASI score in a dose-related fashion with the maximum improvement seen in the 10 and 20 mg dosing albeit at the cost of a greater number of adverse events. No impact on Qmax was seen. Interestingly, Dmochowski et al. studied 200 men randomized to 20 mg tadalafil vs. placebo over 12 weeks, focusing specifically on urodynamic parameters.<sup>69</sup> Despite improvements in AUASI score over placebo, no significant changes were seen in urodynamic parameters, specifically P<sub>det</sub>Q<sub>max</sub>, Q<sub>max</sub>, Q<sub>avg</sub>, or maximum P<sub>det</sub>. In 2012, Oelke et al conducted a randomized, double-blind, multicenter placebo controlled study with randomization to either placebo, tamsulosin 0.4mg or tadalafil 5mg. Results revealed similar improvements versus placebo in AUASI and BPH Impact Index in both tamsulosin and tadalafil groups and compared to previous literature Q<sub>max</sub> increased significantly compared to placebo (2.4ml/s p=0.009).<sup>71</sup> Additionally, Roehrborn et al conducted a randomized placebo controlled trial including 1500 patients and found a small but statistically significant median max flow rate improvement that increased with voided volume.<sup>72</sup> **Pooled analysis of 4 studies investigating the use of tadalafil 5mg did show AUASI improvement in two-thirds of patients with at least 50% of patients with significant response at 1 week and at least 70% demonstrating improvement at 4 weeks.** These results suggest speed of onset comparable with alpha blockade.<sup>73</sup>

Symptom score improvements have been observed in the 4.3-9.2 range (**Table 5**). While no consensus currently exists regarding what role PDE5i should play in the LUTS/BPH treatment pathway, daily tadalafil 5 mg has been FDA approved in the US for daily use in men with LUTS/BPH and has now been included in the updated **AUA guidelines**.

**Table 5. Summary of PDE5i Efficacy**

Agent	Reference	N	Change in Qmax (ml/s)	Change in Boyarsky symptom score	Change in AUASI
Sildenafil on demand	Sairam, et al. <sup>54</sup>	112	N/A	N/A	N/A
Sildenafil on demand	Mulhall, et al. <sup>55</sup>	48	N/A	-4.6*	N/A
Alfuzosin 10mg daily + sildenafil 25mg every other day	Kaplan, et al. <sup>59</sup>	62	+2.0*	-4.3*	-21*
Sildenafil 50mg titrated to 100mg daily	McVary, et al. <sup>60</sup>	366	+0.31	-6.3*	N/A
Tadalafil 5mg titrated to 20mg daily	McVary, et al. <sup>61</sup>	281	+0.5	-2.8*	+1.4
Tadalafil up to 20mg daily	Roehrborn, et al. <sup>64</sup>	1,058	+1.96	-5.2	-3.95
Tadalafil 20mg daily	Dmochowski, et al. <sup>65</sup>	200	-0.1	-9.2*	-13

Vardenafil 10mg twice daily	Stief, et al. <sup>62</sup>	222	+1.6	-5.8*	-1.0
Tadalafil 5 mg	Oelke <sup>71</sup>	511	2.4*	-2.1*	-4.6
Tadalafil 5mg	Roehrborn <sup>72</sup>	1500	+1.8*	1.6*, 2.5*,4.1*	N/A
* denotes p<0.05					
<a href="#">View Image.</a>					

*Adverse Effects:* The most common side effects associated with the use of PDE-5 inhibitors include headache (15%), dyspepsia (4-10%), and flushing (3-11%). A summary table of all agents for the treatment of BPH is shown in **Table 6**.

**Table 6. Pharmacokinetics and Adverse Effects of Medical Treatments for BPH**

Agent	T1/2 (hours)	Food Effect	Adverse effects
Doxazosin	22	12% reduction in AUC	Cardiovascular including dizziness, congestive heart failure, peripheral edema, palpitations, chest pain, and tachycardia (25%), floppy iris syndrome
Terazosin	14	None	Dizziness, lightheadedness, palpitations and weakness (30%), floppy iris syndrome
Tamsulosin	5-7	30% decrease in AUC	Decline in blood pressure that can result in dizziness (5-15%), retrograde ejaculation (<1% to 28%), and rhinitis (12%), floppy iris syndrome. IFIS most associated with tamsulosin use. Retrograde ejaculation rates lowest with alfuzosin and highest with silodosin.
Alfuzosin	10	50% increase in AUC when taken with food	
Silodosin	13.3	Should be taken with food	
Finasteride	6	None	Decreased libido (6.4%), erectile dysfunction (8.1%), ejaculatory disorder (0.8%), gynecomastia (0.5%), breast tenderness (0.4%), rash (0.5%)
Dutasteride	5 weeks	10-15% decrease in Cmax	
Oxybutynin	2-3	25% increase in AUC	Dry mouth (71.4%), dizziness (16.6%), constipation (15.1%), somnolence (14%), nausea (11.6%), urinary hesitancy (9.5%), urinary

			retention (6%)
Tolterodine	3	53% increase in bioavailability	Dry mouth (39.5%), dysuria (1-10%), blurred vision (5%), urinary retention (1.7%)
Darifenacin	13-19	None	Dry mouth (35%), constipation (21%), dyspepsia (9%), UTI (5%), abdominal pain (4%)
Solifenacin	45-68	3% increase in AUC	Dry mouth (28%), constipation (13%), UTI (5%), blurry vision (5%)
Trospium	20	80% decrease in AUC	Dry mouth (20%), constipation (10%), headache (4%)
Sildenafil	4	29% decrease in Cmax	Headache (16%), flushing (10%), dyspepsia (7%), nasal congestion (4%), UTI (3%)
Tadalafil	17.5	None	Headache (15%), dyspepsia (10%), back pain (6%), myalgia (3%), nasal congestion (3%), flushing (3%)
Vardenafil	4-5	18-50% reduction in Cmax	Headache (15%), flushing (11%), rhinitis (9%), dyspepsia (4%), sinusitis (3%)

Data taken from [www.drugs.com](http://www.drugs.com)

[View Image.](#)

## 5.7 Beta-3 Adrenoceptor Agonists (Mirabegron)

*Rationale:* Mirabegron interacts primarily with the beta-3 adrenoreceptor to relax the detrusor muscle of the bladder both increasing bladder storage volumes and decreasing bladder overactivity. The mechanism by which mirabegron may contribute to  $\alpha_1$ -adrenoceptor blockade is still not well understood.<sup>74,75</sup>

*Outcomes:* In 2013, Nitti et al. conducted a randomized, double-blind, parallel group, placebo controlled, multicenter phase II study with 12 weeks duration, 200 men more than 45 years of age with LUTS and BOO were randomized (1 : 1 : 1) into three groups (mirabegron 50 mg : mirabegron 100 mg : placebo). **After 12 weeks of treatment, mirabegron 50 or 100 mg did not compromise PdetQmax or Qmax as compared to placebo**. Both treatment arms showed significant decrease in voiding frequency versus placebo. In addition, the 50 mg mirabegron group showed a statistically significant decrease of urgency. Across all three groups, rates of adverse events were similar. These findings suggest an emerging safe and promising treatment for storage symptoms in men with LUTS/BPH.<sup>76</sup>

Efficacy and safety of mirabegron was assessed via systematic review and meta-analysis.<sup>77</sup> Eight trials were included evaluating 10,248 patients although these could include both men and women. Comparisons were made to both tolterodine and placebo. Authors concluded that mirabegron significantly reduced nocturia episodes, incontinence episodes and mean number of micturitions. The 50 mg mirabegron dose had similar treatment-emergent adverse event rates as placebo.

Mirabegron was studied as an adjunct treatment to men already on alpha blocker (tamsulosin).<sup>78</sup> A 4-week run with tamsulosin was followed by randomization to placebo or mirabegron. At 4 weeks after randomization, the mirabegron dose could be titrated from 25mg to 50mg. Tamsulosin with mirabegron reduced the number of micturitions per day (-2.0 vs -1.6) and urgency episodes per day. While higher rates of urinary retention were noted with mirabegron, post void residuals and maximum urinary flow were not clinically different than placebo.

*Adverse Effects:* Reported adverse events include higher rates of urinary retention and hypertension; however, the occurrence of these events did not differ from placebo.<sup>76,78</sup>

## 6. Clinical Care Pathway

## International Prostate Symptom Score (IPSS)

Name:

Date:

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
<b>Incomplete emptying</b> Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
<b>Frequency</b> Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
<b>Intermittency</b> Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
<b>Urgency</b> Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
<b>Weak stream</b> Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
<b>Straining</b> Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	

	None	1 time	2 times	3 times	4 times	5 times or more	Your score
<b>Nocturia</b> Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

<b>Total IPSS score</b>	
-------------------------	--

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

Figure 1: AUS Symptom Index (AUASI)

Patients should be evaluated with a history and physical exam. Subjective questionnaire data including AUASI is helpful in both characterizing symptom severity and for longitudinal changes with treatment. Post void residual volume is helpful to exclude urinary retention and an increasing post void residual over time may also be helpful in identifying patients with decompensating urinary tracts. As Qmax may suggest either BOO or detrusor underactivity, urodynamic pressure-flow readings are the only way to definitively diagnose between these two conditions. Urodynamics are invasive and should be used judiciously, particularly when the diagnosis of BOO is unclear.<sup>14,16</sup> Urodynamics can help distinguish the etiology for a low Qmax and may uncover other lower urinary tract specific problems including sensation issues, Valsalva only voiding and dangerous storage pressures.

Most providers will select an alpha blocker as first line treatment for men with LUTS/BPH<sup>15</sup> even in men with primarily storage symptoms due to the safety of the medications and frequency at which storage symptoms improve after relief of obstruction. In men with symptoms unrelieved by alpha blockers or unwilling to take/continue medications, both additional medication options and surgical procedures can be considered. These should be tailored to the patient's urinary complaints. In men with persistent storage symptoms, anticholinergics or beta 3 agonists may be added to the medical regimen. In men with unrelieved obstructive type symptoms, addition of a 5ARI or office-based procedures/surgical interventions may be offered. For patients with minimal symptoms but recurrent urinary infection, bladder stones, persistent gross hematuria, urinary retention or renal function deterioration, surgical options should be considered.

In patients with stable and well controlled symptoms, annual or semi-annual visits with a provider are reasonable with periodic monitoring of PSA/DRE and evaluations with Qmax, PVR, and AUASI. Worsening interval symptoms or new findings like changes in renal function or urinary tract infections may warrant additional workup and more advanced treatment.

## Presentations

Medical BPH Presentation 1

## References

- 1 Abrams, P., Cardozo, L., Fall, M. et al.: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology*, 61: 37, 2003
- 2 Roehrborn, C.: Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History. In: *Campbell-Walsh Urology*,. Edited by A. Wein: Elsevier Saunders, vol. 3, pp. 2570-2610, 2011
- 3 &star; Wei, J. T., Calhoun, E., Jacobsen, S. J.: Urologic diseases in America project: benign prostatic hyperplasia. *J Urol*, 173: 1256, 2005
- 4 Kupelian, V., Wei, J. T., O'Leary, M. P. et al.: Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample - The Boston Area Community Health (BACH) Survey. *Archives of Internal Medicine*, **166**: 2381, 2006
- 5 Boyle, P., Robertson, C., Mazzetta, C. et al.: The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. *BJU Int*, **92**: 409, 2003
- 6 &star; Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, Holmberg L, Kantoff P, Konety BR, Murad MH, Penson DF, Zietman AL. Early detection of prostate cancer: AUA Guideline. *J Urol*. 2013 Aug;190(2):419-26.

- 7 &star; Foster HE, Barry MJ, Dahm P, Gandhi MC, Kaplan SA, Kohler TS, Lerner LB, Lightner DJ, Parsons JK, Roehrborn CG, Welliver C, Wilt TJ, McVary KT. Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA Guideline. J Urol. 2018. In press.
- 8 Roehrborn, C. G., Boyle, P., Gould, A. L. et al.: Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. Urology, 53: 581, 1999
- 9 Bohnen, A. M., Groeneveld, F. P., Bosch, J. L.: Serum prostate-specific antigen as a predictor of prostate volume in the community: the Krimpen study. Eur Urol, 51: 1645, 2007
- 10 Kobayashi T, Mitsumori K, Kawahara T, Nishizawa K, Ogura K, Ide Y. Prostate gland volume is a strong predictor of biopsy results in men 70 years or older with prostate-specific antigen levels of 2.0-10.0 ng/mL. Int J Urol. 2005 Nov;12(11):969-75. doi: 10.1111/j.1442-2042.2005.01189.x. PMID: 16351653.
- 11 &star; Welliver C, Sulaver R, Whittington A, Helfand BT, Çakır ÖÖ, Griffith JW, McVary KT2. Analyzing Why Men Seek Treatment for Lower Urinary Tract Symptoms and Factors Associated With Nonimprovement. Urology. 2015 Nov;86(5):862-7
- 12 &star; McVary, K. T., Roehrborn, C. G., Avins, A. L. et al.: Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol, **185**: 1793, 2011
- 13 Reynard JM, Yang Q, Donovan JL, Peters TJ, Schafer W, de la Rosette JJ, Dabhoiwala NF, Osawa D, Lim AT, Abrams P. The ICS-'BPH' Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. Br J Urol. 1998 Nov;82(5):619-23. doi: 10.1046/j.1464-410x.1998.00813.x. PMID: 9839573.
- 14 &star; Lerner LB, McVary, KT, Barry MJ et al: Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline part I, initial work-up and medical management. J Urol 2021; 206: 806.
- 15 &star; Welliver C, Feinstein L, Ward JB, Fwu CW, Kirkali Z, Bavendam T, Matlaga BR, McVary KT; Urologic Diseases in America Project. Trends in Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia, 2004 to 2013: the Urologic Diseases in America Project. J Urol. 2020 Jan;203(1):171-178. doi: 10.1097/JU.0000000000000499. Epub 2019 Aug 20. PMID: 31430232.
- 16 &star; Lerner LB, McVary, KT, Barry MJ et al: Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline part II, surgical evaluation and treatment . J Urol 2021; 206: 818.

Habib, F. K., Wyllie, M. G.: Not all brands are created equal: a comparison of selected components of different brands of *Serenoa repens* extract. *Prostate Cancer Prostatic Dis*, 7: 195, 2004

† Barry, M. J., Meleth, S., Lee, J. Y. et al.: Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial. *Jama*, **306**: 1344, 2011

This article represents the results of a definitive NIH-sponsored trial examining the efficacy of saw palmetto in treating lower urinary tract symptoms in men.

Tacklind, J., Macdonald, R., Rutks, I. et al.: *Serenoa repens* for benign prostatic hyperplasia. *Cochrane Database Syst Rev*, 12: CD001423, 2012

Wilt, T., Ishani, A., MacDonald, R. et al.: Beta-sitosterols for benign prostatic hyperplasia. *Cochrane Database Syst Rev*: CD001043, 2000

Wilt, T., Ishani, A., Mac Donald, R. et al.: *Pygeum africanum* for benign prostatic hyperplasia. *Cochrane Database Syst Rev*: CD001044, 2002

Wilt, T. J., Ishani, A., Rutks, I. et al.: Phytotherapy for benign prostatic hyperplasia. *Public Health Nutr*, **3**: 459, 2000

\* Kirby, R. S., Coppinger, S. W., Corcoran, M. O. et al.: Prazosin in the treatment of prostatic obstruction. A placebo-controlled study. *Br J Urol*, **60**: 136, 1987

Chapple, C. R., Christmas, T., Milroy, E. J.: A 12-week placebo-controlled double-blind study of prazosin in the treatment of prostatic obstruction due to benign prostatic hyperplasia. *BJU Int*, **70**: 285, 1992

\* Lepor, H., Auerbach, S., Puras-Baez, A. et al.: A randomized, placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. *J Urol*, **148**: 1467, 1992

Kirby, R. S., Lepor, H.: Evaluation and nonsurgical management of benign prostatic hyperplasia. In: *Campbell-Walsh Urology*. Edited by A. Wein

Chapple, C., Carter, P., Christmas, T. et al.: A three-month double-blind study of doxazosin as treatment for benign prostatic obstruction. *BJU Int*, **74**: 50, 1994

\* Fawzy, A., Braun, K., Lewis, G. P. et al.: Doxazosin in the treatment of benign prostatic hyperplasia in normotensive patients: a multicenter study. *J Urol*, **154**: 105, 1995

- 29       &star; Gillenwater, J. Y., Conn, R. L., Chrysant, S. G. et al.: Doxazosin for the treatment of benign prostatic hyperplasia in patients with mild to moderate essential hypertension: a double-blind, placebo-controlled, dose-response multicenter study. *J Urol*, **154**: 110, 1995
- 30       Lepor, H.: Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. *Urology*, **51**: 892, 1998
- 31       &star; Narayan, P., Tewari, A.: A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. United States 93-01 Study Group. *J Urol*, **160**: 1701, 1998
- 32       Roehrborn, C. G., Van Kerrebroeck, P., Nordling, J.: Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. *BJU Int*, **92**: 257, 2003
- 33       &star; Marks, L. S., Gittelman, M. C., Hill, L. A. et al.: Rapid efficacy of the highly selective alpha1A-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. *J Urol*, **181**: 2634, 2009
- 34       Marks, L. S., Gittelman, M. C., Hill, L. A. et al.: Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. *Urology*, **74**: 1318, 2009
- 35       Chapple, C. R., Montorsi, F., Tammela, T. L. et al.: Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. *Eur Urol*, **59**: 342, 2011
- 36       &star; Hellstrom, W. J., Sikka, S. C.: Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. *J Urol*, **176**: 1529, 2006
- 37       Cantrell, M. A., Bream-Rouwenhorst, H. R., Steffensmeier, A. et al.: Intraoperative floppy iris syndrome associated with alpha1-adrenergic receptor antagonists. *Ann Pharmacother*, **42**: 558, 2008
- 38       Chatziralli, I. P., Sargentanis, T. N.: Risk factors for intraoperative floppy iris syndrome: a meta-analysis. *Ophthalmology*, **118**: 730, 2011
- 39       Oshika, T., Ohashi, Y., Inamura, M. et al.: Incidence of intraoperative floppy iris syndrome in patients on either systemic or topical alpha(1)-adrenoceptor antagonist. *Am J Ophthalmol*, **143**: 150, 2007

40 &star; Roehrborn, C. G., Siami, P., Barkin, J. et al.: The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. J Urol, 179: 616, 2008

41 Gormley, G. J., Stoner, E., Bruskewitz, R. C. et al.: The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. N Engl J Med, **327**: 1185, 1992

+

42 Andersen, J., Ekman, P., Wolf, H. et al.: Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo controlled study. Urology, **46**, 1995

43 Marberger, M.: Long-term effects of finasteride in patients with benign prostatic hyperplasia: A double-blind, placebo-controlled, multicenter study. Urology, **51**: 677, 1998

44 Stoner, E.: Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. Urology, **43**: 284, 1994

45 † McConnell, J. D., Bruskewitz, R., Walsh, P. et al.: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med, **338**: 557, 1998

The PLESS trial was one of the first to examine the use of finasteride to treat LUTS.

46 Roehrborn, C. G., Boyle, P., Nickel, J. C. et al.: Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology, **60**: 434, 2002

47 Roehrborn, C. G., Lukkarinen, O., Mark, S. et al.: Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. BJU Int, **96**: 572, 2005

48 Nickel, J. C., Gilling, P., Tammela, T. L. et al.: Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). BJU Int, 108: 388, 2011

49 Toren, P., Margel, D., Kulkarni, G. et al.: Effect of dutasteride on clinical progression of benign prostatic hyperplasia in asymptomatic men with enlarged prostate: a post hoc analysis of the REDUCE study. BMJ, 346: f2109, 2013

50 &star; Fwu CW, Eggers PW, Kirkali Z, McVary KT, Burrows PK, Kusek JW. Change in sexual function in men with lower urinary tract symptoms/benign prostatic hyperplasia associated with long-term treatment with doxazosin, finasteride and combined therapy. J Urol. 2014 Jun;191(6):1828-3

† Lepor, H., Williford, W. O., Barry, M. J. et al.: The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. N Engl J Med, **335**: 533, 1996

The VA Cooperative Study was one of the first studies to examine the use of combination therapy to treat LUTS.

Kirby, R. S., Roehrborn, C., Boyle, P. et al.: Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology, **61**: 119, 2003

Debruyne, F. M., Jardin, A., Colloi, D. et al.: Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. European ALFIN Study Group. Eur Urol, **34**: 169, 1998

† McConnell, J. D., Roehrborn, C. G., Bautista, O. M. et al.: The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med, **349**: 2387, 2003

The MTOPS study represents the largest combination therapy trial and underpins the use of 5ARI and  $\alpha$ -blockers for medical treatment.

Roehrborn, C. G., Siami, P., Barkin, J. et al.: The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: 4-Year Results from the CombAT Study. Eur Urol, 2009

Oelke, M., Bachmann, A., Descaseaud, A. et al.: EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol, **64**: 118, 2013

Issa, S. A., Dagres, E.: Intraoperative floppy-iris syndrome and finasteride intake. J Cataract Refract Surg, **33**: 2142, 2007

Wong, A. C., Mak, S. T.: Finasteride-associated cataract and intraoperative floppy-iris syndrome. J Cataract Refract Surg, **37**: 1351, 2011

\* Kaplan, S. A., Walmsley, K., Te, A. E.: Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol, **174**: 2273, 2005

† Kaplan, S. A., Roehrborn, C. G., Rovner, E. S. et al.: Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA, **296**: 2319, 2006

+

The TIMES trial re-examined the use of anticholinergics in the setting of men with LUTS and OAB symptoms.

61 Blake-James, B. T., Rashidian, A., Ikeda, Y. et al.: The role of anticholinergics in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. *BJU Int*, **99**: 85, 2007

62 Kaplan, S., Gonzalez, R., Te, A.: Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. *Eur Urol*, **51**: 1717, 2007

63 Van Kerrebroeck P1, Haab F, Angulo JC, Vik V, Katona F, Garcia-Hernandez A, Klaver M, Traudtner K, Oelke M. Efficacy and safety of solifenacin plus tamsulosin OCAS in men with voiding and storage lower urinary tract symptoms: results from a phase 2, dose-finding study (SATURN). *Eur Urol*. 2013 Sep;64(3):398-407.

64 Sairam, K., Kulinskaya, E., McNicholas, T. A. et al.: Sildenafil influences lower urinary tract symptoms. *BJU Int*, **90**: 836, 2002

65 Mulhall, J. P., Guhring, P., Parker, M. et al.: Assessment of the impact of sildenafil citrate on lower urinary tract symptoms in men with erectile dysfunction. *J Sex Med*, **3**: 662, 2006

66 &star; McVary, K. T., Monnig, W., Camps, J. L., Jr. et al.: Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. *J Urol*, **177**: 1071, 2007

&star; † McVary, K. T., Roehrborn, C. G., Kaminetsky, J. C. et al.: Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol*, **177**: 1401, 2007

67 This represents the largest trial to date that examines the use of PDE-5 inhibitors for the treatment of LUTS.

68 &star; Roehrborn, C. G., McVary, K. T., Elion-Mboussa, A. et al.: Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *J Urol*, **180**: 1228, 2008

69 &star; Dmochowski, R., Roehrborn, C., Klise, S. et al.: Urodynamic Effects of Once Daily Tadalafil in Men With Lower Urinary Tract Symptoms Secondary to Clinical Benign Prostatic Hyperplasia: A Randomized, Placebo Controlled 12-Week Clinical Trial. *J Urol*, 2010

- 70 Stief, C. G., Porst, H., Neuser, D. et al.: A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol*, **53**: 1236, 2008
- 71 Oelke, M., Giuliano, F., Mirone, V. et al.: Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. *Eur Urol*, **61**: 917, 2012
- 72 &star; Roehrborn, C. G., Chapple, C., Oelke, M. et al.: Effects of tadalafil once daily on maximum urinary flow rate in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *J Urol*, **191**: 1045, 2014
- 73 &star; Oelke, M., Shinghal, R., Sontag, A. et al.: Time to onset of clinically meaningful improvement with tadalafil 5 mg once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: analysis of data pooled from 4 pivotal, double-blind, placebo controlled studies. *J Urol*, **193**: 1581, 2015
- 74 Alexandre, E. C., Kiguti, L. R., Calmasini, F. B. et al.: Mirabegron relaxes urethral smooth muscle by a dual mechanism involving beta3 -adrenoceptor activation and alpha1 -adrenoceptor blockade. *Br J Pharmacol*, **173**: 415, 2016
- 75 Calmasini, F. B., Candido, T. Z., Alexandre, E. C. et al.: The beta-3 adrenoceptor agonist, mirabegron relaxes isolated prostate from human and rabbit: new therapeutic indication? *Prostate*, **75**: 440, 2015
- 76 &star; Nitti, V. W., Rosenberg, S., Mitcheson, D. H. et al.: Urodynamics and safety of the beta(3)-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. *J Urol*, **190**: 1320, 2013
- 77 Sebastianelli A, Russo GI, Kaplan SA, McVary KT, Moncada I, Gravas S, Chapple C, Morgia G, Serni S, Gacci M. Systematic review and meta-analysis on the efficacy and tolerability of mirabegron for the treatment of storage lower urinary tract symptoms/overactive bladder: Comparison with placebo and tolterodine. *Int J Urol*. 2018 Mar;**25**(3):196-205. doi: 10.1111/iju.13498. Epub 2017 Dec 3. PMID: 29205506.
- 78 &star; Kaplan SA, Herschorn S, McVary KT, Staskin D, Chapple C, Foley S, Cambronero Santos J, Kristy RM, Choudhury N, Hairston J, Schermer CR. Efficacy and Safety of Mirabegron versus Placebo Add-On Therapy in Men with Overactive Bladder Symptoms Receiving Tamsulosin for Underlying Benign Prostatic Hyperplasia: A Randomized, Phase 4 Study (PLUS). *J Urol*. 2020 Jun;**203**(6):1163-1171. doi: 10.1097/JU.0000000000000738. Epub 2020 Jan 2. PMID: 31895002.