Phosphodiesterase Type 5 Inhibitors for the Treatment of BPH/LUTS Evidence Summary and Recommendations

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

All phosphodiesterase type 5 inhibitors (PDE5I) have an FDA label indication for the treatment of erectile dysfunction (ED) and tadalafil has a label indication for the treatment of benign prostatic hyperplasia (BPH) and ED/BPH. The intent of this document is to summarize the evidence on the efficacy of the PDE5I for the treatment of BPH and lower urinary tract symptoms (LUTS).

Literature searches were conducted to identify clinical trials, systematic reviews, meta-analyses, and other pertinent publications using PubMed from July 2014 to January 2022 using the following terms: avanafil, sildenafil, tadalafil, vardenafil, PDE5I, BPH, and LUTS. Relevant citations were reviewed, and their references searched for additional papers.

PDE5I to Treat BPH/LUTS

BPH/LUTS prevalence rates range from 50% to 75% among men 50 years of age and older to 80% among men 70 years of age and older.[1]

LUTS consists of frequency, nocturia, slowed stream, hesitancy, sense of incomplete emptying, intermittent stream which may or may not accompany urinary incontinence. The International Prostate Symptom Score (IPSS) is used in clinical trials and practice to quantify LUTS.[2] The IPSS has a possible score range of 0 to 35 (asymptomatic to very symptomatic). A decrease in the score corresponds improvement, while a 3-point improvement in the IPSS is considered the minimal detectable difference.[3] (Appendix 1). Maximum urinary flow rate (Qmax) is another outcome measure frequently used in clinical trials. There are no thresholds for monitoring changes in Qmax to help guide therapy but improvements between 1-5 ml/second may be seen.[3]

Several systematic reviews with meta-analyses of placebo-controlled trials of the use of PDE5I for BPH/LUTS have been published.[4,18,21-23] Additionally, an updated treatment guideline has been published.[3] Three PDE5I have been studied: sildenafil, tadalafil, and vardenafil. The majority of the PDE5I studies were conducted with tadalafil. Overall, PDE5I as monotherapy resulted in a significantly greater absolute difference in mean change in the IPSS score compared to placebo (Tables 1-4). However, only sildenafil, albeit with a single study, achieved the minimal detectable difference of 3 points for the IPSS measure. (Table 1). Qmax was not significantly changed by any of the PDE5I.

PDE5I vs an Alpha Blocker BPH/LUTS

Guo et al conducted a meta-analysis of randomized controlled trials (7, N=1601) comparing the effectiveness of tadalafil to tamsulosin in BPH/LUTS.[18] They reported that, compared with tamsulosin monotherapy, tadalafil showed no significant difference in reducing IPSS (4 studies, N=863), voiding sub scores (5 studies, N=1381), storage sub scores (5 studies, N=1386), quality

of life [(Qol); 4 studies, N=1264], postvoid residual [(PVR); 4 studies, N=863], and Qmax (4 studies, N=854).

PDE5I plus an Alpha Blocker BPH/LUTS

Sun et al evaluated nineteen studies (N=2426) to compare the improvement in LUTS with PDE5I, alpha blockers alone or in combination in males with BPH. They found that the combination treatment was significantly better than PDE5I or alpha blockers alone at improving IPSS and Qmax.[24] Sebastianelli et al, in a systematic review, concluded that the combination of tadalafil and tamsulosin provided better improvement in LUTS compared to monotherapies.[27] Qiangzhao et al completed a network meta-analysis of 20 trials (N=4131) evaluating the efficacy of combination therapy with an alpha blocker and different PDE5I in patients with LUTS. They found that the IPSS was most improved with the combination of vardenafil, and an alpha blocker followed by sildenafil and tadalafil with an alpha blocker.[25] Ma and colleagues also completed a network meta-analysis of seven trials (N=531) using tamsulosin, as the alpha blocker, in combination with different PDE5I.[26] They found that sildenafil combined with tamsulosin provided the most effective treatment for BPH/LUTS in patients with or without ED. The results of these systematic reviews and meta-analyses contrasts that with the recommendation of the American Urological Association (AUA). The updated AUA guideline states that the combination of low-dose tadalafil with an alpha blocker for the treatment of BPH/LUTS does not offer symptom improvement over either agent alone and recommends against their combined use.[3]

Table 1 Sildenafil BPH/LUTS, drug vs placebo. [16]

Study	N	IPSS	Qmax (ml/sec)
McVary 2007	369	- 6.3 vs -1.9 **Δ - 4.4**, p<0.0001	0.31 vs 0.16 Δ 0.15, NS

IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; ml/sec, milliliter/second; NS, non-significant

Table 2 Tadalafil BPH/LUTS, drug vs placebo. [5-14]

Study	N	IPSS	Qmax (ml/sec)
McVary 2007	281	-2.9 vs -1.5 **Δ -1.4**, p=0.003	0.5 vs 0.6 Δ 0.1, NS
Roehrborn 2008	1058	-4.87 vs -2.27 **Δ - 2.6**, p<0.001	1.64 vs 1.24 Δ 0.4, NS
Kim 2011	151	-5.8 vs -4.2 **Δ -1.6**, p=0.07	2.5 vs 2.3 Δ 0.2, NS
Porst 2011	325	-5.6 vs -3.6 **Δ -2.0**, p=0.004	1.6 vs 1.2 Δ 0.4, NS
Oelke 2012	511	-6.3 vs -4.2 **Δ -2.1**, p=0.001	2.4 vs 1.2 Δ 1.2, p=0.009
Takeda 2012	422	-4.9 vs -3.8 **Δ -1.1**, p=0.062	0.6 vs 1.4 Δ 0.8, NS
Egerdie 2012	606	-6.1 vs – 3.8 **Δ – 2.3**, p<0.001	N/A
Yokoyama 2013	612	-4.7 vs -3.0 **Δ – 1.7**, p=0.004	1.3 vs 2.1 Δ 0.8, NS
Takeda 2014	610	-6.0 vs -4.5 **Δ -1.5**, p<0.001	1.2 vs 0.6 Δ 0.6, NS
Zhang 2019	908	-5.5 vs -4.1 **Δ -1.4**, p<0.001	1.9 vs 1.5 Δ 0.4, NS

IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; ml/sec, milliliter/second; NS, non-significant; N/A, not available

Table 3 Vardenafil BPH/LUTS, drug vs placebo.[20]

Study	N	IPSS	Qmax (ml/sec)
Stief 2008	222	- 5.8 vs -3.6 **Δ – 2.2**, p<0.0013	1.6 vs 1.0 Δ 0.6, p=0.56

IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; ml/sec, milliliter/second

Table 4. PDE5I Meta-analysis: IPSS[3]

Drug (formulary status)	Studies (patients)	MD (95% CI)
Sildenafil (F)	1 (336)	-3.15 (-5.29, -1.01)
Vardenafil (NF)	1 (214)	-2.18 (-4.61, 0.25)
Tadalafil (PA-F)	9 (6436)	-1.87 (-2.44, -1.29)

F, formulary; NF, nonformulary; MD, mean difference from reference (placebo); CI, confidence interval

Table 5. Alpha-1 blockers Meta-analysis: IPSS[3]

Drug (formulary status)	Studies (patients)	MD (95%CI)
Doxazosin (F)	3 (1639)	-3.67 (-4.33, -3.02)
Terazosin (F)	2 (2489)	-3.37 (-4.24, -2.50)
Silodosin (NF)	2 (1479)	-2.44 (-3.24, -1.64)
Tamsulosin (F)	9 (4161)	-2.13 (-2.56, -1.71)
Alfuzosin (F)	5 (2626)	-2.07 (-2.66, -1.49)

F, formulary; NF, nonformulary; MD, mean difference from reference (placebo); CI, confidence interval

Clinical Practice Guidelines[3]

The 2021 AUA practice guidelines on BPH 2021 state:

1. Clinicians should offer one of the following alpha blockers as a treatment option for patients with bothersome, moderate to severe LUTS/BPH: alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin. (Moderate Recommendation; Evidence Level: Grade A)
2. For patients with LUTS/BPH irrespective of comorbid erectile dysfunction (ED), 5mg daily tadalafil should be discussed as a treatment option. Sildenafil may be offered when tadalafil is not available and alpha blockers are not tolerated. (Moderate Recommendation; Evidence Level: Grade B)
3. Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C)

Recommendations (Appendix 2)

A PDE5I should not be used routinely for the management of LUTS-BPH either as monotherapy or in combination with other drugs to treat BPH.

A Formulary PDE5I should be considered when more established pharmacotherapies are not an option or have not demonstrated benefit.

- Initiate a formulary alpha blocker (doxazosin, terazosin, tamsulosin, alfuzosin) using shared decision making and patient specific factors.
    - If ED present, may consider initiating a formulary PDE5I (with quantity limits) in addition to an alpha blocker. (Note: if the patient is already taking a PDE5I, alpha-blocker therapy should be initiated at the lowest dose to help prevent hypotension).
- If unable to tolerate or lack of response to an adequate trial (i.e.,12 weeks) of a formulary alpha blocker (titrated to maximum therapeutic dose), consider substituting or adding a formulary PDE5I. If adding a PDE5I, current labeling for PDE5Is recommends that a patient who is taking an alpha-blocker should be on a stable dose prior to initiating the PDE5I (which should then be started at the lowest recommended dose).
- Consider Formulary PDE5I monotherapy
    - In place of an alpha blocker in the interim if cataract surgery is planned or likely. Cases of intraoperative floppy iris syndrome have been noted as long as 9 months after discontinuing an alpha blocker prior to surgery.

- When an alpha blocker is contraindicated or not tolerated **and** an antimuscarinic is not appropriate because of a post void residual >250 mL, is contraindicated, a trial was either not tolerated or ineffective, or would contribute substantially to the patient's existing anticholinergic burden.

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Appendix 1: IPSS

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 Times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Appendix 2: Recommendation Algorithm