# Tadalafil in BPH:
# An Old Dog with New Tricks

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Objectives

1. Describe the use of PDE-5 inhibitors in men with BPH
2. Identify potential areas of therapy where PDE-5 inhibitors may be beneficial and postulate future places in therapy

## Background

### *Benign Prostatic Hyperplasia (BPH)*[1-5]

- Benign prostatic hyperplasia (BPH) is nearly universal in aging men with a prevalence exceeding 80% in those over the age of 80
- Lower urinary tract symptoms (LUTS) occur as a result of bladder outlet obstruction (BOO) and increases in muscle tone.
- Voiding symptoms
  - Urinary hesitancy, weak urinary stream, Sensation of incomplete bladder emptying.
- Storage symptoms (may occur later)
  - Urinary frequency, nocturia, urinary urgency, rge incontinence
- The American Urological Association Symptom Index (AUA-SI) and International Prostate Symptom Score (IPSS)
  - Self-administered questionnaires
  - Mild = 0-7, Moderate 8-19 and Severe 20-35 indicate moderate and severe symptoms, respectively.
  - Of note, a reduction of three or more points on the AUA-SI is considered clinically important.

*Management of BPH*[5-8]

- In patients with moderate to severe BPH, standard pharmacologic treatment includes two classes: alpha-1 ($\alpha_1$) adrenergic receptor antagonists (ARA) and 5-α reductase inhibitors (5ARI).
- All currently available $\alpha_1$-ARA are effective in reducing LUTS by relaxing muscle tissue in the prostate and bladder neck.
    - Available meds:
        - Selective: tamsulosin (Flomax®), silodosin (Rapaflo®), alfuzosin's (Uroxatral®)
        - Non-selective: doxazosin (Cardura®), terazosin (Hytrin®)
    - Equally efficacious – takes one week to have therapeutic benefit
- The enzyme 5-α reductase is an important regulator of prostate growth by controlling conversion of testosterone to dihydrotestosterone (DHT). Inhibition of 5-α reductase reduces volume of the prostate
    - Available Meds:
        - Finasteride (Proscar®), Dutasteride (Avodart®)
    - Equally efficacious – takes 6 – 12 months to have therapeutic benefits
- Can be taken together for a more enhanced effect
    - Tamsulosin/dutasteride (Jalyn®)

*Phosphodiesterase (PDE) – 5 inhibitors*[9-10]

- First approved in 1998 for erectile dysfunction
- Four FDA approved medications for prostate
    - Sildenafil (Viagra®), vardenafil (Levitra®), tadalafil (Cialis®), avanafil (Stendra®)
- Discovered 2001 may be beneficial in BPH associated LUTS

*Mechanism of Action in BPH*[11-12]

- PDE-5 inhibitors may improve LUTS via several biological mechanisms; including alterations in nitric oxide (NO), rho-kinase deactivation, and reductions in pelvic atherosclerosis.
- All currently available PDE-5 inhibitors reverse the tension induced by norepinephrine in prostate tissue with effects ranging from 17% with sildenafil, 35% with vardenafil and 52% with tadalafil.

<u>Clinical Trials</u>

- 5 studies evaluated use of PDE-5 inhibitors vs. placebo in evaluating BPH associated LUTS
    - Inclusion/exclusion

| Trial (publication date) | Intervention | Population | Primary End Points results |
|---|---|---|---|
| McVary et al (2007)[13] | TAD 5mg/day (week 0-6) dose escalated to 20mg/day (week7-12) vs. PBO (week 0-12) | PBO (143); TAD (138) | Week 6: +1.6 (p=0.003)<br><br>Week 12: +2.1 (p<0.001) |
| Roehrborn et al (2008)[14] | TAD 2.5mg/day, 5mg/day, 10mg/day, 20mg/day, PBO x 12 weeks | PBO (212); TAD 2.5mg/day (209); TAD 5mg/day (212); TAD 10mg/day (216); TAD 20mg/day (209) | -4.87 (p<0.001) |
| Stief et al (2008)[15] | VAR 10mg PO BID vs. PBO x 8 weeks | VAR (108); placebo (113) | IPSS: -2.3 (p=0.0013); Qmax +0.6 (p=0.5613) |
| Porst et al (2011)[16] | TAD 5mg/day vs. PBO x 12 weeks | PBO (164); TAD (161) | IPSS: +1.9 (p=0.004) |
| Egerdie et al (2012)[17] | TAD 2.5mg/day, TAD 5mg/day; PBO (1:1:1) x 12 weeks | TAD 2.5mg/day (198); TAD 5mg/day (208); PBO (200) | IPSS: Placebo (-3.8; p=N/A); TAD 2.5mg/day (-4.6; p=0.18); TAD 5mg/day (-6.1; p<0.01)<br>IIEF-EF: PBO (+1.8; p=N/A); TAD 2.5mg/day (+5.2; p<0.001); TAD 5mg/day (+6.5; p<0.001) |

- Oelke and colleagues compared tamsulosin 0.4 mg (n = 168), tadalafil 5 mg (n = 171), or placebo (n = 172) daily in a 12 week randomized, double-blind analysis. Compared to placebo, both tadalafil and tamsulosin improved IPSS, BII, and $Q_{max}$. Tadalafil—but not tamsulosin—improved quality of life measurements compared to placebo. There were no significant differences in TEAEs. Superiority of one treatment option over the other (tadalafil or tamsulosin) could not be assessed as the study was not adequately powered.[18]

- In the second double-blind, crossover-trial, 30 patients received tamsulosin 0.4 mg/day for 6 weeks followed by tadalafil 5 mg/day or placebo for an additional 6 weeks. Both tamsulosin plus placebo (-6.7, $p < 0.001$) and tamsulosin plus tadalafil (-9.2, $p < 0.001$) reduced IPSS compared to baseline. Tamsulosin plus tadalafil compared to tamsulosin plus placebo significantly improved scores (-2.5, $p < 0.05$). There were more adverse events with the combination compared to tamsulosin and placebo, specifically headaches (n = 12), dyspepsia (n = 3), and hypotension (n = 2).[19]

Adverse Drug Reactions / Drug Interactions

- In a similar randomized, double-blind, crossover study, subjects received either doxazosin titrated to 4 mg/day plus tadalafil 5 mg/day or doxazosin plus placebo or tamsulosin 0.4 mg/day plus tadalafil or tamsulosin plus placebo. Clinically important hypotension was reported in a higher frequency in doxazosin arms. Standing SBP decreased to <85 mmHg in 7.7% and 2.6% of subjects receiving doxazosin plus tadalafil and doxazosin plus placebo, respectively. Despite blood pressure changes all patients remained asymptomatic. For the tamsulosin arms, mean change in standing SBP, DBP, and heart rate were not considered clinically important. Myalgia occurred in 17% and 7% of subjects receiving doxazosin plus tadalafil and doxazosin plus placebo, respectively; while back pain occurred in 17% and 2% of subjects, respectively. In the tamsulosin plus tadalafil arm, commonly reported adverse events included myalgia (43%), headache (32%), back pain (27%), and dizziness (8%).[21]
- Tadalafil is a substrate of the hepatic enzyme CYP3A4 and is affected by several medications that induce or inhibit this enzyme.[21]
- Tadalafil exacerbated the hypotensive effect of sublingual nitroglycerin for up to 24 hours after concomitant administration; these findings support the well-established contraindication of PDE-5 inhibitors use with organic nitrates.[22]

Dosing and Administration

- Tadalafil (Cialis®) was approved for BPH by the Food and Drug Administration (FDA) in October 2011. The dose is 5 mg by mouth approximately the same time every day with or without food. Use of once daily tadalafil is not recommended in patients with a creatinine clearance (CrCl) < 30 ml/min. Tadalafil should be initiated at 2.5 mg daily in patients with a CrCl of 30 – 50 ml/min and titrated to 5 mg based on response. Tadalafil for daily use has not been evaluated extensively in patients with hepatic impairment. Caution is recommended for patients with mild to moderate impairment and should not be used in patients with severe impairment. Tadalafil is predominantly metabolized by

cytochrome P450 (CYP) 3A4. With the concomitant use of a CYP 3A4 inhibitor, the maximum recommended dose is 2.5 mg daily.[23]

Place in Therapy[5]

- The most recent AUA guidelines does not include where tadalafil would be used.
- There are limited well-designed clinical trials comparing PDE-5 inhibitor use to $\alpha_1$-ARA which remain first line agents.
- Additional studies are needed to determine if PDE-5 inhibitors should be considered as an alternative to $\alpha_1$-ARA or as adjunctive therapy.
- Likely best used as monotherapy in men with BPH associated LUTS and ED

Conclusion

- Tadalafil daily has an FDA approved indication for BPH
- Appears to be safe an effective; however, more studies are likely needed to determine its exact place in therapy.

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# Annotated Bibliography


Roumeguere T, Boujeltia KZ, Hauzer C, et al. Is there a rationale for chronic use of phospho-diesterase inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia? *BJUI.* 2009;104:511-517.

> This review article discusses the available literature regarding the potential impact of PDE-5 inhibitors on BPH associated LUTS. Here, article with secondary outcomes purporting improvements in LUTS is described in detail. The potential pathophysiology relationship between ED and BPH associated is addressed. The proposed mechanisms of action of PDE-5 inhibitors on a molecular level are also discussed based on available literature.

Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *J Urol.* 2008;180(4):1228-1234.

> This trial compares the use of tadalafil 2.5mg, 5mg, 10mg, 20mg by mouth daily to placebo for 12 weeks to evaluate the reduction in subjective IPSS (International Prostate Symptom Score) to determine an appropriate dose for BPH associated LUTS. Additionally, these doses were evaluated for peak urine flow and quality of life. There was a statistically significant improvement in IPSS for 2.5mg (3.88), 5mg (4.87), 10mg (5.17), and 20mg (5.21) compared to placebo. There was no improvement across any of the doses compared to placebo in regards to peak urine flow. Finally, there was improvement in quality of life, based on a questionnaire, for 5mg, 10mg, and 20mg doses; however, there was no difference in 2.5mg and placebo ($p$>0.05).

Stief CG, Porst H, Neuser D, Beneke M, Ulbrich E . 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.* 2008;53(6):1236-1244.

> This trial compared the use of vardenafil 10mg by mouth twice daily to placebo for eight weeks to evaluate the reduction in subjective IPSS. Additionally, this trial assessed the peak urine flow and post-void residual (PVR) volume. There was a statistically significant improvement in IPSS of 2.3 points compared to placebo ($p$=0.0013). However, there was no improvement in peak urine flow (p=0.5613) or PVR volume ($p$=0.6994).

Oelke M, Guiliano 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.* 2012;(print ahead):1-9.

> This trial compared the use of tamsulosin 0.4mg by mouth daily, tadalafil 5mg by mouth daily, and placebo for 12 weeks to evaluate the reduction in subjective IPSS. Additionally, this trial evaluated BPH Impact Index (BII) and nocturia. There was a significant reduction in IPSS compared to placebo for both tamsulosin (1.5 points; $p$=0.023) and tadalafil (2.1 points; $p$=0.001). This study was not powered to assess superiority between the two agents in BPH. There was also a significant reduction on the BII for both tamsulosin (0.6 points; $p$=0.026) and tadalafil (0.8 points; $p$=0.003). There was no significant improvement in either treatment group in regards to nocturia.

Bechara A, Romano S, Casabe A, Haime S, et al. Comparative efficacy assessment of tamsulosin vs. tamsulosin plus tadalafil in the treatment of LUTS/BPH. Pilot Study. *J Sex Med.* 2008;5:2170-2178.

> In this pilot study, tamsulosin 0.4mg by mouth daily plus placebo was compared to tamsulosin 0.4mg by mouth daily plus tadalafil 5mg by mouth daily for 45 days each in a cross-over designed trial to evaluate subjective IPSS. The use of tamsulosin (6.7 points; $p<0.001$) and tamsulosin plus tadalafil (9.2 points; $p<0.001$) both significantly improved IPSS compared to baseline. Additionally, there was a significant improvement in IPSS in the combination tamsulosin plus tadalafil compared to tamsulosin plus placebo (2.5 points; $p<0.05$). In evaluating adverse drug events, only headache (12 vs. 0), hypotension (2 vs. 1), and dyspepsia (3 vs 1) occurred more often in the tamsulosin plus tadalafil group compared to tamsulosin plus placebo.

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Post-Test

1. Which of these PDE- 5 inhibitors is approved for use in BPH?
    a. Avanafil
    b. Sildenafil
    c. Tadalafil
    d. Vardenafil

2. With which additional BPH medication can a PDE-5 inhibitor be administered with for treatment of LUTS?
    a. Tamsulosin
    b. Terazosin
    c. Dutasteride
    d. Further studies needed

3. What mechanism of tadalafil may make tadalafil superior to other PDE-5 inhibitors?
    a. Selectivity for the PDE-11 receptor
    b. Avoids interactions with selective alpha-antagonists
    c. Avoids CYP 3A4 interactions
    d. Longer half-life

4. FR is a 59 year old male who currently complains of difficulty maintaining an erection. His physical exam is significant for DRE 30, IPSS of 7, BP 112/68, HR 55. His PMH include BPH and atrial fibrillation. He is currently taking diltiazem 240mg PO daily, ASA 325mg PO daily, terazosin 10mg PO QHS, and vitamin 1000 int units PO daily. Which of the following would be the preferred recommendations?
    a. Initiate tadalafil 5mg PO daily
    b. Discontinue terazosin and initiate tadalafil 5mg PO daily
    c. Change terazosin to silodosin 8mg PO daily and initiate tadalafil 5mg PO daily
    d. Change terazosin to silodosin 8mg PO daily, initiate finasteride 5mg PO daily, and initiate tadalafil 5mg PO daily.

5. UH is a 56 year old male who presents to the urologist for issues with urination (post-urine dribbling, incomplete voiding, and weak stream) and difficulty achieving an erection. On exam, DRE 25g and AUA-SI score 17. UH has PMH significant for diabetes type 2, erectile dysfunction, and post-MI (2 years prior). His medication list includes: metformin 1000mg PO BID, pioglitazone 30mg PO daily, ASA 81mg PO daily, enalapril 20mg PO BID, isosorbide mononite ER 60mg PO daily, atenolol 50mg PO daily, and rosuvastatin 10mg PO daily. Which of the following medications is the best option for UH?
    a. Alfuzosin ER 10mg PO daily
    b. Dutasteride 0.5mg PO daily
    c. Fesoterodine 4mg PO daily
    d. Tadalafil 5mg PO daily