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

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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 lower urinary tract symptoms (LUTS) in men. The intent of this document is to summarize the evidence on the safety and efficacy of the PDE5I for the treatment of benign prostatic hyperplasia (BPH) and LUTS, and in penile rehabilitation post-prostatectomy.

Literature searches were conducted to identify clinical trials, systematic reviews, meta-analyses and other pertinent publications using OVID Medline from January 2000 to July 2014 using the following terms: PDE5Is, BPH, LUTS, erectile dysfunction, and penile rehabilitation. Relevant citations were reviewed and their references searched for additional papers.

PDE5I to Treat BPH/LUTS

BPH is present in >50% of men age >50 years.[1] An estimated 30% or greater of men between the age 50 and 80 years have moderate to severe LUTS and nearly 50% report some degree of ED.[2]

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. A 3 point, non-placebo corrected improvement from baseline is considered the minimal change perceived as beneficial by patients.[3] Maximum urinary flow rate (Qmax) is another outcome measure frequently used in clinical trials. Study participants may be stratified by ED status and the International Index of Erectile Function (IIEF) is used measure change in erectile function. Another consideration is whether the PDE5I is being used as monotherapy or in combination with an $alpha_1$-blocker.

Two systematic reviews with meta-analyses of placebo-controlled trials have been published (Table 1).[4,5] Three PDE5I had been studied: sildenafil, tadalafil, and vardenafil. Liu et al. stratified their findings by BPH with and without ED.[4] Overall, PDE5I as monotherapy resulted in a significantly greater absolute difference in mean change in the IPSS score compared to placebo regardless of the presence of ED (Table 1). Gacci et al determined PDE5I monotherapy or in combination with an $alpha_1$-blocker resulted in a significantly greater absolute difference IPSS score from placebo and $alpha_1$-blocker alone (Table 1).[5] Maximum urinary flow rate (Qmax) was not significantly improved with PDE5I monotherapy, but was with the combination (Table 2). In men with ED at baseline, PDE5I monotherapy or in combination with an $alpha_1$-blocker significantly improved IIEF scores (Table 2).

Table 1 PDE5I Monotherapy or with an Alpha$_1$-blocker Meta-analysis: LUTS

PDE5I	# Studies	# Wks	N	Mean Absolute Difference in IPSS Score from Control
w/BPH (Lui)				
• Tadalafil	3	12	1062	-2.57 (-3.15, -1.98)
• Vardenafil	1	8	104	-2.20 (-3.57, -0.83)
• Sildenafil	1	12	179	-1.40 (-6.87, -1.93)
Overall	5		1345	-2.60 (-3.12, -2.07)
BPH & ED (Lui)				
• Tadalafil	2	12	526	-2.30 (-3.26, -1.34)
• Sildenafil	1	12	179	-4.40 (-6.87, -1.93)
Overall	3		705	-2.57 (-3.47, -1.68)
All (Gacci) Monotherapy Overall	7	8-12	3214	-2.85 (-3.60, -2.11)
PDE5I + α-blocker vs. α-blocker alone	5	8-12	278	-1.85 (-3.73, 0.00)

Table 2. PDE5I Monotherapy or with an Alpha1-blocker Meta-analysis: Qmax and IIEF

PDE5I	# Studies	N	Mean Absolute Difference in Qmax from Control	Mean Absolute Difference in IIEF from Control
w/BPH (LUI)				
• Tadalafil	6	1043	0.20 (-0.24, 0.64)	
• Vardenafil	1	104	0.60 (-1.42, 2.62)	
• Sildenafil	1	189	0.15 (-2.54, 2.84)	
Overall	8	1336	0.21 (-0.21, 0.64)	
All (Gacci) Monotherapy Overall	8		-0.01 (-0.58, 0.56)	5.49 (4.10, 6.88)
PDE5I + α-blocker vs. α-blocker alone	5		1.53 (0.91, 2.16)	3.60 (3.07, 4.12)

Other Comparisons Published Post SR and Meta-analyses

PDE5I vs. Placebo

A 12-week Phase 3 trial in 606 men with ED for at least 3 months and BPH-LUTS for 6 months or more compared tadalafil 2.5 mg and 5mg daily to placebo.[6] Following a 4-week placebo washout/lead-in period, men with an IPSS ≥13 and a Qmax ≥4 to ≤15 mL/sec were randomized 1:1:1. Both doses of tadalafil significantly improved IIEF-EF domain scores compared to placebo. Only tadalafil 5 mg resulted in a significant change from placebo in total IPSS and BPH Impact Index scores. Tadalafil 2.5 mg did not separate from placebo in any IPSS sub-scores, while the 5 mg dose differed significantly from placebo in voiding, storage, and modified IPSS, but not nocturia or quality of life index.

PDE5I vs. Alpha$_1$-blocker

One randomized, double-blind trial has been published comparing monotherapy with tadalafil, tamsulosin, and placebo in men with LUTS.[7] After 12-weeks all three treatments decreased IPSS scores from baseline with the mean change being significantly greater for both tadalafil and tamsulosin compared to placebo (Table 3). The difference in Qmax between active treatments and placebo was small and not clinically significant. Among men with ED, only those assigned to tadalafil reported a significant

improvement in IIEF score. A 1-year open-label extension trial with tadalafil 5 mg found that subjects maintained their improvement in erectile function and reported a mean decrease in post void residual of 19 mL.[8]

Table 3 Tadalafil or Tamsulosin vs. Placebo for LUTS[7]

Outcome	Tadalafil, n=171	Tamsulosin, n=171	Placebo, n=172
IPSS baseline	17.2 ± 4.9	16.8 ± 5.3	17.4 ± 6.0
Δ IPSS baseline	-6.3 ± 0.5	-5.7 ± 0.5	-4.2 ± 0.5
Δ IPSS vs. placebo	-2.1 (-3.3, -0.8)	-1.5 (-2.8, -0.2)	
Qmax, mL/sec			
Baseline	9.9 ± 3.6	9.4 ± 3.3	10.5 ± 4.1
Δ baseline	2.4 ± 5.5	2.2 ± 4.1	1.2 ± 4.8
p-value vs. placebo	0.0009	0.014	
Men w/ED			
Δ IIEF from baseline	4.0 ±1.0, p<0.001	-0.4± 1.0, p=-0.699	Not reported

PDE5I vs. Anitmuscarinics

After 12-weeks in a randomized, double-blind in men with ED post prostatectomy or TURP both tadalafil 5mg/day (n=26) and solifenacin 5 mg/day (n=25) significantly decreased IPSS scores from 8.8 to 3.8 and 8.7 to 3.5, respectively.[9] The change was primarily in daytime frequency and urgency as opposed to nocturia. IIEF scores improved only with tadalafil. Neither drug improved Qmax.

Hemodynamic Effects

The hemodynamic safety of using a PDE5I and alpha$_1$-blocker in combination is a concern recognized in the labeling of drugs in both classes. The hemodynamic effect of adding daily tadalafil 5 mg or placebo to existing alpha$_1$-blocker was assessed in a randomized, double-blind, parallel group trial.[10] Men ≥45 years with BPH >6 months who'd been taking an alpha$_1$-blocker for ≥4 months were eligible. Men who had experienced symptoms associated with orthostatic changes or taking alpha$_1$-blocker as an antihypertensive were excluded. After a 2-week, placebo washout/run-in period, subjects were randomized for a 12-week study period. The primary outcome variable was treatment-emergent dizziness.

Overall no significant difference was found in any treatment-emergent dizziness by the addition of tadalafil or placebo to any α_1-blocker whether non-selective or uroselective (Table 4). The proportion of subjects experiencing dizziness or at least one orthostatic change in vital signs was greater in those taking a non-selective α_1-blocker than those taking a selective α_1-blocker, but the within group differences were not significant (Table 4). Men 75 years and older were more likely to have at least one orthostatic change in vital signs but this did not differ by treatment group. A greater number (percent) of subjects assigned to tadalafil demonstrated orthostatic changes independent of the type of α_1-blocker, but these changes were not significant. None of the six adverse events determined to be severe were attributed to orthostatic changes.

Table 4 Number (%) Reporting a treatment emergent adverse effects after tadalafil or placebo added to alpha$_1$-blocker by uroselectivity[10]

Outcome	Any α_1-blocker		Non-selective α_1-blocker		Selective α_1-blocker	
	Placebo N=159	Tadalafil N=158	Placebo	Tadalafil	Placebo	Tadalafil
≥1 Primary Outcome	9 (5.7)	11 (7.0)	5 (9.4)	8 (15.4)	5 (4.6)	4 (3.8)
• Dizziness	8 (5.0)	10 (6.3)	5 (9.4)	6 (11.5)	3 (2.8)	4 (3.8)
• Dizziness, postural	1 (0.6)	1 (0.6)	0	1 (1.9)	1 (0.9)	0
≥1 Orthostatic Δ	-	-	10 (18.9)	15 (28.8)	21 (19.4)	15 (14.2)
• SBP ↓ ≥20 mmHg	-	-	4 (7.5)	3 (5.8)	12 (11.1)	7 (6.6)
• DBP ↓ ≥10 mmHg	-	-	5 (9.4)	8 (15.4)	13 (12.0)	7 (6.6)
• HR ↑ ≥20 BPM	-	-	1 (1.9)	4 (7.7)	3 (2.8)	2 (1.9)
• Unable to remain standing	-	-	0	0	0	0

Other Safety Analyses

In the SR/MA by Liu all three PDE5I were associated with an increased relative risk for adverse events (AE): tadalafil 2.27 (95% CI 1.36, 3.81), vardenafil 1.86 (1.11, 3.11), and sildenafil 1.22 (0.99, 1.51) with a larger proportion exposed to PDE5I (37%) experiencing at least one AE compared to placebo (24%). Serious AEs were reported by <2% in any group.[4] The SR/MA by Gacci, AEs were more commonly reported by PDE5I subjects (16%) than placebo (6%). When a PDE5I was used in combination with a α_1-blocker, 6.8% reported an AE compared to 5.1% taking a α_1-blocker and placebo.[5] Common AEs were flushing, gastrointestinal reflux, headache, dyspepsia, back pain, and sinusitis.

Clinical Practice Guidelines

The American Urological Association practice guidelines on BPH from 2010 and overactive bladder from 2012 were both reaffirmed in 2014 and do not discuss PDE5I as a treatment for LUTS.[11] The European Association of Urology guidelines from 2014 on the management of non-neurogenic LUTS recommend PDE5I with or without an alpha$_1$-blocker for moderate-to-severe (storage and voiding) LUTS in men with or without ED (Level of evidence: 1a; Grade of recommendation: A).

PDE5I Dose

Sildenafil: 50 mg – 100 mg once a day taken 2, 4 or 7 days a week as monotherapy; 25 mg once a day in combination with alfuzosin or tamsulosin.
Tadalafil: Label dose 5 mg once daily; higher doses not more effective and 2.5 mg dose ineffective.
Vardenafil: 10 mg twice daily or 20 mg daily.

Recommendations

- 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 PDE5I should be considered when more established pharmacotherapies are not an option or have not demonstrated benefit.
    - Consider PDE5I monotherapy
        - In place of an alpha$_1$-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$_1$-blocker prior to surgery.
        - When an alpha$_1$-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.

- Consider a PDE5I in combination
  - When symptoms are not relieved with an alpha$_1$-blocker alone and an antimuscarinic agent would not be appropriate (see above) while waiting for improvement from a 5-alpha-reductase inhibitor (usually 6 to 9 months).

PDI5 Inhibitors and Penile Rehabilitation

Prostatectomy, external beam radiotherapy or brachytherapy are effective and often employed treatments for prostate cancer. Erectile dysfunction is a common complication of these treatments and recovery, if it occurs, can take as long as 4 years. Analysis by PROSTQA investigators of 1027 men who underwent one of these interventions for prostate cancer between 2003 and 2006 who provided 2-year follow-up data determined that 52% of men who were without ED prior to treatment reported ED 2 years later.[12] Predictors of the preservation or return of erectile function after prostatectomy were the following: better pre-surgery erectile function, age, a nerve-sparing (NS) procedure, and a PSA $\leq$10 ng/mL. For example, a 50 year old man with a PSA <10 ng/mL in the 25% percentile of pre-treatment erectile function has a 35% predicted probability of suitable erectile function after a NS prostatectomy compared to 15% for a man age 70 with the same characteristics. If the procedure was non-NS, then the probabilities are 13% and 5%, respectively. The probability of normal erectile function 2-years after external radiotherapy and brachytherapy were 37% and 43%, respectively. Two-years after treatment 14 men reported having a penile prosthesis and 53% reported using a medication or device to assist in erectile function including 61% of men with normal erective function prior to treatment.

The PDE5Is are a treatment option for ED occurring after prostatectomy, external radiotherapy and brachytherapy. It has been hypothesized that regular use of a PDE5I may improve erectile function by reversing the effects of neuropraxia (hypoxia, apoptosis, venous leakage and fibrosis of the corpora cavernosa) secondary to surgery or radiotherapy. This hypothesis was tested in several trials prior to 2009 of varying quality. Findings suggested regular use of a PDE5I for >6 months post-prostatectomy increases spontaneous erections, quality of erections, and ability to attain an erection with or without additional PDE5I compared to no treatment. It was also clearly established that response was affected by the preservation of 1 or both neurovascular bundles, i.e., unilateral or bi-lateral NS. These earlier findings raised additional questions. Was there a difference in efficacy among the PDE5Is? What dose and frequency is best? When is the optimal time to begin treatment? How long is treatment necessary? Since PBM's initial review in 2009, multiple clinical trials have been published on the efficacy of PDE5Is for penile rehabilitation and one trial on whether vardenafil improves continence post-prostatectomy. Between 2009 and 2013, 2347 to 2672 radical prostatectomies were performed in VHA annually.[13] Through the 3rd quarter of FY14, 2300 radical prostatectomies were performed in VHA.[14] The CPT codes for the group includes both nerve sparing and non-nerve sparing procedures, thus it is not possible to forecast how many veterans are potential candidates for post-prostatectomy penile rehabilitation with a PDE5I.

Studies of a PDE5I in men with normal erectile function prior to BNSRP

The efficacy of PDE5I as penile rehabilitation in men with normal erectile function prior to bilateral nerve sparing radical prostatectomy (BNSRP) has been reported in four randomized, double-blind, controlled trials published since 2008.[15-18] These trials either compared the efficacy of nightly and/or on-demand PDE5I to placebo or to each other throughout a 3 to 12 month double-blind period and after a 1 or 2 month washout period. In general, study participants were men age 18 years and older with T_1 or T_2

prostate cancer, a Gleason score of <7 to 10, and a PSA ≤10 ng/mL scheduled to undergo a BNSRP. Randomization and treatment took place 2 to 4 weeks after surgery.

Padna-Nathan et al. randomized (1:1:1) 125 men to nightly sildenafil 50 mg or 100 mg, or placebo for 36 weeks followed by an 8 week untreated washout period.[15] The primary outcome was "responders" defined as having a combined score of 8 or greater to IIEF-EF Q3 and Q4, plus a "Yes" response to the question asking if the erection quality for the past 4 weeks was sufficient for satisfactory sexual activity during the 8-week washout period. IIEF-EF Q3 and Q4 asked if over the past 4 weeks their erections were sufficient to penetrate their partner (Q3) and if erections were sufficient for intercourse after penetration. In other words, responders demonstrated the return of spontaneous erections without assistive drugs or devises. At the end of the 8 week placebo washout period the proportion of responders were 4% (1/25) placebo, 26% (6/23) sildenafil 50 mg and 29% (8/28) sildenafil 100 mg. The overall response rate for sildenafil was 27%. The study was stopped prematurely due to a low overall response rate.

Montorsi et al. conducted the largest trial to date with 628 men randomized (1:1:1) to vardenafil 10 mg nightly (V_N) or on demand (V_{OD}), both with corresponding placebo, i.e., dummy design), or nightly and on demand placebo.[16] The dose of vardenafil could be increased to 20 mg or decreased to 5 mg if needed. Throughout and at the end of the 9 month double-blind period the proportion of subjects assigned to V_{OD} reported significantly improved erectile function compared to placebo and V_N (Table 5) as measured by an IIEF-EF ≥22 (mild ED) and ≥26 (normal), and responded "Yes" to SEP3 (if erections were of sufficient duration for intercourse). During the single-blind, placebo, 2-month washout and the 2-month, V_{OD} open-label periods there were no significant differences between the treatment groups in any outcome measures (Table 5). Neither the number of on-demand provided or taken is provided.

Table 5 Outcome measures as percent of study subjects by treatment and treatment period[16]

Outcome Measure	Treatment	Double-blind, 9 mo.	Washout, 2 mo.	Open label, 2 mo.
IIEF-EF ≥22	V_{OD} V_N Placebo	48.2 32.0 24.8	29.1 24.1 28.9	54.2 52.6 47.8
IIEF-EF ≥26	V_{OD} V_N Placebo	36.2 20.1 16.8	NS, data not provided	39.3 37.8 32.5
SEP3	V_{OD} V_N Placebo	45.9 34.5 25.0	NS, data not provided	62.6 59.8 57.1

Pavlovich conducted a single-institution, randomized, double-blind trial in 102 men scheduled to undergo laparoscopic or robot-assisted nerve sparing radical prostatectomy (NSRP).[17] The study compared nightly sildenafil 50 mg plus on-demand placebo to on-demand sildenafil 50 mg plus nightly placebo with a primary outcome of erectile function recovery over time as measured by IIEF-EF. Assessments were repeated over a 12-month double-blind period and then after a 1-month washout period without sildenafil, placebo or other ED treatment. During the 12 month double-blind period mean IIEF-EF scores, percent of subjects returning to baseline, and percent with a IIEF-EF score >21 did not differ significantly between treatments. At the end of the washout, there was no difference between treatments in any outcome measures after adjustment for nerve sparing score. The extent of nerve sparing was a significant predictor of IIEF-EF score and recovery of erectile function towards baseline, odds ratio 1.25 (95% CI 1.06, 1.46). The efficacy of on-demand sildenafil (mean 4.4 doses/month) was equivalent to nightly sildenafil 13 months after NSRP.

One trial has been conducted comparing intraurethral alprostadil 125 µg nightly to sildenafil 50 mg nightly as penile rehabilitation after NSRP.[18] The dose of alprostadil was increased to 250 µg nightly after 1 month for the duration of the trial. Two hundred twenty-seven men consented to participate prior to surgery and 212 entered the trial; exclusions were 7 men who underwent unilateral radical prostatectomy and 8 who withdrew consent. Within 1month of surgery subjects were randomized (2:1) to open-label alprostadil (n=139) or sildenafil (n=73) with 97 and 59, respectively, completing the trial. After 9 months, both treatments were stopped during a 1 month washout period, followed by sildenafil 100 mg on-demand for the final month. The study does not appear to have a primary outcome measure; however, response was assessed by the IIEF-EF, SEP, Global Assessment Questionnaire (GAQ) which asks "Has the treatment you have been taking during this study improved your erection?", and measured stretched penile length.

IIEF scores in both groups increased in both groups without a significant difference between groups. The proportion of men with an IIEP score >17 (mild-moderate ED) or >26 (normal) did not differ significantly at any time point. Response to the GAQ only differed at the 6 month time point favoring alprostadil. Intercourse success rates did not differ between treatments and penile length did not change in either group of the course of the study. Unfortunately this study design did not allow for the assessment of outcome measures at the end of the washout period, thus no conclusions can be drawn on the rate of spontaneous erections after treatment had been completed. The dropout rate was great in the alprostadil group than in the sildenafil group, 30% vs. 19%.

PDE5I for penile rehabilitation after radiotherapy for prostate cancer

One randomized trial has been conducted to determine whether tadalafil maintains spontaneous erections in men treated with either external or brachytherapy for prostate cancer.[19] Men with clinical stage II prostate adenocarcinoma whose Gleason score was<7 and PSA was <20 ng/mL, or whose Gleason score was ≥7 and PSA <15 ng/mL, and were able to achieve an erection ≥50% of the time were eligible to participate in this multicenter, placebo-controlled, double-blind, parallel-group trial. Randomization to either daily tadalafil 5mg or placebo was stratified by type of radiotherapy and age ≤65 and >65 years (1:1). Treatment for ED started within 7 days after the start of radiotherapy and continued for 24-weeks, then discontinued during a 4-week washout period. Assessments were made during the 24-week double-blind period and between weeks 28 and 30, then at 1-year using the IIEF-EF, the Sexual Adjustment Questionnaire, and the Locke Marital Adjustment Test. The primary outcome measure was the proportion of subjects capable of spontaneous erections 4 to 6 weeks after ED treatment had been stopped (between weeks 28 and 30). The primary outcome was determined by asking participants "How often were you able to get an erection during sexual activity?" Men who replied "about half the time or more" were categorized as capable of spontaneous erections, while those responding "much less than half the time" were considered to have ED.
A total of 242 men were randomized equally to both ED treatment groups. Of those randomized to tadalafil, 96 completed the trial and 112 were included in the primary analysis; the corresponding numbers assigned to placebo were 78 and 109, respectively. The change from baseline (pre-radiotherapy) in outcome measures was less than that seen after prostatectomy, e.g., IIEF-EF declined from points at baseline to ~21 points in both groups 30 weeks after starting radiotherapy. Regarding the study's primary outcome, 79% (95% CI 70%-88%) assigned to tadalafil and 74% (63%-85%) assigned to placebo retained spontaneous erectile function, p=0.49. The results were similar after 1 year, tadalafil 72% (60%-80%) and placebo 71% (59%-84%), p=0.93. Compared to placebo, daily tadalafil demonstrated zero benefit over placebo across all measures of erectile function, sexual satisfaction and partner responses in men whose prostate cancer was treated with radiotherapy.

Safety

Review of the safety reports from the above trials did not identify any safety concerns with the PDE5Is that are not already known.

Recommendations

PDE5Is have been hypothesized to aid penile rehabilitation and increase the likelihood of spontaneous erections following prostatectomy or radiotherapy. Not surprisingly, recent clinical trials have shown on-demand and daily use of a PDE5I to be effective treatment for ED in the months following prostatectomy, or during and after radiotherapy. Based on the available evidence, on-demand or daily use of a PDE5I for up to 12 months does not appear to improve the chances of spontaneous erections unaided by drugs or devices after prostatectomy or radiotherapy. Therefore, the following recommendations are put forth:

- A PDE5I should not be prescribed for the sole purpose of penile rehabilitation after prostatectomy or radiotherapy.
- On-demand PDE5I can be prescribed for the treatment of ED after prostatectomy or radiotherapy as it would be for other causes of ED. Currently PBM recommends limiting a PDE5 inhibitor to 4 doses per month, but larger quantities can be dispensed as stated in the Sildenafil Quantity Limits recommendations.

References

1. Norman RW, Nickel JC, Fish D, et al. Prostate-related symptoms in Canadian men 50 years of age and older: prevalence and relationships among symptoms. Br J Urol 1994;74:542-550.
2. Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol 2003;44:637-649.
3. American Urological Association (AUA) Benign Prostatic Hyperplasia (BPH) Guideline Update Panel. Guideline on the management of benign prostatic hyperplasia. American Urological Association; 2006.
4. Liu L, Zheng S, Han P, et al. Phosphodiesterase-5 inhibitors for lower urinary tract symptoms secondary to benign prostate hyperplasia: A systematic review and meta-analysis. Urology 2011;77:123-130.
5. Gacci M, Corona G, Salvi M, et al. A systematic review and meta-analysis of the use of phosphodiesterase 5 inhibitor alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. European Urology 2012;61:994-1003.
6. Egerdie RB, Aurbach S, Roehborn CG, et al. Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: Results of a randomized, placebo-controlled, double-blind study. J Sex Med 2012;9:271-81.
7. 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, randomized, parallel, placebo-controlled clinical trial. Euro Urology 2012;61:917-25.
8. Donatucci CF, Brock GB, Goldfischer ER, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension trial. BJU International 2011;107:1110-16.
9. Maselli G, Bergamasco L, Sivestri V, et al. Tadalafil versus solifenacin for persistent storage symptoms after prostate surgery in patients with erectile dysfunction: a prospective randomized study. Int J Urology 2011;18:515-20.

10. Goldfischer E, Kowalczyk JJ, Clark WR, et al. Hemodynamic effects of once-daily tadalafil in men with signs and symptoms of benign prostatic hyperplasia in concomitant α_1-adrenergic antagonistic therapy: results of a multicenter randomized, double-blind, placebo-controlled trial. Urology 2012;79:875-82.
11. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011;185:1793-1803.
12. Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. JAMA 2011;306:1205-1214.
13. VHA National Surgery Office. 2013 National Surgery Office Annual Surgery Report. Available at: http://vaww.dushom.va.gov/DUSHOM/surgery/docs/AnnualSurgeryReport.pdf Accessed November 6, 2014.
14. William Gunnar, MD, VHA National Director of Surgery. Personal communication, November 6, 2014.
15. Padam-Nathan H, McCullough AR, Levine LA, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res 2008;20:479-486.
16. Montorsi F, Brock G, Lee J, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol 2008;54-924-931.
17. Pavlovich CP, Levinson AW, Su L-M, et al. Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. BJU Int 2013;112:844-851.
18. McCullough AR, Hellstrom WG, Wang R, et al. Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus sildenafil citrate. J Urol 2010;183:2451-2456.
19. Pisansky TM, Pugh SL, Greenberg RE, et al. Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: the Radiation Therapy Oncology Group [0831] randomized clinical trial. JAMA 2014;311:1300-1307.

Prepared: December 2014 Contact person: Todd Semla, MS, Pharm.D., BCPS, FCCP, AGSF