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Current practice of the combination therapy of phosphodiesterase-5 inhibitors and alpha-1 adrenergic blockers in the treatment of BPH/LUTS in non-neurogenic bladder and the emerging issues in Saudi Arabia – a preliminary report.

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ABSTRACT

Both ED and LUTS secondary to BPH are found to be increasingly prevalent as men age. The presence of PDE5 receptors within corpus cavernosal smooth muscle is well established. However, isoforms PDE1 and PDE4 have also been found distributed throughout the lower urinary tract mediating smooth muscle relaxation at the bladder neck, prostate, and proximal urethra. Recently, PDE5 inhibitors have been approved to treat LUTS/BPH patients with or without ED. Our objective was to report the highs and lows of doctors and patients preliminary experience surrounding the combination of PDE5 inhibitors and alpha-1 adrenergic blockers in the treatment of LUTS/BPH. We aim at highlighting the points necessary to come up with judicious recommendations and guidelines. In this review we have studied the up-to-date papers in PubMed published on the pharmacological effects of PDE5 inhibitors on LUTS/BPH. Furthermore, we focused on the papers ascribed to combining PDE5 inhibitors with alpha-1 adrenergic blockers to treat LUTS/BPH with or without ED. In addition, we presented our early experience in Saudi Arabia surrounding the pros and cons of the combination therapy along with the patients ‘experience. Clinical trials have shown a diversity of clinical applications of PDE5 inhibitors. One of which is in treating LUTS/BPH "patients’ experience" whether alone or in combination with alpha adrenergic blockers. Tadalafil 5 mg has gained the first licensure for the daily use for LUTS/BPH "patients’ concerns" with or without ED. This paper has presented our early experience on the combination therapy and expressed the patients ‘concerns in details. In current practice, the application of the combination therapy of PDE5 "inhibitors’ preparation" and alpha-1 adrenergic blockers fits better patients who complain of LUTS/BPH and ED simultaneously. Patients who have achieved a steady level of improvement on alpha blockers alone, and expect more, might benefit from the dual therapy. In addition, many BPH patients on 5-alpha reductase inhibitors choose to add on PDE5 inhibitors` preparation to their medications in attempt to overcome the sexual dysfunction drawbacks of the former drug. On the other hand, several issues have been encountered like the concomitant use of nitrate preparations with PDE5 inhibitors, the exorbitant cost of the uninsured daily dose, and the existing comorbidity that patients in Saudi Arabia often have.

Keywords: LUTS/BPH, ED, combination therapy, PDE5 inhibitors, Alpha blockers.

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INTRODUCTION

Since the invention of the oral treatment of ED using sildenafil, the first-born of the PDE5 inhibitors family, in 1998; the nitrous oxide (NO) mechanism of corporal smooth muscle relaxation has been reported to be a ground-breaking discovery. The pharmacological indications of this class of medicine have broadly expanded to include a wide array of clinical usages. In 2005, the Food and Drug Administration (FDA) in the United States has approved sildenafil for the treatment of pulmonary hypertension. Not too long after that, tadalafil gained the first approval for LUTS/BPH in 2011 in the United States; and was subsequently approved in the European Union, Russia, Canada, and several countries in Central and South America and Asia [1]. Recently, in Marsh 2016, Shokeir et al, have published a promising usage of sildenafil citrate as a medical expulsive therapy for distal ureteric stones [2]. The daily dosing of PDE5 inhibitors was another challenge. It has been tried first in the treatment of pulmonary hypertension using sildenafil 25mg tablets every 6 to 8 hours. The presence of PDE5 receptors within corpus cavernosal smooth muscle is well established. However, various isoforms of PDEs have also been found distributed throughout the lower urinary tract. Uckert et al [3], have reported the presence of multiple isoforms of PDEs within the transition zone of the prostate using polymerase chain reaction techniques. PDE4 receptors were found in highest abundance, followed by PDE5`s. Specifically, PDE4 receptors were present in the fibromuscular stroma as well as the glandular tissue of the transition zone of the prostate. Furthermore, the authors showed that sildenafil could mediate relaxation of prostatic transition zone tissue. Inhibition of PDE1 and 4 receptors have been shown to influence detrusor function in several experimental models [4-8]. Werkstrom et al [9], have shown the presence of the PDE5 isoform in urethral and vascular smooth muscle cells. Moreover, in the presence of PDE5 inhibitors, smooth muscle relaxation was observed. Several studies have examined the role of NO pathway in the treatment of LUTS secondary to BPH through the use of PDE5 inhibitors. An open labeled study by Sairam et al [10], examined the effects of sildenafil on patients presenting with concomitant ED and LUTS. Of 112 patients included, 20 patients reported LUTS, with 32% experiencing moderate to severe symptoms as measured by the IPSS. After 12 weeks of treatment, an improvement in IPSS and LUTS-specific QoL was reported. Patients with severe LUTS have shown remarkable symptomatic improvement; and 60% of patients with initially moderate symptoms reported mild symptoms at the conclusion of the study. A similar open-labeled study was performed by Mulhall et al [11], where 48 men (mean age 64±11 years) with moderate LUTS

(IPSS≥10) completed IPSS and IIEF surveys before and after 12 weeks of sildenafil 100 mg treatment (mean number of uses per week 2±0.6). IPSS scores improved in 63%, with 37% experiencing an improvement of 4+ points in their IPSS. Ying et al [12], have reported similar results with changes in IPSS in 32 men presenting with ED and LUTS treated over 24 weeks with sildenafil.

Tadalafil, too, has been investigated for the treatment of moderate to severe LUTS secondary to BPH in a randomized, double-blind, placebo-controlled study involving 281 men by McVary et al.[13] Patients were stratified by baseline IPSS (moderate: 13–19, severe: 20–35), geographic region, and earlier therapy. After a 4-week placebo run-in phase to establish baseline IPSS and uroflowmetry values, patients were randomized to either treatment with tadalafil (5 mg for 6 weeks subsequently increased to 20 mg for 6 weeks) or placebo for 12 weeks. Efficacy was established through changes in IPSS at 6 and 12 weeks of therapy. Secondary end points included changes in IPSS QoL index, uroflowmetry values (Q-max). At both 6 and 12 weeks of treatment, the tadalafil treatment group experienced improvement in LUTS with significant decrease in IPSS compared with placebo: −2.8 vs −1.2 (6 weeks) and −3.8 vs −1.7 (12 weeks). Sub-analysis of irritative and obstructive voiding symptoms also showed significant improvements in the treatment arm. It was found, however, that there was no change in Q-max compared with placebo.

On parallel studies, Stief et al.[14] have examined vardenafil for the treatment of LUTS in a multi-center, randomized, double-blind, placebo-controlled trial. A group of 222 men with LUTS (IPSS≥12) were randomized to either vardenafil (10 mg twice daily) or placebo, and studied over an 8-week period. Efficacy was assessed by changes in IPSS, UROLIFE QoL, Q-max, and post void residual (PVR) parameters. After treatment, a significant reduction of 5.9 points on the IPSS was noticed in the treatment group vs 3.6 points seen with placebo. Sub-scores for storage and voiding symptoms also showed a significant improvement with treatment, as did UROLIFE QoL. However, no significant change was noted in either PVR or Q-max.

Roehrborn et al.[15] have performed a dose-finding study using tadalafil for LUTS. They examined 1058 men in a randomized, double-blind, placebo controlled, parallel group study. The patients were assigned to placebo or one of four different tadalafil dosing regimens (2.5, 5, 10, or 20 mg daily). Participating patients initially presented with an IPSS≥11. After using a 4-week single-blind placebo run-in phase, men were stratified by baseline IPSS (<20 or ≥20), uroflowmetry parameters, and ED history (<3 months, or ≥3 months). End points assessed included IPSS, irritative and obstructive sub-scores, QoL assessment, Q-max, and LUTS GAQ. In the 5-mg

treatment group, a statistically significant reduction in IPSS was observed, with a decrease of 4.9 vs 1.8 in placebo. IPSS QoL, and LUTS GAQ all significantly improved at this dosage level. Urinary flow and Q-max were not affected by any dosage level in comparison with placebo. It was noted that when increasing the tadalafil dose beyond 5 mg, it produces similar improvements in IPSS, but higher incidence of adverse effects.

All the aforementioned clinical studies show significant improvement in IPSS after PDE5 inhibitor therapy compared with placebo. These improvements are in line with the results seen in earlier studies involving alpha adrenergic-1antagonists (alpha blocker) therapy alone. A study by Roehrborn [16], has shown that when following treatment with 10 mg alfuzosin (12 weeks) instead of placebo, the IPSS has significantly decreased by 3.8 vs 1.7 points in favor of the alfuzosin arm.

A study by Gacci et al.[17] in men with neurogenic bladders secondary to spinal cord injury showed that open-labeled vardenafil treatment resulted in significant improvements in maximum detrusor pressure, total capacity, and volume-triggered bladder spasms. Thus, PDE5 inhibitors may act at an alternative site of action, separate from alpha blockers [18]. Their effects may be secondary to relaxation of smooth muscle present in the prostate, urethra, and bladder neck, as well as their vascular supply [19-22]. In-vitro studies have also shown that NO donor drugs and PDE5 inhibitors may stimulate anti-proliferative or apoptotic effects in the prostate, improve pelvic blood flow, and have effects on afferent nerves from the prostate or bladder, resulting in their improvement of LUTS symptoms [23,24]. A study by Dmochowski et al,[25] has examined LUTS and urodynamic parameters in 200 men (baseline IPSS≥13) randomized to tadalafil (20 mg) treatment or placebo for 12 weeks. In addition, bladder outlet obstruction (BOO) index was examined after treatment. Although no difference was noted in urodynamic parameters after treatment (including BOO index), IPSS improved significantly in the treatment group compared with placebo. Furthermore, at the conclusion of the study, the proportion of obstructed patients in the treatment group decreased, whereas the proportion in the placebo group increased. Thus, the exact mechanism by which PDE5 inhibitors exert their effect on urinary symptoms is not completely understood.

A plausible link involves the NO/cGMP pathway. The role of NO/cGMP in corpus cavernosal smooth muscle relaxation is well understood. Immediate relaxation of cavernosal tissue is induced by neurogenic NO, whereas endothelial NO is involved in maintenance of relaxation 26. Increased levels of NO lead to increases in cGMP production through guanylyl cyclase activity. Cyclic GMP subsequently phophorylates several other targets, leading to depletion of

intracellular calcium [27]. This leads to a dissociation of calmodulin from myosin light chain (MLC) kinase and its inactivation (phosphorylation). Myosin is subsequently dephosphorylated by MLC phosphatase, detaching from actin. This cascade ultimately results in smooth muscle relaxation [28].The inactivation of cGMP is mediated by phophodiesterases (PDEs).

Further studies have shown the presence of NO and PDE receptors in the remainder of the lower urinary tract, including the prostate, bladder, and urethra. Through inhibition of neurotransmission in the urethra and bladder afferent nerves, NO may also be involved in the micturition process [29]. NO has also been found to be involved in prostatic smooth muscle tone, glandular secretion, and blood flow [30, 31]. The distribution of various isoforms of NO synthase (NOS) has been shown in prostatic tissue through immunohistologic means. Burnett et al [32], have shown the presence of neurogenic NOS in nerve tissue in the prostate's transition zone. Studies by Richter et al. [33] and Bloch et al [34], detected endothelial NOS in the vascular supply of the prostate and neurogenic NOS in the nerve fibers of the fibromuscular stroma, respectively. Gradini et al [35] through immunohistochemical and polymerase chain reaction (PCR) analysis showed expression of endothelial NOS in normal and hyperplastic prostatic tissue, whereas neurogenic NOS was prevalent in the secretory layer of glandular epithelium.

Bloch et al [34] have found NOS/NO levels to be low in the prostate's transition zone when comparing hyperplastic to normal tissue. Furthermore, nitrinergic innervation is decreased in hyperplastic prostatic tissue. These findings were confirmed by mRNA analysis of NOS gene levels in prostatic specimens extracted from TURP specimens from patients with BPH compared with normal prostatic tissue. There was a positive correlation between the decline in NOS level in relation to age and increased prostate volume [36]. Consequently, it can be postulated that decreased nitrinergic innervation in BPH coupled with a reduction in NO-mediated smooth muscle relaxation may have a role in the pathophysiology of LUTS.

Long–term efficacy of tadalafil was evaluated in an extension study (N = 427) of tadalafil 5 mg once–daily in men with LUTS/BPH [37.] Improvements during the placebo–controlled period or the first months of the extension were maintained during one year of therapy as assessed by total IPSS [37]. After 1 month of treatment in the extension phase, men who changed from placebo or 2.5 mg of tadalafil to the 5 mg dose had a statistically significant ($P < 0.01$) reduction in IPSS, while men who remained on tadalafil 5 mg or decreased their dose to 5 mg (from 10 or 20 mg) maintained the improvement. Data on tadalafil once daily for LUTS/BPH efficacy with follow up longer than 1 year are lacking.

The concept of combination therapy in the treatment of BPH is not novel. Alpha blockers, the first line treatment of symptomatic LUTS/BPH, have been used in combination with 5-alpha reductase inhibitors (5ARI) in the management of moderate to severe symptomatic LUTS/BPH. Furthermore, anti-cholinergic along with alpha blocker is the combination of choice for BPH with bothering irritative LUTS. Phytotherapeutic agents and dietary supplements are widely used in conjunction with pharmaceutical products in the treatment of LUTS/BPH. The same may hold true in combining PDE5 inhibitor with alpha blockers. The 2013 Guidelines on the Management of Male LUTS (including Benign Prostatic Obstruction) published by the European Association of Urology (EAU) and guidelines compiled by the American Urological Association (AUA) recommend the use of several different pharmacotherapies for the treatment of LUTS, depending on the clinical situation [38,39].

Given that alpha blockers are often first–line treatments for LUTS/BPH, tamsulosin 0.4 mg once daily was included as the active control in a double–blind placebo–controlled study (N = 511) of tadalafil 5 mg for 12 weeks [40]. Although not designed for statistical testing of superiority, this study found that the change from baseline to week 12 in total IPSS was statistically significant for both tadalafil and tamsulosin versus placebo (P = 0.001 and P = 0.023, respectively). The magnitude of improvement in total IPSS at the 12 week endpoint with tadalafil was comparable to that with tamsulosin and consistent with other reports. As measured by IIEF–EF, tadalafil significantly improved erectile function (P <0.001) compared with placebo in sexually active men with ED (approximately 60% of subjects), while tamsulosin did not (P = 0.699) [40, 41]. Overall, evidence from this study indicates that tadalafil 5 mg or tamsulosin 0.4 mg once daily results in similar improvements in LUTS/BPH symptoms at 12 weeks. Well controlled clinical trials that thoroughly evaluate the potential action of combination therapy with tadalafil and an alpha blocker are lacking. A preliminary report of alfuzosin 10 mg once daily, tadalafil 20 mg on alternative days or a combination of both in men with LUTS/BPH indicated that the dual therapy has improved symptom and uroflowmetry measures [42]. A small placebo controlled study (N = 40) of tamsulosin 0.4 mg/tadalafil 5 mg versus tamsulosin 0.4 mg/placebo once daily in LUTS/BPH detected a significant decrease in total IPSS (P = 0.01) from baseline to week 4 in the tamsulosin/tadalafil group [43]. A small crossover study (N = 30) of tamsulosin 0.4 mg/tadalafil 20 mg or tamsulosin 0.4 mg/placebo once daily in LUTS/BPH showed significant improvements in IPSS with both treatments [44]. Evidence from these non–registration studies suggests an additive effect with combination therapy. However, the dual therapy database is limited and further research is needed. The manufacturer of tadalafil has not conducted a well controlled

head–to–head or combination study with alpha blockers other than for safety reasons. At present, prescribing instructions do not recommend tadalafil in combination with alpha blockers in LUTS/BPH because efficacy has not been adequately studied and because of the potential risk of lowering blood pressure [45].

DISCUSSION:

Both ED and LUTS secondary to BPH are found to be increasingly prevalent as men age. Several large epidemiologic studies have shown an association between LUTS and ED independent of age and other co-morbidities, implying a causal relationship. Few studies have examined a temporal association, and further research is required. Several possible pathophysiologic mechanisms have been described and may explain the role of PDE5 inhibitor therapy in LUTS. Moreover, chronic treatment with PDE5 inhibitors seems to increase blood perfusion and oxygenation in the LUT [46]. Finally, PDE5 inhibitors could reduce chronic inflammation in the prostate and bladder [47]. The exact mechanism of PDE5 inhibitors on LUTS remains unclear. Although clinical trials of several selective oral PDE5 inhibitors have been conducted in men with LUTS, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS with or without ED. Several RCTs have demonstrated that PDE5 inhibitors reduce IPSS, storage and voiding LUTS, and improve QoL. However, Q-max did not significantly differ from placebo in most trials. In a meta-analysis, PDE5 inhibitors were found to improve IPSS and IIEF score, but not Q-max [48]. Tadalafil 5 mg reduces IPSS by 22-37% and improvement may be seen within a week of initiation of treatment [49]. The longest open-label trial was 52 weeks [50]. A subgroup analysis of pooled data from 4 RCTs demonstrated a significant reduction in LUTS, regardless of baseline severity, age, previous use of alpha blockers or PDE5 inhibitors, total testosterone level or predicted prostate volume [51]. Among sexually active men who are > 45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [52.] An integrated data analyses from 4 placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%, $p < 0.001$) vs. indirect (7.5%, $p=0.32$) treatment effects via IIEF-EF improvement [53]. Another analysis showed a small but significant increase in Q-max without any effect on PVR [54].

The combination of PDE5 inhibitors and alpha blockers has also been evaluated. A meta-analysis of 5 RCTs (two studies with tadalafil 20 mg, two with sildenafil 25 mg, and one with vardenafil 20 mg), showed that combination therapy significantly improved IPSS score (-1.8), IIEF score (+3.6) and Q-max (+1.5 mL/s) compared with alpha blockers alone [48]. The effects of tadalafil 5

mg combined with finasteride 5 mg were assessed in a recent 26 week placebo-controlled RCT. The combination of tadalafil and finasteride provided an early improvement in urinary symptoms ($p < 0.022$ after 4, 12 and 26 weeks), with a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function [48.]

Reported adverse effects in RCTs comparing the effect of all PDE5 inhibitors vs. placebo in men with LUTS include flushing, gastro-esophageal reflux, headache, dyspepsia, back pain and nasal congestion [48]. Discontinuation rate due to adverse effects for tadalafil was 2.0% [56] and did not differ by age, LUTS severity, testosterone levels, or prostate volume in the pooled data analyses [51].

PDE5 inhibitors are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the alpha 1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (< 3 months) or stroke (< 6 months), myocardial insufficiency (New York Heart Association stage > 2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5 inhibitors.

To date, only tadalafil 5 mg once daily has been authorized for the treatment of male LUTS with or without ED. The meta regression suggested that younger men with low body mass index and more severe LUTS profit the most from treatment with PDE5 inhibitors [48]. Long-term experience with tadalafil in men with LUTS is limited to one trial with 1 year follow up [50], and therefore conclusions about its efficacy or tolerability > 1 year are not possible. There is limited information on reduction of prostate size and no data on disease progression.

Current practice in Saudi Arabia:

The concept of combination therapy in Saudi population is well accepted. Herbal preparations and dietary supplements are widely used. Furthermore, plant therapy is deeply ingrained in Arabic culture and patients' background. Therefore, amid of the medications BPH patients take for various concomitant ailments, PDE5 inhibitor mini-dose is quite accommodated. In practice, there are several applications for the combination of PDE5 inhibitors and alpha blockers. Firstly, the dual therapy is a better fit for patients complaining of LUTS/BPH and ED simultaneously. A second plausible application is when a given patient has come up to a steady level of urinary flow quality on using alpha blockers alone, but expecting further improvement. A third application in real life experience is that prescribing the dual therapy is based not only on the expectancy that PDE5 inhibitors are erectile function enhancers, but also on the premise that the

erectile dysfunction effects of 5-alpha reductase inhibitors will be ameliorated. Finasteride is infrequently associated with problems of ejaculation (2.1-7.7%), erection (4.9-15.8%), and libido (3.1-5.4%) [57].

For the seek of achieving a satisfactory erection, the full therapeutic dose of PDE5 inhibitors must be taken; bearing in mind that clients in Saudi Arabia have had heavy anamnesis and comorbidity. In Saudi population aging 50 years or over almost half are type-II diabetics and another 10-15% are pre-diabetics 48. A community based study that evaluated 10,735 participants in Saudi Arabia has shown that 28.7% were obese (body mass index ≥30 kg/m^2)59. Hyperlipedimia has reached a sky-high prevalence rates in Saudi Arabia. This finding may suggest that coronary artery disease (CAD) will soon be a major health problem. Alarming results have been reported from a study that has included 16,819 samples and revealed that hypertriglycemia prevalence was 40.3%, while the prevalence of hypercholestremia was 54% with mean cholesterol level of 5.4+/-1.52 mmol/l 60. Based on the foregoing data, Patients who are on PDE5 inhibitors mini-dose are still in need for the full dose of the medication for ED usage. The full dose of PDE5 inhibitors tablet is undividable. Moreover, it would be cumbersome to sum up the full dose out of the mini-dose pills. Naturally, patients are up against swallowing handsome medications altogether. An additional obstacle is the nitrate preparations for CAD being a solid contraindication when taken with PDE5 inhibitors medications. Ischemic heart disease is a serious health issue to consider as the overall prevalence of CAD in the country is 5.5% 60. Practically, patients are reluctant to take the PDE5 inhibitors pill at the same day they receive nitrate preparation; resulting in omitting the PDE5 inhibitors daily dose.

To date, the Saudi Drug and Food Authority (SFDA) hasn`t approved PDE5 inhibitors mini-dose for daily administration to treat LUTS/BPH. Another issue to consider is that health insurance companies don't cover the daily dose expenses yet. By law, all PDE5 inhibitors preparations are prescribed medications regardless of the dosing. In a street pharmacy, the 28 tablet package of 5 mg Cialis (a product of Lilly company) is sold for SR280 ($75), which is too expensive for an average person to afford.

Future experimental research is needed to discover new clinical usages of PDE5 inhibitors than what originally thought to be preposterous. One of which could be the probable use of PDE5 inhibitors in the treatment of LUTS in women.

CONCLUSION

Currently, in Saudi Arabia the prime application of the combination therapy of PDE5 inhibitors and alpha blockers is for those who complain of LUTS/BPH and ED simultaneously. Moreover, patients who have achieved a steady level of improvement on alpha blockers alone, and expect more, might benefit from the dual therapy. In addition, many BPH patients on 5-alpha reductase inhibitors choose to add on PDE5 inhibitor preparation to their medications in attempt to overcome the sexual dysfunction drawbacks of the former drug. On the other hand, several issues have had been encountered that include but not limited to, the concomitant use of nitrate preparations with PDE5 inhibitors, the exorbitant cost of PDE5 inhibitors at the street pharmacies, the daily dosing being uncovered by health insurance companies yet, and the existing comorbidity that patients often have. Clear guidelines and general agreements, by international authorities, on the proper indications of the combination therapy are pending.

REFERENCES:

1- PRNewswire (Oct. 30, 2012). European Commission approves Cialis® (tadalafil) tablets for the treatment of the signs and symptoms of benign prostatic hyperplasia. Available fromhttp://newsroom.lilly.com/releasedetail.cfm?releaseid=717071. Accessed April 4, 2013.

2- Shokeir A, Tharwat M, Abolazm A, et al. Sildenafil citrate as a medical expulsive therapy for distal ureteric stones: A randomised double-blind placebo-controlled study. Arab Association of Urology. 2016, Mar,14(1):1-6.

3- Uckert S, Oelke M, Stief CG, et al. Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE) isoenzymes in the human prostate. Eur Urol 2006; 49: 740–745.

4- Morley DJ, Hawley DM, Ulbright TM, et al. Distribution of phosphodiesterase in normal human tissues. J Histochem Cytochem 1987; 35: 75–82.

5- Truss MC, Stief CG, Uckert S, et al. Phosphodiesterase 1 inhibition in the treatment of lower urinary tract dysfunction: from bench to bedside. World J Urol 2001; 19: 344–350.

6- Longhurst PA, Briscoe JA, Rosenberg DJ, et al. The role of cyclic nucleotides in guinea-pig bladder contractility. Br J Pharmacol 1997; 121: 1665–1672.

7- Snyder PB, Loughney K, Florio VA. Relaxation of bladder strips by inhibition of cyclic nucleotide phosphodiesterase type 4 (PDE4) (abstract 159). J Urol 2005; 173: 43.

8- Gillespie JI. Phosphodiesterase-linked inhibition of nonmicturition activity in the isolated bladder. BJU Int 2004; 93: 1325–1332.

9- Werkstrom V, Svensson A, Andersson K-E, et al. Phosphodiesterase 5 in the female pig and human urethra: morphological and functional aspects. BJU Int 2006; 98: 414–423.

10- Sairam K, Kulinskaya E, McNicholas TA, et al. Sildenafil influences lower urinary tract symptoms. BJU Int 2002; 90: 836–839.

11- Mulhall JP, 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 2006; 3: 662–667.

12- Ying J, Yao D, Jiang Y, et al. The positive effect of sildenafil on LUTS from BPH while treating ED.Zhonghua Nan Ke Xue 2004; 10: 681–683.

13- Yokoyama O, Igawa Y, Takeda M, et al. Tadalafil for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a review of clinical data in Asian men and an update on the mechanism of action. Therapeutic Advances in Urology. 2015;7(5):249-264.

14- Stief CG, Porst H, Neuser D, et al. A randomized, 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: 1236–1244.

15- Roehrborn CG, McVary KT, 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 2008; 180: 1228–1234.

16- Roehrborn RC. Efficacy and safety of once-daily alfuzosin in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a randomized, placebo controlled trial. Urology 2001; 58: 953–959.

17- Gacci M, Del Populo G, Macchiarella A, et al. Vardenafil improves urodynamic parameters in men with spinal cord injury: results from a single dose, pilot study. J Urol 2007; 178: 2040–2043.

18- Guh JH, Hwang TL, Ko FN, et al. Antiproliferative effect in human prostatic smooth muscle cells by nitric oxide donor. Mol Pharmacol 1998; 53: 467–547.

19- Adolfsson PI, Ahlstrand C, Varenhorst E,et al. Lysophosphatidic acid stimulates proliferation of cultured muscle cells from human BPH tissue: sildenafil and papaverine generate inhibition. Prostate 2002; 51: 50–58.

20- Deng CH, Chen HR, Qiu SP, et al. Effect of nitric oxide donor and alpha1-receptor antagonist on proliferation/apoptosis of hyperplastic prostatic stromal cells in vitro. Zhonghua Wai Ke Za Zhi 2004; 42: 201–204.

21- Uckert S, Kuthe A, Jonas U, et al. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol 2001; 166: 2484.

22- Dmochowski R, Roehrborn C, Kraus S, et al. Changes in bladder outlet obstruction index in men with signs and symptoms of benign prostatic hyperplasia treated with tadalafil. J Urol 2009; (suppl): 181: (abstract 1924).

23- Deng CH, Chen HR, Qiu SP, et al. Effect of nitric oxide donor and alpha1-receptor antagonist on proliferation/apoptosis of hyperplastic prostatic stromal cells in vitro. Zhonghua Wai Ke Za Zhi 2004; 42: 201–204.

24- Uckert S, Kuthe A, Jonas U, et al. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol 2001; 166: 2484.

25- Dmochowski R, Roehrborn C, Kraus S, et al. Changes in bladder outlet obstruction index in men with signs and symptoms of benign prostatic hyperplasia treated with tadalafil. J Urol 2009; (suppl): 181: (abstract 1924).

26- Andersson KE. Erectile physiological and pathophysiological pathways involved in erectile dysfunction. J Urol 2003; 170: S6–14.

27- Carvajal JA, Germain AM, Huidobro-Toro JP, et al. Molecular mechanism of cGMP-mediated smooth muscle relaxation. J Cell Physiol 2000; 184: 409–420.

28- Kohler TS, McVary KT. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. Eur Urol 2009; 55: 38–48.

29- Andersson KE, Persson K. Nitric oxide synthase and the lower urinary tract: possible implications for physiology and pathophysiology. Scand J Urol Nephrol 1995; 175 (Suppl): 43–53.

30- Hedlund P. Nitric oxide/cGMP-mediated eVects in the out-Xow region of the lower urinary tract—is there a basis for pharmacological targeting of cGMP? World J Urol 2005; 23: 362–367.

31- Andersson KE. LUTS treatment: future treatment options. Neurourol Urodyn 2007; 26: 928–933.

32- Burnett AL, Maguire MP, Chamness SL, et al. Characterization and localization of nitric oxide synthase in the human prostate. Urology 1995; 45: 435–439.

33- Richter K, Heuer O, ckert S, et al. Immunocytochemical distribution of nitric oxide synthases in the human prostate. J Urol 2004; 171 (Suppl 4): 347 (abstract).

34- Bloch W, Klotz T, Loch C, et al. Distribution of nitric oxide synthase implies a regulation of circulation, smooth muscle tone, and secretory function in the human prostate by nitric oxide.Prostate 1997; 33: 1–8.

35- Gradini R, Realacci M, Ginepri A, et al. Nitric oxide synthases in normal and benign hyperplastic human prostate: immunohistochemistry and molecular biology. J Pathol 1999; 189: 224–229.

36- Luo J, Dunn T, Ewing C, et al. Gene expression signature of benign prostatic hyperplasia revealed by cDNA microarray analysis. Prostate 2002; 51: 189–200.

37- 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 study. BJU Int. 2011;107:1110–1116.

38- Oelke M, Bachmann A, Descazeaud A, et al. European Association of Urology; 2013. M. Guidelines on the management of male lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO) Available from http://www.uroweb.org/gls/pdf/13_Male_LUTS_LR.pdf. Accessed July 2, 2013.

39- 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.

40- 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. 2012;61:917–925.

41- Giuliano F, Oelke M, Jungwirth A, et al. Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo– and tamsulosin–controlled, 12–week double–blind study. J Sex Med. 2013;10:857–865.

42- Liguori G, Trombetta C, De Giorgi G, et al. Efficacy and safety of combined oral therapy with tadalafil and alfuzosin: an integrated approach to the management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report. J Sex Med. 2009;6:544–552.

43- Regadas RP, Reges R, Cerqueira JB, et al. Urodynamic effects of the combination of tamsulosin and daily tadalafil in men with lower urinary tract symptoms secondary to

benign prostatic hyperplasia: a randomized, placebo–controlled clinical trial. Int Urol Nephrol. 2013;45:39–43.

44- Bechara A, Romano S, Casabé A, 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.

45- CIALIS® (tadalafil) Prescribing Information. Eli Lilly and Company. Revised October 2013.http://pi.lilly.com/us/cialis–pi.pdf.

46- Morelli, A., et al. Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. J Sex Med, 2011. 8: 2746.

47- Vignozzi, L., et al. PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. Prostate, 2013. 73: 1391.

48- Gacci, M., et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol, 2012. 61: 994.

49- Oelke, M., 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. 61: 917.

50- Donatucci, C.F., et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. BJU Int, 2011. 107: 1110.

51- Porst, H., et al. Efficacy and safety of tadalafil 5 mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: subgroup analyses of pooled data from 4 multinational, randomized, placebo-controlled clinical studies. Urology, 2013. 82: 667.

52- Porst, H., et al. Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies. J Sex Med, 2013. 10: 2044.

53- Brock, G.B., et al. Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analyses from 4 placebo controlled clinical studies. J Urol, 2014. 191: 405.

54- Roehrborn, C.G., 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, 2014. 191: 1045.

55- Casabe, A., et al. Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. J Urol, 2014. 191: 727.

56- Gacci, M., et al. The use of a single daily dose of tadalafil to treat signs and symptoms of benign prostatic hyperplasia and erectile dysfunction. Res Rep Urol, 2013. 5: 99.

57- Carbone DJ, Jr, Hodges S. Medical therapy for benign prostatic hyperplasia: Sexual dysfunction and impact on quality of life. Int J Impot Res. 2003;15:299–306.

58- Bahijri SM, Jambi HA, Al Raddadi RM. The Prevalence of Diabetes and Prediabetes in the Adult Population of Jeddah, Saudi Arabia- A Community-Based Survey. PLoS One. 2016 Apr 1;11(4):e0152559.

59- Memish ZA, El Bcheraoui C, Tuffaha M, et al. Obesity and Associated Factors — Kingdom of Saudi Arabia, 2013. Prev Chronic Dis 2014;11:140236.

60- Al-Nozha MM, Arafah MR, Al-Maatouq MA, et al. Hyperlipidemia in Saudi Arabia. Saudi Med J. 2008 Feb;29(2):282-7.