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**Is phosphodiesterase type 5 inhibitor effective for the management of lower urinary symptoms suggestive benign prostatic hyperplasia?**

Zhang LT *et al.* PDE5-Is on LUTS/BPH

Li Tao Zhang, Jong Kwan Park

**Li Tao Zhang**, **Jong Kwan Park,** Department of Urology, Chonbuk National University of Medical School, Jeonju-si 561-180, South Korea

**Jong Kwan Park,** Department of Urology, Biomedical Research Institute and Clinical Trial Center for Medical Devices of Chonbuk National University Hospital, Jeonju-si 561-180, South Korea

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**Correspondence to:** **Jong Kwan Park, MD, PhD,** Department of Urology, Biomedical Research Institute and Clinical Trial Center for Medical Devices of Chonbuk National University Hospital, Gungiro, deokjin-gu, Jeonju-si 516-180, Jeollabuk-do, South Korea. rain@chonbuk.ac.kr

**Telephone:** +82-63-2501510 **Fax:** +82-63-2501564

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**Abstract**

**AIM:** To review efficacy of phosphodiesterase type 5 inhibitors (PDE5-Is) in lower urinary tract symptoms (LUTS) suggestive benign prostate hyperplasia (LUTS/BPH).

**METHODS:** A comprehensive research was conducted to identify all publications relating to benign prostate hyperplasia and treatment with sildenafil, vardenafil and tadalafil. To assess the efficacy, the changes in total International Prostate Symptom Score (IPSS), IPSS subscore including voiding, storage and Quality of Life (QoL), Benign prostatic hyperplasia Impact Index (BII), maximum urinary flow rate (Qmax), and the International Index of Erectile Function (IIEF) were extracted. The analysis of integrated data from the included studies was used meta-analytical technique to evaluate the mean difference in the results.

**RESULTS:** Total IPSS score, IIEF, and BII were significantly improvement in trials in which LUTS/BPH with or without erectile dysfunction (ED) compared with the placebo. For LUTS/BPH, the mean differences of total IPSS score, IIEF, and BII are -2.17, 4.88, and -0.43, *P* < 0.00001, respectively; For LUTS/BPH with comorbid ED, the mean difference are -1.97, 4.54, and -0.52, *P* < 0.00001, respectively. PDE5-Is seem like to improve IPSS storage, voiding and QoL subscore (the mean difference = -0.71, -1.23 and -0.33, *P* < 0.00001, respectively). Although four doses of tadalafil (2.5, 5, 10 and 20 mg) failed to reach significant in Qmax (mean difference = 0.22, *P* = 0.10), the 5 mg dose of tadalafil significantly improved the Qmax (mean difference = 0.33, *P* = 0.03).

**CONCLUSION**: PED5-Is demonstrated the efficacy for improving LUTS in BPH patients with or without ED, and could be considered to be the first line for treatment of LUTS/BPH.

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**Key words:** Phosphodiesterase type 5; Inhibitor; Lower urinary tract symptoms; Benign prostate hyperplasia; Tadalafil

**Core tip:** The efficacy of phosphodiesterase type 5 inhibitor (PDE5-I) in the patients who has lower urinary tract symptoms (LUTS) and benign prostate hyperplasia (BPH) has been evaluated and prescribed. Regardless of the significant improvement of total IPSS and storage subscore, there are controversies about the urine flow rate. Also we do not know the exact mechanism to work in the lower urinary tracts. By the meta-analytic data, PDE5-I could be an alternative therapy for the LUTS/BPH patients whether or not have erectile dysfunction. Therefore, well designed clinical trials of large scale are required to clarify the efficacy and action mechanisms of PDE5-Is in the management of LUTS/BPH.

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### INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histopathological diagnosis characterized by epithelial cell and smooth muscle proliferation in transition zone of the prostate leading to nonmalignant enlargement of the prostate, which may result in lower urinary tract symptoms (LUTS), including storage symptoms, voiding symptoms[1-3]. BPH is a common disease of ageing men. Moderate to severe LUTS secondary to BPH (LUTS/BPH) is predicted that it involve 10% to 25% of the contemporary male population (approximately 900 million men) throughout the world[1-3] and it is considered that presumably 1.1 billion male will suffer from LUTS/BPH by the year 2018[4].

It is widely acceptable that BPH is not exclusive source of LUTS[1-4]. Over the decades, LUTS/BPH treatment of paradigms has shifted from surgical interventions to first-line pharmacotherapy against objectives of symptoms reduction and improvement in quality of life. However, clinical trials of drugs often enroll men based partially on a clinical diagnosis of non-neurogenic LUTS/BPH.

Pharmacotherapy for LUTS/BPH currently consists of alpha-blockers, 5 alpha-reductase inhibitor, or combined therapy[1-4]. Although they are proved to be efficacious, these therapies have the potentially side-effects linked to sexual dysfunction such as reduced libido and ejaculatory disorders, dizziness and hypotension[5]. These side-effects may be exacerbated by combination therapy. Phosphodiesterase type 5 (PDE5) inhibitors (PDE5-Is) consisting mainly of sildenafil, vardenafil, and tadalafil are extensively approved for curing erectile dysfunction (ED)[6,7]. Recently, significant improvement in LUTS/BPH has been reported by a large body of clinical studies on PDE5-Is[8-25]. Although improvement of the PDE5-Is mechanisms in LUTS/BPH have yet not be clearly clarified, proposed contributors include inhibition of PDE5 iso-enzymes being present in the bladder, prostate, urethra, and vasculature supporting and consequently elevation in intracellular nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) concentration which function as inhibition of RhoA/Rho kinase signaling pathways, mediates relaxation of the smooth muscle cells in these structures, improves blood perfusion, and reduces afferent signaling in the urogenital tract[26-29]. The comprehension of these complicated mechanisms begins to be elucidated how PDE5-Is play a role in the treatment of LUTS/BPH and is indispensable for health care professionals to optimize both patient screening and treatment. Nevertheless, recent researches have showed that PDE5-Is, either served as a monotherapy or combined alpha blockers, also enhance LUTS/BPH presumably via relaxation of smooth muscle in the bladder neck, urethra and prostate induced by NO/cGMP signal pathway.

With the increasing interests in those efficacy, therefore, we systematically reviewed the literatures to explore the up-to-date evidence on the efficacy of PDE5-Is in LUTS/BPH.

### *Epidemiologic survey: Two common conditions* *between LUTS/BPH and ED?*

Two conditions of LUTS associated with BPH and ED that occur with relatively high frequency in aging have triggered a great deal of concern over the last few decades. As the incidence of histopathological stromoglandular hyperplasia rises, so does the prevalence of moderate to severe LUTS[30]. Correspondingly, the rate of ED also raises with aging. As such, it is not surprise that many patients complaint of LUTS will also suffer from ED, and vice versa when queried. The link between LUTS/BPH and ED has recently been the subject of significant studies[1,31]. Numerous publications have demonstrated a link between ED and LUTS, of which epidemiologic were summarized in a review[32]. It points that the majority of well-designed longitudinal studies, have been proposed to interpret the relationship between ED and LUTS in this review. Those consist of varying NO level, activated RhoA/Rho kinase, and atherosclerosis in pelvis.

An recent abstract from a larger cross-sectional and multinational assessment of LUTS and sexual function was conducted[33]. Logistic regression analysis showed that patients suffer from severe LUTS were estimated presumably 2 folds as likely to suffer from erectile dysfunction (OR, 2.0, 95%CI: 1.4, 2.8), and decreased ejaculate (OR, 1.8, 95%CI: 1, 2.5). Furthermore, patients suffering severe LUTS were 6 folds as likely to complain of discomfort or pain on ejaculation. Another cross-sectional data analysis are from the Multinational Survey of the Aging Male (MSAM-7), in which patients ageing fifty to eighty years demonstrated high rates of LUTS/BPH in the United States and Europe (United Kingdom, France, Germany, Netherlands, Italy, and Spain)[34]. In this survey, more than 50% of patients were bothered by ejaculatory dysfunction as prevalent as erection problems and also showed the link between LUTS and ejaculatory dysfunction still existed after controlling for age and other comorbidities.

### *Clinical studies of PDE5-I: Are there independent between LUTS/BPH and ED?*

It was speculated that enhancement in LUTS/BPH could be as a result of ED improvement because PDE5-Is significantly mitigated the symptoms of LUTS/BPH and ED. As such, a couple of clinical studies have addressed if the improvement of BPH symptoms is linked to improved ED symptoms[9,34]. In one study of dose-ranging tadalafil including 716 ED patients and 340 non-ED patients, alterations in LUTS/BPH after 3-mon of medication with distinct doses of tadalafil once daily and placebo was analogous in patients with or without comorbidity of erectile dysfunction, demonstrating the enhancement in LUTS/BPH was not relying on ED alterations[35]. Another tadalafil study also confirmed these finding[36]. As a consequence, those are independent of each other even though the mechanism by which PDE5-Is enhance LUTS/BPH could participate in analogous wayswith that PDE5-Is enhance ED.

### *PDE5-I localization in prostate*

Much evidence from experimental research confirmed the cGMP-degrading PDE5 as well as NO/cGMP signaling pathway are responsible for the regulation of normal functions of prostate, by which regulates proliferation of glandular epithelial cells and smooth muscle as well as stromal connective tissue[29,37]. As early as 1970 year, the activity of PDE5-Is isolated from human prostate tissue was confirmed by Kuciel and Ostrowski. However, this method could not tender sufficient data on the PDE5 localization in the prostate.

The golden criteria to detect the PDE5 distribution in distinct histopathlogical portions of prostate was disclosed by immunohistochemistry (IHC). It was demonstrated that cGMP PDE iso-enzyme localized in glandular zone, the smooth musculature of stroma as well as blood vessels by utilization of antibodies[35]. It was also shown that PDE5 is detected in the tight conjunction to other critical regulators of NO/cGMP pathway. The concentration of tadalafil in prostate and plasma was 385.7 ± 83.8 and 305.8 ± 41.1 ng/mL, respectively. In addition, the ratio between tissue and plasma is 1.3[38]. Tatalafil and udenafil significantly enhanced the cGMP and cAMP levels in plasma and prostate tissue[38].

### *PDE5-I - mechanism of action*

Briefly, current postulated action mechanism in improvement of LUTS/BPH including: (1) ascend of nitric oxide (NO) synthase/NO activity in the prostate; (2) cGMP mediated ρ kinase/endothelin inactivation; (3) decrease of autonomic hyperactivity of afferent nerve in the bladder, prostate; and (4) reduction of pelvic ischemia caused by atherosclerosis of pelvic vessels.

**MATERIALS AND METHODS**

### *Identification of studies and study design*

We searched the following sources from inception to the specified date: (1) The Cochrane Library; (2) MEDLINE; and (3) EMBASE.

The studies involving in present review met the following standards: (1) double blinded, clinical controlled trials; (2) LUTS/BPH was involved; and (3) control groups was given placebo drug. Studies involved in PED5-Is monotherapy versus alpha blocker or combination of both were excluded.

To assess the efficacy of PED5-Is, the outcomes of measurement at least contain one list below: (1) International Prostate Symptom Score (IPSS); (2) International Index of Erectile Dysfunction (IIEF) score; (3) maximal urinary flow rate (Qmax); (4) IPSS Quality of Life Index (IPSS-QoL); and (5) IPSS irritative (storage) subscore and IPSS obstructive (voiding) subscore and BPH impact index (BII).

### *Statistical analysis*

The meta-analysis were used the Review manager (Version 5.3, the Cochrane Collaboration, Oxford, UK). The heterogeneity test was by χ2 and I2 (I2 ≤ 50%, low heterogeneity; 50% < I2 ≤ 75%, moderate heterogeneity, and I2 > 75%, high heterogeneity). If the heterogeneity is less than 50%, the fixed-effects model was considered to estimate integrated effect of the outcomes. For being moderate or high heterogeneity, a random-effect will be used. The continuous value was used as the mean difference with 95% confidence intervals (CI).

### Results

***Clinical trials with PED5-Is for LUTS/BPH***

A total of 16 randomized, double blind and placebo-controlled trials investigated the efficacy, and safety of tadalafil (*n* = 14), sildenafil (*n* = 1) and vardenafil (*n* = 1) for the therapy of LUTS/BPH, and in men comorbidities of LUTS/BPH and ED (5 trials: Brock *et al*[39], 2013, Donatucci *et al*[14], 2011, Egerdie *et al*[15], 2012, McVary *et al*[18], 2007 and Porst *et al*[21], 2009, respectively). The characteristics of studies were summarized in the Table 1. These studies about designs were analogous, followed by up to 4 wk of washout periods in order to eliminate the medications prior to trials.

***The efficacy of PDE5-Is of Sildenafil, Tadalafil, and Vardenafil***

**Sildenafil:** In 2007, McVary *et al*[10] firstly reported that 189 patients given sildenafil had improved significantly in total IPSS score (sildenafil *vs* placebo: -6.3 *vs* -1.93, *P* < 0.0001), IPSS QoL subscore (sildenafil *vs* placebo: -0.97 *vs* -0.29, *P* < 0.0001), BII (sildenafil *vs* placebo: -2.0 *vs* -0.9, *P* < 0.001) as well as IIEF-EF domain score (sildenafil vs placebo: 9.17 *vs* 1.86, *P* < 0.0001) in sildenafil group compared to placebo group after 12 wk of daily treatment (50 mg for 2 wk, then increase to 100 mg). No significant difference of Qmax were observed between two groups (*P* = 0.08), it is possible that relaxation of the urethra and prostate musculature would tend to enhance urinary flow, but relaxation of the bladder could more or less counteract those effects after administration of PDE5-Is (Table 2).

**Vardenafil:** In one randomized, double blind, placebo-controlled study, Stief *et al*[40] investigated the efficacy of 10 mg vardenafil inLUTS/BPH patients with or without concomitant ED. After 8 wk of therapy, significant improvement in Total IPSS score (vardenafil *vs* placebo: -5.8 *vs* -3.1, *P* < 0.05), IPSS voiding subscore, IPSS storage subscore, IPSS QoL score were observed in the vardenafil group compared to placebo group (*P* < 0.0001, respectively) (Table 2). Although Qmax was enhanced in vardenafil group, there was no significantly difference (vardenafil *vs* placebo: 1.6 mL/s *vs* 1 mL/s) (Table 2). Overall, the most frequent adverse events (AEs) consisted of headaches, flushing, and dyspepsia and it was reported that 32 (29.6%) patients in vardenafil groups and 18 ones (15.9%) in placebo groups had AEs. None of the serious AEs was linked to the vardenafil medication. Nevertheless, it is too soon to consider the underlying role for vardenafil in the therapy of LUTS/BPH patients because further data that clearly needed to ascertain the benefit-risk details relative to the existing treatment options was not provided.

**Tadalafil:** A total of 14 randomized, double-blind, placebo-controlled studies have showed the efficacy and safety of tadalafil once daily medication in management of LUTS/BPH. A one year open label trial has demonstrated the sustainability of efficacy and safety of tadalafil once daily for the long term[14]. The efficacy outcomes were summarized in Table 2.

Brock *et al*[39] (2013), investigating the efficacy of tadalafil once daily in the treatment of LUTS/BPH patients with or without ED, firstly noted that the effects of therapy in men without ED were analogous to that with ED in LUTS/BPH. In patients without ED, the LUTS/BPH including total IPSS score (tadalafil *vs* placebo: -5.4 *vs* -3.3, *P* < 0.01), IPSS voiding subscore (tadalafil *vs* placebo: -3.5 *vs* -2.0, *P* < 0.01), IPSS storage subscore (tadalafil *vs* placebo: -1.9 *vs* -1.3, *P* < 0.05) from baseline to end points was reduced significantly, and IPSS QoL (tadalafil vs placebo: -1.0 *vs* -0.7, *P* < 0.05) and BII (tadalafil *vs* placebo: -1.4 *vs* -1.0, *P* < 0.05) were significantly improved. However, small Qmax improvement was still consistent with the poor link between Qmax and LUTS/BPH in the updated BPH guidelines[41]. The limitation of methodology in choosing ED or non-ED population is when sexually active patients with LUTS/BPH but no ED history were managed in blind, placebo-controlled trials. Therefore, clinical ED determination alone could not fully exclude ED in this reference groups enrolled for LUTS/BPH.

In another multicenter, randomized, double-blind, placebo-controlled clinical trial consisting of patients LUTS/BPH once daily 20 mg tadalafil during 12 wk, Dmochowski *et al*[13] (2010) pointed out that tadalafil significantly improved in total IPSS score (tadalafil *vs* placebo: -9.2 *vs* -5.1, *P* < 0.001), voiding subscore (tadalafil *vs* placebo: -5.6 *vs* -2.8, *P* < 0.001) and storage subscore (tadalafil *vs* placebo: -3.6 *vs* -2.3, *P* = 0.006) than did those treated placebo. Qmax from baseline to endpoints showed a small alterations with no significant difference was observed (tadalafil *vs* placebo: -2.1 *vs* 0.1, *P* = 0.33). In addition, several points should be noted when considering these trials. It used a relatively high tadalafil dose and did not assess rigorous intent to treat patients. Thus, cautions should be focused on the magnitude of improvement investigated in these trials in future clinical utilization.

Donatucci *et al*[14] (2011) completed a double blind, placebo controlled, 12 wk tadalafil (2.5 mg, 5 mg, 10 mg or 20 mg once daily) to shift open-label extended period of 1 year. The changes from baseline to endpoint in the total IPSS, IPSS voiding subscore, IPSS storage subscore, IPSS health-related quality of life (QoL) and BII were sustained after one year. Besides, the IIEF-EF was also maintained after 1 year. Higher treatment-induced emergent AEs (57.6% of patients) were observed in higher dose group, but 5 mg tadalafil was well tolerated. Although the efficacy of improvement from baseline or 12 wk to endpoint was noted, the changes from baseline to 12 wk were not reported. Qmax was not evaluated in this trial.

Egerdie *et al*[15] (2012) conducted a multinational phase 3 (12 wk) randomized, double blind and control-placebo trial to assess the effcacy of tadalafil 2.5 or 5 mg in management of LUTS/BPH with erectile dysfuction patients. In this study, both doses of tadalafil significantly improved the IIEF-EF (tadalafil *vs* placebo: 6.5, 5.2 *vs* 1.8, both *P* < 0.001). The improvement with 5 mg, but not 2.5 mg, in IPSS voiding subscore (tadalafil *vs* placebo: -3.6 *vs* -2.2, *P* < 0.001), storage subscore (tadalafil *vs* placebo: -2.5 *vs* -1.6, *P* < 0.001), and BII (tadalafil *vs* placebo: -1.6 *vs* -1.2, *P* < 0.001) was observed. But QoL subscore (tadalafil *vs* placebo: -1 *vs* -0.8, *P* = 0.082) failed to reach significantly difference (Table 2).

Kim *et al*[16] (2011) reported a randomized, double-blind, controlled-placebo trials during 12 wk on LUTS/BPH in Korean men for once daily tadalafil 5 mg. From baseline to endpoint, the total IPSS and Qmax mean changes were numerically but not improved significantly compared with placebo (tadalafil *vs* placebo: IPSS, -5.6 *vs* -3.6, *P* > 0.05 and Qmax, 2.5 *vs* 2.3, *P* > 0.05).

McVary *et al*[18] in 2007 conducted 281 men allocated randomly to 5 mg tadalafil once daily for 6 wks and then dose escalation to 20 mg for another 6 wks. There was significant difference in IIEF-EF (tadalafil *vs* placebo: 8.4 *vs* 1.6, *P* < 0.001), total IPSS score (tadalafil *vs* placebo: -7.1 *vs* -4.5, *P* < 0.001), voiding subscore (tadalafil *vs* placebo: -4.4 *vs* -2.8, *P* < 0.0001), storage subscore (tadalafil *vs* placebo: -2.7 *vs* -1.8, *P* < 0.001) and QoL (tadalafil *vs* placebo: -0.5 *vs* -0.2, *P* < 0.001). However, the difference of Qmax was not significant difference when comparing tadalafil to placebo (tadalafil *vs* placebo: 0.5 *vs* 0.9, *P* > 0.05).

Oelke *et al*[19] (2012) investigated the efficacy of 5 mg tadalafil once daily monotherapy through 12 weeks of therapy of LUTS/BPH in a randomized, double- blind, international controlled-placebo study. Total IPSS score significantly improved with tadalafil (tadalafil *vs* placebo: -6.3 *vs* -4.2, *P* = 0.001). Significant improvement in voiding subscore (tadalafil *vs* placebo: -4.1 *vs* -2.6, *P* < 0.001), but not storage subscore (tadalafil *vs* placebo: -2.2 *vs* -1.6, *P* = 0.055) and QoL subscore (tadalafil *vs* placebo: -1.3 *vs* –1.0, *P* = 0.022) was observed from baseline to endpoint in this trial. Qmax increased significantly (tadalafil *vs* placebo: 2.4 *vs* 1.2, *P* = 0.009). Nevertheless, this trial was of 12 wks duration for evaluating the efficacy of LUTS/BPH and not address longer term efficacy of tadalafil on disease progression. Maybe this kinds of trials would trigger great interests in future.

In a phase 2 to 3, multinational, randomized, double-blind, controlled-placebo study, Porst *et al*[21] (2009) randomly assigned the patient to tadalafil 2.5 mg, 5 mg, 10 mg, 20 mg once daily for 12 wk. The least square mean difference of IIEF-EF compared to placebo (the value: 2) were significant for all four dose of tadalafil (2.5 mg dose, 8.2; 5 mg dose, 7.9; 10 mg dose, 6.8, and 20 mg dose, 5.4) (all *P* < 0.001). The mean changes of total IPSS score from baseline to endpoint reached a significantly difference (tadalafil *vs* placebo: 2.5 mg, -4.2 *vs* -2.1, *P* = 0.015; 5 mg, -4.7 *vs* -2.1, *P* < 0.001; 10 mg, -4.7 *vs* -2.1, *P* < 0.001, and 20 mg, -3.6 *vs* -2.1, *P* < 0.001). However, Qmax failed to reach significance for treatment groups. The limitation could be the absence of parallel group without LUTS/BPH as a control reference and not summarize the minimal times of sexual intercourse monthly before allocation and the trial duration, which could measure the risk-benefit of once daily tadalafil for IIEF-EF improvement.

In a second randomized, double-blind, placebo-controlled, 12-wk of study, Porst *et al*[36] (2011) pointed out that 5 mg tadalafil significantly improved total IPSS score (tadalafil *vs* placebo: -5.6 *vs* -3.6, *P* = 0.004), voiding subscore (tadalafil *vs* placebo: -3.3 *vs* -2.3, *P* = 0.020), storage subscore (tadalafil *vs* placebo: -2.3 *vs* -1.3, *P* < 0.002), QoL Index (tadalafil *vs* placebo: - 1.0 *vs* - 0.7, *P* = 0.013) and BII (tadalafil *vs* placebo: -1.8 *vs* -1.2, *P* = 0.029) from baseline to endpoint. However, uroflometry parameters did not significantly difference at the endpoint. The IIEF-EF in ED men was significantly improved through 12 wk (tadalafil *vs* placebo: 6.7 *vs* 2.0, *P* < 0.001).

In 2013, Porst *et al*[20] pooled data from 4 multinational, randomized, placebo-controlled clinical trials to investigate the 5 mg tadalafil once daily for LUTS/BPH through 12 wk. The pooled data confirmed that tadalafil resulted in improvement in total IPSS score from baseline to endpoint (tadalafil *vs* placebo: -7.9 *vs* -5.1, *P* < 0.001) and also IPSS QoL index and BII (both *P* < 0.01).

Roehrborn *et al*[22] (2008) conducted a randomized, double-blind, placebo-controlled, dose-finding studies through 12 wk in a total of 10 countries. They randomly assigned the patient to tadalafil 2.5 mg, 5 mg, 10 mg, 20 mg once daily for 12 wk. The least square mean difference of IIEF-EF compared to placebo (the value: 2.2) were significant for all four doses of tadalafil (2.5 mg dose, 5.59; 5 mg dose, 6.97; 10 mg dose, 7.98; and 20 mg dose, 8.34) (all *P* < 0.001). The mean changes of total IPSS score from baseline to endpoint reached a significantly difference (tadalafil vs placebo: 2.5 mg, -3.9 *vs* -2.3, *P* = 0.015; 5 mg, -4.9 *vs* -2.3, *P* < 0.001; 10 mg, -5.2 *vs* -2.3, *P* < 0.001, and 20 mg, -5.2 *vs* -2.3, *P* < 0.001). And the voiding subscore, storage subscore, QoL index and BII all reach a significant difference (*P* < 0.01, 0.001, 0.05, and 0.05, respectively). However, Qmax failed to reach significance for medication groups.

In the second study of Roehrborn *et al*[12] (2013), 5 mg tadalafil for the LUTS/BPH for 12 wk and investigated the effects on the Qmax with LUTS/BPH. Qmax changes were assessed severity of baseline Qmax. For baseline Qmax < 10 mL/s, increases were higher in tadalafil compared with placebo group (tadalafil vs placebo: 2.8 *vs* 2.4, *P* = 0.189), for Qmax of 10 to 15 mL/s, (tadalafil *vs* placebo: 1.4 *vs* 0.9, *P* = 0.044), and for Qmax > 15 ml/s, (tadalafil *vs* placebo: -1.1 *vs* -2.7, *P* = 0.246).

Takeda *et al*[24] (2014) pooled data of randomized, double-blind, placebo-controlled studies of tadalafil 5 mg from 39 sites in Japan and Korea. Total IPSS score significantly improved with tadalafil (-6 *vs* -4.5, *P* = 0.001). Significant improvement in IPSS voiding subscore (tadalafil *vs* placebo: -4 *vs* -3.1, *P* = 0.002), IPSS storage subscore (tadalafil *vs* placebo: -2 *vs* -1.4, *P* = 0.002) and IPSS QoL subscore (tadalafil *vs* placebo: -1.1 *vs* -0.9, *P* = 0.038) was observed significant improvement from baseline to endpoint in this trial.

Yokoyama *et al*[25] investigated the effects of tadalafil 2.5 mg and 5 mg in a multicenter, randomized, double-blind, placebo-controlled study from 34 sites in Japan, South Korea and Taiwan in Asian countries. Except Qmax and BII index, the total IPSS score, voiding subscore, storage subscore and QoL subscore reached a significant difference.

***The outcomes of meta-analysis of PDE5-Is on LUTS/BPH from integrated studies***

The data were pooled for calculations and computed for the integrated analysis. The heterogeneity was not observed (I2 < 30%) and fixed effect models was used.

According to the participants with comorbid LUTS/BPH and ED, the total IPSS, BII and IIEF-EF were divided into two subgroups: subgroup with LUTS/BPH and subgroup with LUTS/BPH and ED. Irrespective of overall group or subgroup analysis, PDE5-Is, especially tadalafil, improvement of total IPSS, BII, and IIEF domain were shown (*P* < 0.0001 or *P* < 0.00001, Table 3). The changes in the storage, voiding and QoL were also reported (*P* < 0.00001, Table 3). The changes of Qmax for tadalafil at a dose of 5 mg was calculated in LUTS/BPH patients and showed a significant improvement [0.33 (-0.13, 0.80), *P* < 0.03, Table 3].

**DISCUSSION**

PDE5-Is significantly improved total IPSS score, IPSS voiding score, IPSS storage score, IPSS QoL score and IIEF-EF score. Significant improvement of total IPSS score and IIEF-EF score was observed in patients with comorbid ED and BPH. As such, PDE5-Is as the first line for management of ED, also demonstrated effective for LUTS/BPH. Therefore, well designed clinical studies of large scales, extension are required to ascertain the efficacy and specific mechanisms of action of PDE5-Is in the management of LUTS/BPH.

### COMMENTS

***Background***

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) are increasing frequent in aging men. The majority coexisted erectile dysfunction, while they will not. Irrespective of coexisting erectile dysfunction (ED), LUTS/BPH patients frequently suffered from a declined quality of life.

***Research frontiers***

Until recently, surgical therapy was the cornerstone of management of male LUTS. As early as 1990s, medical therapy confronted the surface as a possible treatment option for voiding suffering. Since then, the surgical option has dropped gradually, and currently the prior option for treatment in male LUTS is medical therapy. 5-ARIs and α-blockers have ever dominated the management for LUTS for many years. Nowdays, a couple of new drugs have cast a light on the treatment of LUTS, including PDE5-Is and anticholinergics. In the traditionally sense, LUTS occurred in ageing have frequently been associated with outlet obstruction in bladder resulting from the BPH, whereas, the complaints may be explained by the detrusor overactivity. More recently, increasing evidence showed that phosphodiesterase type 5 inhibitors (PDE5-Is) could exert improvement in LUTS in ageing men, of whom frequently suffer from BPH.

***Innovations and breakthroughs***

PDE5-Is including mainly tadalafil, sildenafil, and vardenafil were ever the first line medications to treat ED patients. More and more randomized controlled trials (RCT) have been done to examine the efficacy of PDE5-Is for treatment of LUTS/BPH. As reported, PDE5-Is might have influenced the terminal decision because of distinct pharmacological profiles and side effect, and the enthusiasm for PDE5-Is has been decreased by being lack of objective improvement. And furthermore urodynamic parameters did not change. What’s more important, how to coherently explain the disconnection between objective and subjective changes is still pending. Therefore, it would be necessary to determine whether PDE5-Is are effective in the treatment of LUTS/BPH on the basis of systematic review and meta-analysis of published evidence. Ever since the meta-analysis was introduced to assess the clinical data in the urological community by Peter Boyle, they have been utilized increasingly. In particular, it could give rise to benefit for those invaluable insights. To a large extent, even though where large database had been available, it still could identify some predictive characteristics for those responders and non-responders. However, all the studies convincing showed that LUTS were significantly alleviated by the regular use of PDE5-Is. In other words, the available studies on the use of PDE5-Is for the treatment of LUTS are promising. Especially in aging males, there is an increased prevalence of LUTS/BPH. Daily PDE5-Is might represent a useful treatment for this conditions. Such a pharmacological strategy has the potential to become the treatment to manage the aging process of the male urogenital tract. Although the present manuscript underscores PDE5-Is is a promising therapy for LUTS/BPH from other researchers, still a couple of questions are worthy of considering, including patient selection, durability and health economics in case of PDE5-Is for treatment of LUTS. It is in an ideal world that some of situations could inevitably be avoided between the doctors and patients while using PED5-Is for patients with any given conditions. Firstly, best candidates should be screened for patients with male LUTS alone receiving any given treatment. Secondly, the patients should be informed about the potential limitations of PDE5-Is during the treatment of their complaints. Thirdly, who is going to have what kind of treatment and when? In addition, the best practice not only includes the doctor's choice but also the patient’s.

***Applications***

PDE5-I: Phosphodiesterase type 5 inhibitor: LUTS/BPH: Lower urinary tract symptoms suggestive benign prostate hyperplasia; ED: Erectile dysfunction; IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Dysfunction score; Qmax: Maximal urinary flow rate; IPSS-QoL: IPSS Quality of Life Index; IPSS irritative (storage) subscore; IPSS obstructive (voiding) subscore; BII: BPH impact index.

***Peer review***

This is an interesting review regarding the efficacy of phosphodiesterase type 5 inhibitor in lower urinary tract symptoms and benign prostate hyperplasia.

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**P-Reviewer:** Gacci M, Wang YH **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Characteristics and qualities of the studies included in the analysis of Tadalafil, Sildenafil and Vardenfil**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Sample size** | **Drug (mg)** | **Duration (wk)** | **Run-in****period (wk)** | **Inclusion criteria** | **Publications** |
| **Trial** | **Control** |
| **Tadalafil** |  |  |  |  |  |  |  |
| Brock *et al*[39] | 1089 | 5 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 mo, IPSS ≥ 13, Qmax 4-15 mL/s | *BJU Int* |
| Dmochowski *et al*[13] | 200 | 20 | Placebo | 12 | 4 | Mean age ≥ 40, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, | *J Urol* |
| Donatucci *et al*[14] | 427 | 2.5, 5, 10, 20 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13 | *BJU Int* |
| Egerdie *et al*[15] | 606 | 2.5, 5 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *J Sex Med* |
| Kim *et al*[16] 2011 | 102 | 5 | Placebo | 12 | 6 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *LUTS* |
| McVary *et al*[18] | 281 | 5 + 20 | Placebo | 6 + 6 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *J Urol* |
| Oelke *et al*[19] | 343 | 5 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *Eur Urol* |
| Porst *et al*[21] | 581 | 2.5, 5, 10, 20 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *Eur Urol* |
| Porst *et al*[36] | 325 | 5 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *Eur Urol* |
| Porst *et al*[20] | 1500 | 5 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *Urology* |
| Roehrborn *et al*[22] | 1058 | 2.5, 5, 10, 20 | Placebo | 12 | 4 | Mean age ≥ 45-60, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s, PVR 150-550 ml | *J Urol* |
| Roehrborn *et al*[12] | 1500 | 5 | Placebo | 12 | 4 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s | *J Urol* |
| Takeda *et al*[24] | 610 | 5 | Placebo | 12 | 4 | Mean age ≥ 40, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, | *J Urol* |
| Yokoyama *et al*[25] | 460 | 2.5, 5 | Placebo | 12 | 2 | Mean age ≥ 45, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 13, Qmax 4-15 mL/s, prostate volume ≥ 20 ml | *Int J Urol* |
| **Sildenafil** |  |  |  |  |  |  |  |
| McVary *et al*[10] | 369 | 50, 100 | Placebo | 12 | 4 | Mean age ≥ 45, IIEF ≤ 25, IPSS ≥ 12 | *J Urol* |
| **Vardenafil** |  |  |  |  |  |  |  |
| Stief *et al*[40] | 222 | 10 | Placebo | 8 | 4 | Mean age ≥ 45-64, LUTS/BPH ≥ 6 *mo*, IPSS ≥ 12, | *Eur Urol* |

IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom; LUTS/BPH: Lower urinary tract symptoms/benign prostatic hyperplasia; Qmax: Maximum urinary flow rate; PVR: Postvoid residual volume.

**Table 2 Least squares mean changes from baseline to end-point in Lower urinary tract symptoms/benign prostatic hyperplasia in clinical studies for the treatment in subjects with erectile dysfunction and without erectile dysfunction**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Drug****mg** | **Remarks** | **Total****IPSS** |  | **IPSS voiding****subscore** |  | **IPSS storage****subscore** |  | **IPSS QoL** **subscore** |  | **BII** |  | **Qmax** |  | **IIEF** |
| **T** | **P** |  | **T** | **P** |  | **T** | **P** |  | **T** | **P** |  | **T** | **P** |  | **T** | **P** |  | **T** | **P** |
|  | **Tadalafil** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brock *et al*[39] | 5 | ED | -5.7 | *-*3.3 |  | *-*3.5 | *-*1.9 |  | *-*2.2 | *-*1.3 |  | *-*1.1 | -0.7 |  | *-*1.6 | *-*0.9 |  |  |  |  |  |  |
| 5 | No ED | *-*5.4 | *-*3.3 |  | *-*3.5 | *-*2 |  | *-*1.9 | *-*1.3 |  | *-*1 |  | *-*1.4 | *-*1 |  |  |  |  |  |  |
| Dmochowski *et al*[13] | 20 |  | *-*9.2 | *-*5.1 |  | *-*5.6 | *-*2.8 |  | *-*3.6 | *-*2.3 |  |  |  |  |  |  |  | 0.4 | 0.5 |  |  |  |
| Donatucci *et al*[14] | 2.5 |  | *-*5.7 | *-*4.1 |  | *-*3.8 | *-*2.5 |  | *-*1.9 | *-*1.6 |  | *-*1.2 | *-*0.9 |  | *-*1.3 | *-*1.2 |  |  |  |  | 5.5 | 7.2 |
| 5 |  | *-*5.0 |  | *-*2.8 |  | *-*2.1 |  | *-*1.1 |  | *-*1.4 |  |  |  |  | 5.3 |
| 10 |  | *-*5.7 |  | *-*3.6 |  | *-*1.8 |  | *-*1.3 |  | *-*1.4 |  |  |  |  | 3.7 |
| 20 |  | *-*4.6 |  | *-*3 |  | *-*2.1 |  | *-*1.0 |  | 1.2 |  |  |  |  | 7.6 |
| Egerdie *et al*[15] | 2.5 |  | *-*6.1 | *-*3.8 |  | *-*2.7 | *-*2.2 |  | *-*1.9 | *-*1.6 |  | *-*0.9 | *-*0.8 |  | *-*2.1 | *-*1.2 |  |  |  |  | 6.5 | 1.8 |
| 5 |  | *-*4.6 |  | *-*3.6 |  | *-*2.5 |  |  | *-*1 |  | *-*1.6 |  |  |  |  | 5.2 |
| Kim *et al*[16] | 5 |  | *-*5.6 | *-*3.6 |  |  |  |  |  |  |  |  |  |  |  |  |  | 2.5 | 2.3 |  |  |  |
| McVary *et al*[18] | 5 |  | *-*6.2 | *-*3.9 |  | *-*4.0 | *-*2.5 |  | *-*2.2 | *-*1.4 |  | *-*0.7 | *-*0.3 |  | *-*0.7 | *-*0.4 |  | 0.5 | 0.9 |  | 6.7 | 0.7 |
| 5/20 |  | *-*7.1 | *-*4.5 |  | *-*4.4 | *-*2.8 |  | *-*2.7 | *-*1.8 |  | *-*0.5 | *-*0.2 |  | *-*1.3 | *-*0.6 |  | 0.5 |  | 8.4 | 1.6 |
| Oelke *et al*[19] | 5 |  | *-*6.3 | *-*4.2 |  | *-*4.1 | *-*2.6 |  | *-*2.2 | *-*1.6 |  | *-*1.3 | *-*1 |  |  |  |  | 2.4 | 1.2 |  |  |  |
| Porst *et al*[21] | 2.5 |  | *-*4.2 | *-*2.1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 8.2 | 2 |
| 5 |  | *-*4.7 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 7.9 |
| 10 |  | *-*4.7 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 6.8 |
| 20 |  | *-*3.6 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 5.4 |
| Porst *et al*[36] | 5 |  | *-*5.6 | *-*3.6 |  | *-*3.3 | *-*2.3 |  | *-*2.3 | *-*1.3 |  |  |  |  | *-*1.8 | -1.3 |  |  |  |  | 6.7 | 2 |
| Porst *et al*[20] | 5 |  | -7.9 | -5.1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Roehrborn *et al*[22] | 2.5 |  | -5.17 | -2.27 |  | -2.94 | -1.26 |  | -1.96 | -0.99 |  | -0.92 | -0.49 |  | -1.38 | -0.83 |  | 1.96 | 1.24 |  | 8.34 | 2.2 |
| 5 |  | -3.88 |  | -2.23 |  | -2.07 |  | -0.88 |  | -1.4 |  | 1.41 |  | 7.98 |
| 10 |  | -5.21 |  | -3.12 |  | -1.58 |  | -0.74 |  | -0.96 |  | 1.64 |  | 6.97 |
| 20 |  | -4.87 |  | -3.13 |  | -1.89 |  | -0.86 |  | -1.45 |  | 1.58 |  | 5.59 |  |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Roehrborn *et al*[12] | 5 | Qmax < 10 | -5.2 | -3.6 |  | -3.2 | -2.1 |  |  |  |  |  |  |  |  |  |  | 2.8 | 2.4 |  |  |  |
| 5 | Qmax of 10-15 | -6.3 | -3.8 |  | -3.9 | -2.5 |  |  |  |  |  |  |  |  |  |  | 1.4 | 0.9 |  |  |  |
| 5 | Qmax > 15 | -6.8 | -2.7 |  | -3.9 | -1.2 |  |  |  |  |  |  |  |  |  |  | -1.1 | -2.7 |  |  |  |
| Takeda *et al*[24] | 5 |  | -6 | -4.5 |  | -2 | -1.4 |  | -2 | -1.4 |  | -2 | -1.4 |  |  |  |  |  |  |  |  |  |
| Yokoyama *et al*[25] | 2.5 |  | -5 | -3 |  | -3.3 | -1.9 |  | -1.7 | -1.1 |  | -0.8 | -0.5 |  | -1 | -0.8 |  | 1.3 | 2.1 |  |  |  |
| 5 |  | -5.1 |  | -3.72 |  | -1.5 |  | -0.8 |  | -1.1 |  | 1.6 |  |  |  |
|  | **Sildenafil** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| McVary *et al*[10] | 50100 |  | -6.3 | -1.9 |  |  |  |  |  |  |  | -0.9 | -0.3 |  | -2.0 | -0.9 |  | 0.31 | 0.16 |  | 9.17 | 1.86 |
|  | **Vardenafil** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stief *et al*[40] | 10 |  | - 5.8 | - 3.6 |  |  |  |  |  |  |  |  |  |  |  |  |  | 1.6 | 1 |  |  |  |

IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom; LUTS/BPH: Lower urinary tract symptoms/benign prostatic hyperplasia; Qmax: Maximum urinary flow rate; PVR: Postvoid residual volume; QoL: Quality of Life; BII: Benign prostatic hyperplasia impact index; T: Treatment; P: Placebo.

**Table 3 Outcomes of the meta-analysis of total International Prostate Symptom Score, International Prostate Symptom Score storage subscore, International Prostate Symptom Score voiding subscore, International Prostate Symptom Score Quality of Life subscore, Benign prostatic hyperplasia Impact Index, maximum urinary flow rate, and International Index of Erectile Function score in lower urinary tract symptoms/benign prostatic hyperplasia or lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction patients**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome or****subgroup** | **Studies** | **Participants** | **Weight** | **Statistical****method** | **Effect Estimate****(Mean difference, 95%CI)** | **Heterogeneity** | **Overall** ***Z* value** | ***P* value** |
| **χ2** | **I2 (%)** |
| Total IPSS in LUTS/BPH | 13 | 9131 | 100% | Fixed | - 2.17 (-2.42, -1.91) | 16.44 | 0 | 16.75 | < 0.00001 |
| Tadalafil | 11 | 8576 | 95.5% | Fixed | -2.14 (-2.40, -1.88) | 13.27 | 0 | 16.18 | < 0.00001 |
| Sildenafil | 1 | 341 | 1.0% | Fixed | -4.40 (-6.87, -1.93) |  | 3.48 | 0.0005 |
| Vardenafil | 1 | 214 | 3.4% | Fixed | -2.20 (-3.57, -0.83) |  | 3.14 | 0.002 |
| Total IPSS in LUTS/BPH and ED | 6 | 3626 | 100% | Fixed | -1.97 (-2.43, -1.51) | 12.33 | 3 | 8.41 | < 0.00001 |
| Tadalafil | 5 | 3285 | 96.6% | Fixed | -1.88 (-2.35, -1.41) | 8.49 | 0 | 7.90 | < 0.00001 |
| Sildenafil | 1 | 341 | 3.4% | Fixed | -4.40 (-6.87, -1.93) |  | 3.48 | 0.0005 |
| IPSS storage subscore in LUTS/BPH |  |  |  |  |  |  |  |  |  |
| Tadalafil | 10 | 6848 | 100% | Fixed | -0.71 (-0.85, -0.57) | 12.64 | 0 | 9.96 | < 0.00001 |
| IPSS voiding subscore in LUTS/BPH |  |  |  |  |  |  |  |  |  |
| Tadalafil | 11 | 7916 | 100% | Fixed | -1.23 (-1.41, -1.04) | 24.70 | 15 | 13.28 | < 0.00001 |
| IPSS QoL subscore in LUTS/BPH | 8 | 5999 | 100% | Fixed | -0.33 (-0.40, -0.26) | 8.26 | 0 | 8.70 | < 0.00001 |
| Tadalafil | 7 | 5648 | 97.7% | Fixed | -0.32 (-0.40, -0.25) | 6.26 | 0 | 8.38 | < 0.00001 |
| Sildenafil | 1 | 351 | 2.3% | Fixed | -0.68 (-1.17, -0.19) |  | 2.71 | 0.007 |
| BII in LUTS/BPH |  |  |  |  |  |  |  |  |  |
| Tadalafil | 5 | 3504 | 100% | Fixed | -0.43 (-0.61, -0.25) | 3.89 | 0 | 4.64 | < 0.00001 |
| BII in LUTS/BPH and ED | 4 | 2561 | 100% | Fixed | -0.52 (-0.74, -0.29) | 8.02 | 13 | 4.51 | < 0.00001 |
| Tadalafil | 3 | 2210 | 94.8% | Fixed | -0.48 (-0.71, -0.25) | 6.59 | 9 | 4.11 | < 0.0001 |
| Sildenafil | 1 | 351 | 5.2% | Fixed | -1.10 (-2.08, -0.12) |  | 2.19 | 0.03 |
| Qmax in LUTS/BPH |  |  |  |  |  |  |  |  |  |
| Tadalafil (2.5, 5, 10 and 20 mg) | 9 | 5034 | 64.9% | Fixed | 0.22 (-0.04, 0.49) | 13.43 | 3 | 1.65 | 0.10 |
| Tadalafil (Only 5 mg) | 7 | 2876 | 35.1% | Fixed | 0.33 (-0.13, 0.80) | 8.24 | 24 | 2.14 | 0.03 |
| IIEF in LUTS/BPH |  |  |  |  |  |  |  |  |  |
| Tadalafil | 2 | 2009 | 100% | Fixed | 4.88 (3.31, 8.97) | 2.28 | 0 | 8.96 | < 0.00001 |
| IIEF in LUTS/BPH and ED |  |  |  |  |  |  |  |  |  |
| Tadalafil | 3 | 1746 | 100% | Fixed | 4.54 (3.75, 5.33) | 7.33 | 18 | 11.27 | < 0.00001 |

IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; LUTS/BPH: Lower urinary tract symptoms/benign prostatic hyperplasia; Qmax: Maximum urinary flow rate; PVR: Postvoid residual volume; QoL: Quality of Life; BII: Benign prostatic hyperplasia impact index.