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Review Article

Urinary Tract Symptoms (LUTS) Secondary to Benign Prostatic Hyperplasia (BPH) and LUTS/BPH with Erectile Dysfunction in Asian Men: A Systematic Review Focusing on Tadalafil

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This review assesses lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) with or without erectile dysfunction (ED) and related therapies focusing on tadalafil. A literature search was obtained and reviewed for the epidemiology, treatment therapies, pathophysiology, and efficacy and safety of phosphodiesterase type 5 inhibitor (PDE5i) tadalafil in patients with LUTS/BPH. Approximately 42% of men aged 51 to 60 years have BPH. Approximately 90% of men aged 45 to 80 years have LUTS. Occurrence of LUTS increases with age for almost all racial/ethnic groups (range, 32% to 56%) with prevalence of LUTS highest among Hispanic men, then Blacks, Caucasians, and Asians. There is an independent relationship with LUTS/BPH and ED, with approximately 70% of men with LUTS/BPH having ED with severity of one disease often correlating with the other. The European Urological Association guidelines include the use of the PDE5i tadalafil. Tadalafil is the only therapy recommended for treatment of co-existing BPH and ED, while other therapies have unwanted ED side effects. The mode of action of tadalafil may involve different areas of the lower urinary tract such as smooth muscle cell relaxation in the bladder neck, prostate, and urethra, but there may also be resulting modulation of the afferent nerve activity. Tadalafil (5 mg) in Asian men with LUTS/BPH, similar to global studies, is efficacious and safe. Tadalafil (5 mg) improves co-existing LUTS/BPH and ED, independently. Men with LUTS/BPH likely also have ED. Asian men with LUTS/BPH have similar incidence rates, co-existing ED, comorbid diseases, and risks as non-Asian men. Tadalafil can improve co-existing LUTS/BPH and ED.

Key Words: Erectile dysfunction; Pharmacology; Phosphodiesterase 5 inhibitors; Prostatic hyperplasia; Tadalafil

INTRODUCTION

Lower urinary tract symptoms (LUTS) occur in men and women increasingly with age. In men, LUTS is often concurrent with benign prostatic hyperplasia (BPH). BPH is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostate [1,2]. The progression of BPH can lead to benign prostatic enlargement (BPE). Men with LUTS secondary to BPH (LUTS/BPH) tend to seek medical attention after symp-

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toms have become disruptive to their quality of life (QoL). LUTS/BPH is generally classified as storage symptoms or voiding symptoms.

The prevalence of LUTS has been shown to increase linearly with age [3,4].

The pathophysiology of LUTS and its underlying mechanisms are not fully understood but may have similarity with erectile dysfunction (ED) [5], as many patients with LUTS are found to have co-existing ED and vice versa [6]. Men with LUTS/BPH tend to have one or more physiological diagnoses, comorbidities, and/or risk factors.

Approximately 70% of men with LUTS/BPH have co-existing ED. Recent treatment guidelines for LUTS/BPH include the use of several regulatory-approved pharmacologic classes including the phosphodiesterase type 5 inhibitor (PDE5i) tadalafil (LY450190, Cialis, Adcirca; Eli Lilly, Indianapolis, IN, USA) [7].

Tadalafil is an orally administered, potent, and selective inhibitor of the PDE5 enzyme. Tadalafil (5 to 20 mg dosed as needed; 2.5 mg or 5 mg dose once daily) is approved to treat men with ED in many countries. Tadalafil (40-mg dose once daily) is also approved in many countries under the trade name of Adcirca to treat patients with pulmonary arterial hypertension. Tadalafil (5 mg once daily) is approved under the trade name of Cialis to treat men with LUTS/ BPH with or without ED in several areas including the European Union, United States, and Republic of Korea.

This review will provide an update on the epidemiology, co-existing ED, comorbidities, risk factors, guidelines, and current standard of care in patients with LUTS/BPH. We reviewed global data on the mode of action, safety, and efficacy of tadalafil in patients with LUTS/BPH, with specific attention to Korean men and other Asian men.

Literature was obtained via Medline searches with an attempt to include the latest research available. Review articles and relevant reference lists related to LUTS/BPH were reviewed and selected as appropriate on the topics of treatment, epidemiology with or without ED, the mode of action for tadalafil, and the safety and efficacy of tadalafil. Preference was given to randomized, controlled, double-blind clinical trials for efficacy and safety of tadalafil treatment in patients with LUTS/BPH.

DEFINITION AND DIAGNOSIS OF LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA AND ERECTILE DYSFUNCTION

The European Association of Urology (EAU) and American Urological Association (AUA) [7] guidelines define LUTS as storage (irritative) symptoms (daytime urinary frequency, urgency, and nocturia), voiding (obstructive) symptoms (straining, weak stream, intermittent stream, and incomplete emptying), or postmicturition symptoms (postmicturition dribbling) that affect the lower urinary tract (LUT) [7,8].

BPH is a histologic diagnosis that refers to the nonmalignant proliferation of smooth muscle and epithelial cells of the prostate [1,2]. The exact etiology is unknown. The progression of BPH can lead to BPE, which is determined by the size of the prostate (pathologic). Approximately 50% of men with histologic BPH develop BPE. BPE may eventually cause bladder outlet obstruction (BOO), which is also termed benign prostatic obstruction (BPO) if associated with BPE. BOO and BPO are determined with urodynamic measures. Some patients may present with BPE but not have significant LUTS, while other patients may present with LUTS and have a significant reduction in QoL but not have BPE.

Clinical diagnosis of LUTS/BPH is a multistep process used to eliminate prostate cancer, identify risk factors, and obtain physiological measures. Symptoms of LUTS/BPH are generally assessed using the International Prostate Symptom Score (IPSS) or AUA Prostate Symptom Index (AUA-SI); a transrectal ultrasound of the prostate; the measurement of the maximal urinary flow rate (Qmax) assessed by uroflowmetry; and the measurement of postvoid residual volume assessed by ultrasound, urinalysis, and serum prostate specific antigen (PSA) levels.

The definition of LUTS/BPH used in clinical studies and in the literature varies widely. This paper did not try to standardize the definition of LUTS/BPH. Men with LUTS/BPH have generally been identified histologically with having BPH; with symptom severity assessed by total IPSS as being either mild (0～7), moderate (8～19), or severe (20～35); with the size of the prostate determined (BPE defined as prostate volume ≥20 mL); and with a

Qmax of 4 to15 mL/s, which is indicative of BPO.

The IPSS questionnaire is a validated, 7-part, self-administered questionnaire that is used to assess LUTS/BPH severity and response to treatment [9]. The International Index of Erectile Function (IIEF) questionnaire is a validated self-administered patient questionnaire that assesses ED [10] with erectile function assessed via the erectile function domain (IIEF-EF).

EPIDEMIOLOGY IN THE GLOBAL POPULATION

1. Incidence

Histologic BPH increases with age and occurs in approximately 8% of men aged 31 to 40 years, 42% of men aged 51 to 60 years, 71% of men aged 61 to 70 years, and 88% of men aged 81 years and older [11]. It is estimated that 90% of men between 45 and 80 years of age have LUTS [12]. The BPH registry and patient survey of 6,184 patients reported 33% with mild LUTS (IPSS＜7), 52% with moderate LUTS (IPSS 8～19), and 15% with severe LUTS (IPSS≥20) [13].

The incidence of BPH from 5,667 subjects in the prostate cancer prevention trial (IPSS＞14) was 34.4 per 1,000 persons per year in the United States in men older than 55 years, with the risk of BPH increasing 4% with each additional year of age [14].

The urologic diseases in America BPH project examined the prevalence of moderate to severe LUTS reported in US population-based studies that used the definition of an AUA-SI score of ≥7 [15]. The Olmsted County Study showed a progressive increase in the prevalence of moderate to severe LUTS to nearly 50% by the eighth decade of life [16]. Moderate to severe LUTS was also associated with the development of acute urinary retention (AUR) as a symptom of BPH progression, increasing from 6.8 episodes per 1,000 patient years to 34.7 episodes in men ≥70 years.

A prospective study using data from the health professionals follow-up study reported worsening LUTS increased with age with progression to severe LUTS at 44.9 per 1,000 man-years [17].

2. Racial/ethnic disparities

The prostate cancer prevention trial reported that the highest prevalence of BPH was among Hispanic men, followed by black men, Caucasian (white) men, and Asian American men [14].

A similar finding was noted in a prospective study using the AUA-SI in two large cohorts, including the California men's health study and the research program in genes, environment and health [18]. The highest prevalence of LUTS was among Hispanic men, followed by black, white, and Asian men. Asian men were at lower risk for moderate or severe LUTS than were white men. The incidence rate of LUTS increased with increasing baseline age for almost all racial/ethnic groups (range, 32% to 56%) [18].

3. Co-existing erectile dysfunction

The pathophysiology of LUTS and its underlying mechanisms are not fully understood but may have similarity with those of ED [5]. It has been observed that there is an independent relationship between LUTS/BPH and co-existing ED [19-23]. While increasing age is a known predictor of LUTS/BPH and ED separately, LUTS/BPH severity is an even better predictor of ED than increases in a patient's age [24], thus establishing an independent link between LUTS/BPH and ED [6].

In 6,924 men from the United States with LUTS, 71% had co-existing ED [25]. In 453 men with planned surgery for LUTS/BPH, the incidence of co-existing ED increased with LUTS severity from 36% in men with moderate LUTS to 94% in men with severe LUTS [26].

In a review article, the prevalence of coexisting LUTS and ED was shown to increase with age; the severity of one disease often correlated with the other, with most men who sought treatment for either LUTS or ED having both conditions [19]. However, ＜33% of middle-aged and older men in the general population had coexisting LUTS and ED.

In an integrated analysis of 3 clinical trials of tadalafil in patients with LUTS/BPH, 69% of the patients reported a history of ED [27].

4. Other comorbidities

In addition to the presence of co-existing ED in patients presenting with LUTS/BPH, there are several other comorbidities that have been identified in men with LUTS/BPH. The BPH registry and patient survey [13] re-

ported the following comorbidities in the 6,909 men enrolled: hypertension, 53%; high cholesterol, 45%; erectile or other sexual dysfunction, 36%; digestive tract disorder, 21%; arthritis, 20%; heart disease/heart failure, 18%; diabetes, 17%; depression/anxiety/sleep disorder, 16%; allergies/cold/flu/congestion, 15%; and general pain/inflammation, 11%.

In an integrated analysis of 3 clinical trials of tadalafil in men with LUTS/BPH, the men who also had co-existing ED had higher incidences of comorbid cardiovascular disease (50% vs. 41%), hypertension (43% vs. 35%), and diabetes mellitus (15% vs. 7%) than did men with only LUTS/BPH, respectively [27].

5. Risk factors associated with lower urinary tract symptoms/benign prostatic hyperplasia

The risk factors associated with LUTS/BPH are similar to the risk factors associated with ED, suggesting that the pathophysiology of LUTS and its underlying mechanisms may have a similarity to those of ED. Potential risk factors for LUTS/BPH include age, sedentary lifestyle and lack of exercise, smoking and excessive alcohol intake, depression, hypertension, cardiovascular disease, hyperlipidemia, Type 2 diabetes mellitus, obesity/waist circumference, hypogonadism, prostate disorder, inflammation, and genetic predisposition [6,14,28]. The more notable risk factors that increase the likelihood of LUTS/BPH include age, diabetes, hypertension, obesity, and hypogonadism [15,28]. Factors associated with decreased risks include increased physical activity, moderate alcohol intake, and increased vegetable consumption [29].

EPIDEMIOLOGY IN ASIAN MEN

1. Incidence in Asians

Asian American men have an estimated BPH incidence rate of 29.4 per 1,000 person-years, which is slightly lower than that reported for Caucasians [14]. The prevalence of BPH was 27% in Korean men from a community-based study in Chungbuk province using the definition of BPH that combined a prostate volume >20 mL and IPSS ≥ 8 [30].

In a cross-sectional community-based survey in Korean men 50 years and older, the overall incidence of moderate to severe LUTS/BPH was 21.0% [31]. The incidence of moderate to severe LUTS/BPH increased with increasing age: 11.6% in the 50- to 59-year age group, 18.1% in the 60- to 69-year age group, 30.8% in the 70- to 79-year age group, and up to 50.8% in the 80-year-and-older group. In a community-based epidemiological study in Korean men 50 years and older, the overall incidence of moderate to severe LUTS was 23.3% [32]. The incidence of moderate to severe LUTS increased with age from 17.7% in the 50- to 59-year age group, 23.3% in the 60- to 69-year age group, and up to 35.3% in the 70-year-and-older group. The prevalence of moderate to severe LUTS/BPH increased with age from 44% for men aged 50 to 59 years to 63% for men aged 70 to 79 years from a Japanese community-based study [33].

In a study of 1,224 Korean men (50 to 59 years) with urological diseases including LUTS/BPH, 18% had LUTS/BPH (defined as IPSS >7 and total prostate volume ≥ 30 mL); however, 6.3% had LUTS/BPH with BPO (defined as IPSS >7, a total prostate volume ≥ 30 mL, and a Qmax <15 mL) [34].

In a report on 994 Asian men with LUTS seeking medical help from a urology clinic in a prospective observational registry, the severity of LUTS was approximately 10% mild, 50% moderate, and 40% severe using the IPSS [35]. The incidence of severe LUTS increased with age; 28% of patients younger than 60 years had severe LUTS, while 47% of patients older than 70 years had severe LUTS. The most bothersome LUTS/BPH symptoms reported in these patients included nocturia (64%), followed by a weak urinary stream (56%), and incomplete emptying (53%). A complication of LUTS/BPH is AUR, which was reported in 12% of the Asian patients seeking LUTS/BPH treatment; only 2.3% of the patients had an episode of AUR while receiving BPH treatment [35].

In a multicenter, prospective study conducted in Korea, younger patients (mean, 55.7 years) were more likely to seek treatment because of voiding symptoms, while older patients (mean, 73.8 years) were more likely to seek treatment for both voiding and storage symptoms [36].

2. Co-existing erectile dysfunction in Asians with lower urinary tract symptoms/benign prostatic hyperplasia

Sexual disorders in 1,155 Asian men were shown to in-

crease with increasing age and increasing severity of LUTS [37]. ED increased with age and was present in 33%, 61%, and 87% of men with no or mild LUTS aged 50 to 59, 60 to 69, and 70 to 80 years, respectively, and ED was present in 54%, 84%, and 91%, respectively, of men with moderate to severe LUTS in those age groups [37]. Of 918 sexually active Asian men with LUTS from a prospective observational registry, 80% had co-existing ED with 25%, 19%, and 36% reporting mild, moderate, or severe ED [35]. Approximately 60% of 151 Korean patients with LUTS/BPH reported having co-existing ED from a tadalafil clinical study [38].

3. Other comorbidities in Asians

In addition to the presence of co-existing ED in patients with LUTS/BPH, several other comorbidities have been identified in Asian men with LUTS/BPH and are similar to those identified in non-Asians. Common comorbidities reported in Asian men include hypertension (38%), obesity (36%), diabetes mellitus (15%), and ischemic heart disease (7%) [35].

4. Risk factors in Asians

Few potential risk factors for LUTS/BPH are specific to Asians. The risk factors did not appear to be different from those previously reported from the global population, which include age, sedentary lifestyle and lack of exercise, smoking and excessive alcohol intake, depression, hypertension, cardiovascular disease, hyperlipidemia, Type 2 diabetes mellitus, obesity/waist circumference, hypogonadism, prostate disorder, inflammation, and genetic predisposition [6,14,28]. Factors in Asian patients that may decrease the risk for LUTS/BPH include increased physical activity, moderate alcohol intake, and increased vegetable consumption [29].

In a study of 1,224 Korean men (aged 50 to 59 years) with urological diseases including LUTS/BPH, 29% had metabolic syndrome (MetS) [34]. Patients with 3 or more of the following 5 MetS components were considered to have MetS: (1) blood pressure ≥130/85 mmHg and/or receiving antihypertensive medication, (2) fasting blood sugar ≥110 mg/dL and/or receiving antidiabetic medication, (3) waist circumference ≥90 cm, (4) highdensity lipoprotein cholesterol <40 mg/dL and/or receiving antihypercholesterolemic medication, and (5) triglyceride level ≥150 mg/dL and/or receiving antihypercholesterolemic medication. An increased number of MetS components in a patient was found to increase the risk of LUTS/BPH.

LOWER URINARY TRACT SYMPTOMS/ BENIGN PROSTATIC HYPERPLASIA EUROPEAN ASSOCIATION OF UROLOGY TREATMENT GUIDELINES

There are several guidelines available to assist physicians in the treatment of LUTS/BPH and include the US guideline [7] and recent EAU guideline [7].

The EAU guideline applies to men 40 years and older with non-neurogenic benign forms of LUTS, for example, LUTS/BPO, detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria [7]. Not included in these treatment guidelines are LUTS due to neurologic diseases, urinary incontinence, urogenital infections, ureteral stones, or malignant diseases of the LUT.

Drug treatment guidelines have included the use of alpha-blockers (alpha-adrenergic antagonists), 5-alpha-reductase inhibitors (5ARIs), antimuscarinics (anticholinergics), a PDE5 inhibitor (tadalafil), combination therapies, and vasopressin analogues [7]. The use of combination therapies such as an alpha-blocker with a 5ARI or antimuscarinic were also recommended. Watchful waiting (WW) for men who are not bothered enough by their symptoms to need drug therapy, changes in lifestyle to reduce risk factors, and surgical treatment were also part of the treatment guidelines but are not detailed in this report.

1. Conservative treatment: watchful waiting

Physicians with patients who present with LUTS/BPH but are not bothered enough to need drug or surgical interventions have the option of placing those patients on WW [7]. WW includes periodic monitoring to establish the severity of LUTS, education and lifestyle modifications such as dietary changes, reduction of nighttime fluid intake, avoidance of caffeine, increased physical activity, and weight loss to reduce symptoms and decrease risk factors associated with LUTS [6,7]. Factors associated with decreased risks include increased physical activity, moderate

alcohol intake, and increased vegetable consumption [29].

2. Drug treatments

Complementary alternative medicines (CAMs) were not recommended by the EAU because of inconsistencies in clinical data.

1) Alpha-blockers

Alpha-blockers are suggested for moderate to severe LUTS/BPH [7]. They are the most commonly prescribed type of medication for treating BPH. Alpha-blockers improve urine flow by relaxing the smooth muscles of the prostate and bladder neck and also reduce BOO or resistance [39]. Alpha-blockers are associated with adverse effects such as orthostatic hypotension, dizziness, and sexual dysfunction (ED, abnormal ejaculation). Alpha-blockers on the market include tamsulosin, doxazosin, terazosin, silodosin, and alfuzosin.

2) 5-alpha-reductase inhibitors

The 5ARIs are suggested for moderate to severe LUTS and BPE (prostate volume >40 mL) due to BPH [7]. The 5ARIs prevent progression of growth of the prostate or reduce the volume of the prostate in some men by inhibiting the production of the hormone dihydrotestosterone [39]. The 5ARIs are associated with sexual dysfunction (decreased libido, ED, abnormal ejaculation) and gynecomastia, and treatment effects may be delayed for 6 to 12 months. Among the 5ARIs on the market are dutasteride and finasteride.

3) Antimuscarinic drugs

Antimuscarinics (anticholinergics) are suggested for moderate to severe LUTS/BPH with OAB/storage symptoms [7]. Low treatment compliance in patients taking antimuscarinics has been an issue with reports ranging from 35% to 44% of patients not continuing treatment, possibly due to inadequate drug efficacy or intolerable side effects (dry mouth, dry eyes, and constipation) [40]. Marketed antimuscarinics include oxybutynin, tolderodine, propiverine, darfinacin, solifenacin, trospium, and fesoterodine.

4) A phosphodiesterase type 5 inhibitor

Tadalafil is a PDE5i suggested for moderate to severe LUTS/BPH (with or without ED) [7]. The possible mode of action is summarized later in this paper but is hypothesized to be due to smooth muscle relaxation in the bladder neck, prostate, and urethra; increased pelvic blood perfusion; and modulated afferent nerve activity in LUT tissues. Common adverse events with tadalafil include headache, indigestion, back pain, flushing, and nasal congestion. Tadalafil (5 mg once daily) was approved in October 2011 in Europe and is the only PDE5i approved for LUTS/BPH with or without ED. Tadalafil and tamsulosin were evaluated in patients with LUTS/BPH and ED (Table 1) [41]. Although both treatments resulted in improvement in LUTS/BPH (improved total IPSS scores), tadalafil was effective in improving ED (improving IIEF score) when compared to a placebo but tamsulosin was not.

5) Combination therapy

Combination therapy of an alpha-blocker and a 5ARI is suggested in men with moderate to severe LUTS/BPH, BPE, and a reduced Qmax. Combination therapy of an alpha-blocker and antimuscarinic is suggested if monotherapy with either drug does not provide adequate relief of OAB/storage symptoms. There were insufficient data to provide a recommendation on the potential use of tadalafil and tamsulosin combination therapy.

6) Vasopressin analogues

A vasopressin analogue is suggested for treatment of nocturia due to nocturnal polyuria. Desmopressin is a synthetic analogue of the antidiuretic hormone arginine vasopressin, which decreases urine volume and increases urine osmolality.

7) Surgical treatment

Prostate surgery such as transurethral resection of the prostate is indicated in men with absolute indications or drug treatment-resistant LUTS due to BPO. Indications for surgery include severe conditions such as urinary retention, gross hematuria, urinary tract infection, and bladder stones.

8) Minimally invasive therapies

Minimally invasive treatments suggested include transurethral microwave therapy and transurethral needle

Table 1. Efficacy of tadalafil in men with lower urinary tract symptoms

Reference	Treatment	n	Total IPSS[a]	IPSS storage subscore[a]	IPSS voiding subscore[a]	Qmax (mL/s)[a]	IIEF-EF[a]
Global studies							
McVary et al, 2007 [77]	Placebo	143	−1.7	−1.0	−0.7	0.9	1.4
	Tadalafil 5 mg/20 mg	138	−3.8[b]	−2.2[b]	−1.7[b]	0.5	7.7[b]
Roehrborn et al, 2008 [70]	Placebo	210	−2.3	−1.0	−1.3	1.2	2.2
	Tadalafil 2.5 mg	208	−3.9[b]	−1.6	−2.2[b]	1.4	5.6[b]
	Tadalafil 5 mg	212	−4.9[b]	−1.9[b]	−2.9[b]	1.6	7.0[b]
	Tadalafil 10 mg	216	−5.2[b]	−2.0[b]	−3.1[b]	1.6	8.0[b]
	Tadalafil 20 mg	208	−5.2[b]	−2.1[b]	−3.1[b]	2.0	8.3[b]
Porst et al, 2011 [71]	Placebo	164	−3.6	−1.3	−2.3	1.0	2.0
	Tadalafil 5 mg	161	−5.6[b]	−2.3[b]	−3.3[b]	1.6	6.7[b]
Oelke et al, 2012 [41]	Placebo	172	−4.2	−1.6	−2.6	1.2	-
	Tadalafil 5 mg	171	−6.3[b]	−2.2	−4.1[b]	2.4[b]	-
	Tamsulosin 0.4 mg	165	−5.7[b]	−2.2	−3.5[b]	2.2[b]	-
Egerdie et al, 2012 [72]	Placebo	200	−3.8	−1.6	−2.2	1.2	1.8
	Tadalafil 2.5 mg	198	−4.6	−1.9	−2.7	1.7[b]	5.2[b]
	Tadalafil 5 mg	208	−6.1[b]	−2.5[b]	−3.6[b]	1.6	6.5[b]
Asian studies							
Takeda et al, 2012 [75]	Placebo	140	−3.8	−1.4	−2.4	1.4	-
	Tadalafil 2.5 mg	142	−4.5	−1.6	−2.9	0.7	-
	Tadalafil 5 mg	140	−4.9	−1.6	−3.3[b]	0.6	-
Yokoyama et al, 2013 [76]	Placebo	154	−3.0	−1.1	−1.9	2.1	-
	Tadalafil 2.5 mg	151	−4.8[b]	−1.5	−3.3[b]	1.6	-
	Tadalafil 5 mg	155	−4.7[b]	−1.7	−3.0[b]	1.3	-
	Tamsulosin 0.2 mg	152	−5.5[c]	−1.7[c]	−3.8[c]	2.1	-
Pooled global studies							
Brock et al, 2013 [27]	Placebo (no ED)	167	−3.3	−1.3	−2.0	-	-
	Tadalafil 5 mg (no ED)	163	−5.4[b]	−1.9[b]	−3.5[b]	-	-
	Placebo (with ED)	372	−3.3	−1.3	−1.9	-	-
	Tadalafil 5 mg (with ED)	373	−5.7[b]	−2.2[b]	−3.5[b]	-	-
Porst et al, 2013 [74]	Placebo (with ED)	521	−3.6	−1.5	−2.1	-	1.4
	Tadalafil 5 mg (with ED)	505	−6.0[b]	−2.3[b]	−3.7[b]	-	6.3[b]

IPSS: International Prostate Symptom Score, Qmax: maximum urinary flow rate, IIEF-EF: International Index of Erectile Function erectile function domain, -: value not reported, ED: erectile dysfunction.
[a]Least-squares mean change from baseline to end point. [b]Comparison with placebo was statistically significant, $p<0.05$. [c]Statistical comparison with placebo was not reported.

therapy. An alternative to catheterization for men unfit for surgery are prostate stents.

LOWER URINARY TRACT SYMPTOMS/ BENIGN PROSTATIC HYPERPLASIA TREATMENT GUIDELINES IN ASIAN PATIENTS

The Japanese Urological Association (JUA) guidelines [42] have been provided for physicians in Japan. However, other Asian countries may choose to use the EAU guidelines [7]. The current Korean Prostate Society (KPS) guidelines [43] are based on prior EAU guidelines.

The JUA BPH guideline recommends that patients seeking treatment for LUTS/BPH should have a mandatory assessment that includes a medical history, physical examination, symptom and QoL questionnaires, urinalysis, prostate ultrasonography, measurement of PSA, postvoid residual urine, and uroflowmetry [42].

After the development of the JUA guidelines, there are many similarities with the EAU guideline. With the approval of tadalafil in Korea to treat LUTS/BPH with or without ED and the advent of new EAU guidelines that include tadalafil as a recommended drug therapy [7], future KPS and

JUA guidelines will likely include tadalafil. A brief summary of the commonalities and differences of JUA and KPS guidelines is described below.

In KPS and JUA guidelines, common recommended drug therapies include alpha-blockers, 5ARIs, vasopressin analogues, and combination therapies [42,43]. However, the current JUA guideline has graded the use of monotherapy antimuscarinics or tadalafil therapy as 'reserved' (unable to decide the grade of recommendation).

Like the EAU guideline, the KPS and JUA guidelines also suggest surgical treatment, minimally invasive therapies, and conservative treatment. Use of CAMs was not graded highly by the JUA or EAU because of the lack of consistent clinical data and cost burden to the patient. Of note is that WW in the JUA guideline was graded below drug treatments and surgical interventions.

REVIEW OF ASIAN CLINICAL PRACTICE IN TREATMENT OF LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

From a prospective observational registry in men with BPH from 5 Asian countries (Japan was not included), 78% of the men were started on LUTS/BPH medication, 13% were placed on WW, and 9% underewent surgery [35]. This pattern was substantially different from a large US study in which the majority of patients with LUTS/BPH (approximately 76%) were placed on WW, approximately 21% received medical therapy, and 2% underwent surgery [44]. The most common LUTS/BPH medications used in Asian men were alpha-blockers, with alfuzosin being the most frequently prescribed (59%) [35]. Other medications included other alpha-blockers such as terazosin (20%), doxazosin (14%), and tamsulosin (6%) and 5ARIs, specifically, finasteride (2%), dutasteride (1%), and others (4%). Tadalafil was not an approved drug in these countries and therefore not part of the database. LUTS/BPH was resolved in 93% of patients after surgery, in 83% of those on BPH medication, and in 34% of those on WW [35]. Patients with LUTS/BPH and ED who were receiving LUTS/BPH drug treatment did not have significant changes in the co-existing ED as assessed by mean IIEF-5 scores. The largest IIEF-5 change from baseline (4.5) to end of treatment (5.5) was noted in patients with severe ED [35].

A study conducted using the National Health Insurance (NHI) program of Korea from 2004 to 2008 determined the trends and changes of BPH treatments in 3.8 million Korean men who visited health care centers [45]. The BPH medications allowed to be prescribed (and recorded in the database) were alpha-blockers, 5ARIs, antimuscarinics, and antidiuretics. Combination therapies and PDE5 inhibitors were not assessed in the report because the Korea NHI program did not permit physicians to prescribe them. As the Korean men aged, medical treatments increased, as did surgical interventions. South Korean men with LUTS/BPH in 2008 were prescribed alphablockers (n=2,489,677), 5ARIs (n=939,686), antimuscarinics (n=404,126), and an antidiuretic (desmopressin) (n=38,241). Twice as many patients were prescribed BPH medications in 2008 than in 2004. Desmopressin use increased 14-fold in Korean men for treatment of nocturia during the review period [45].

A survey conducted in 2007 among 251 Korean urologists who completed questionnaires determined that almost all of the patients complained of voiding difficulties such as nocturia (98.8%), weak stream (96.8%), post-voiding residual urine sense (95.6%), and daytime frequency (51.2%) [46]. The initial treatment for approximately 92% of the patients was drug therapy, with the two most common being monotherapy alpha-blockers (57.2%) and combination therapy (alpha-blocker with 5ARI, 41.6%). The use of CAMs with an alpha-blocker comprised 0.8% of initial drug therapy. Use of a monotherapy alpha-blocker decreased with increased severity of LUTS/BPH and was replaced with combination therapy (alpha-blocker with 5ARIs) in such cases [46].

A 5-month (2008 to 2009) prospective study in 1,054 patients with LUTS/BPH who sought treatment from urology centers in Korea [36] had slightly different treatment patterns than those previously observed in Korean men [45]. In the cross-sectional assessment (visit 2, 4 weeks after initial evaluation), alpha-blocker monotherapy was provided for 67.9% of patients, while combination therapy of an alpha-blocker with 5ARIs was provided for 24.8% of patients and an alpha-blocker with an antimuscarinic was provided in 4.3% patients [36]. Patients

with BPE (prostate volume ≥30 mL) and a PSA level ≥1.5 were more likely to receive combination therapy than monotherapy [36].

MODE OF ACTION OF THE PHOSPHODIESTERASE TYPE 5 INHIBITOR TADALAFIL

Voiding symptoms are associated with BPO, which is attributable to BPE as a result of BPH. Storage symptoms are more complex and do not appear to be BPH- or BPE-related because both men and women have these symptoms; more likely, these symptoms are associated with involuntary detrusor contractions or detrusor overactivity (DO) [39,47]. Involuntary detrusor contraction during the storage phase of the voiding cycle [48] seems to lead to OAB symptoms.

LUTS storage symptoms, unlike voiding symptoms, do not appear to be related to BPE but seem to be more closely related with DO [39,47]. Both men and women present with voiding symptoms [3,49]; thus BPE is not the only mechanism by which men present with LUTS voiding symptoms. Storage symptoms also occur in men and women and increase with age in both genders [50]. Storage LUTS may be associated with bladder dysfunction due to changes or alterations in afferent nerves or in interstitial cells within the bladder rather than BPE [51].

There are 4 pathophysiological pathways that lead to increased risk of LUTS: reduced nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling, chronic inflammation/steroid hormone imbalance/increased RhoA-Rho-kinase activity, autonomic hyperactivity, and pelvic atherosclerosis [5,6,20]. These factors can lead to reduced function of nerves and endothelium, alterations in smooth muscle tone, arterial insufficiency, reduced blood flow and hypoxia-related tissue damage, increased smooth muscle cell proliferation in the prostate, and bladder hypertrophy/noncompliance.

PDE5 activity is present in the LUT, specifically in the prostate [52-56], urethra [55-57], and bladder [53,55,56]. The smooth muscle areas of PDE5i interest in LUTS/BPH include the detrusor, prostatic stromal (prostate), vascular (artery), and urethral areas. All these areas have shown PDE5 activity and are potential areas of inhibition activity for tadalafil.

Prostate smooth muscle relaxation, reduction of detrusor muscle overactivity, and normal contraction of prostate tissue were inhibited when cGMP was increased using either NO donors or PDE5 inhibitors [52,58,59]. Additionally, PDE5 inhibitors (including tadalafil, sildenafil, or the NO donor sodium nitroprusside) have been shown to attenuate alpha-adrenergic-induced contraction of isolated human prostate tissue [52,59]. Thus cGMP may contribute to the regulation of prostatic smooth muscle cell contraction.

The vasculature that provides blood flow to the LUT may be affected by smooth muscle cell relaxation mediated through PDE5 inhibition. Decreased oxygenation of LUT tissue may contribute to LUTS/BPH. Atherosclerosis is associated with remodeling of smooth muscle structure and function in the pelvic vasculature [60,61], penis [62,63], prostate [64], and bladder [61]; and chronic ischemia of the LUT is often associated with LUTS/BPH [65].

In addition, there are three nerve systems of interest in LUTS/BPH: the pudendal, pelvic, and hypogastric nerves. The voiding process involves stimulation of the detrusor and inhibition of the parasympathetic innervation of the urethra and bladder neck hypogastric nerves, plus recruitment of motor neurons to the urethral sphincter [66]. The storage process involves inhibition of the parasympathetic innervation of the detrusor muscle with urethral sphincter contraction via sympathetic innervation of the hypogastric nerves and recruitment of the pudendal nerves. Storage symptoms may be the result of bladder dysfunction due to changes or alterations in afferent nerves or in interstitial cells [25]. Improvements in both storage and voiding urinary symptoms observed with tadalafil may be due to smooth muscle cell relaxation and regulation in the bladder neck, prostate, and urethra with potential resulting modulation of the afferent nerve activity. The relaxation of smooth muscle cells may increase blood flow through the supporting LUTS vasculature system. PDE5 inhibition may then have an impact on LUTS/BPH through increased perfusion of the LUT resulting in increased oxygenation. Animal models suggest that the reduced symptoms may also be due in part to an enhancement of NO inhibition of the overactive afferent nerve activity within the LUT [5,66,67]. Long-term efficacy may be due to continued

smooth muscle cell relaxation of the LUT tissues with increased blood perfusion and oxygenation of LUT tissues due to improved function of the supporting vasculature and resulting modulation of the afferent nerve activity.

In summary, the treatment of LUTS/BPH with or without ED with tadalafil is believed to relax smooth muscles in the bladder, prostate, urethra, and supporting vasculature, thereby increasing blood perfusion to the LUT.

EFFICACY AND SAFETY OF PHOSPHODIESTERASE TYPE 5 INHIBITOR

1. Sildenafil and vardenafil

Sildenafil and vardenafil, both PDE5is, have shown improvement in LUTS/BPH in single randomized placebo-controlled studies; however, these results have not been reproduced [68,69].

2. Tadalafil global placebo-controlled trials (pivotal)

Tadalafil has shown reduction in LUTS/BPH storage and voiding symptoms as assessed by the IPSS in several clinical trials (Table 1). Tadalafil has also been shown to independently reduce ED as assessed by the IIEF-EF in men with LUTS/BPH (Table 1).

Efficacy of tadalafil for the treatment of men with LUTS/BPH was demonstrated in 4 randomized, placebo-controlled clinical studies [41,70-72], and long-term efficacy was maintained during a 1-year uncontrolled study [73].

The first study was a double-blind, placebo-controlled, dose-finding randomized study comparing various doses of tadalafil (once daily) with placebo for 12 weeks [70] followed by a 1-year, open-label (OL) extension study [73] of tadalafil (5 mg once daily). Tadalafil (5 mg) significantly reduced LUTS/BPH versus placebo (IPSS, −4.9 vs. −2.3, $p<0.01$; IPSS voiding subscore, −2.9 vs. −1.3, $p<0.001$; IPSS storage subscore, −1.9 vs. −1.0, $p<0.01$) [70]. Changes were maintained after 1 year in the OL extension study [73].

A second study was a double-blind, placebo-controlled, dose-finding randomized study comparing tadalafil (5 mg once daily) with a placebo for 12 weeks [71]. Tadalafil significantly reduced LUTS/BPH versus the placebo (IPSS, −5.6 vs. −3.6, $p=0.004$; IPSS voiding subscore, −3.3 vs. −2.3, $p=0.02$; IPSS storage subscore, −2.3 vs. −1.3, $p=0.002$) [71].

A third study was a double-blind, placebo- and active-controlled, randomized study comparing tadalafil (5 mg once daily) with a placebo for 12 weeks with tamsulosin as an active control [41]. Tadalafil significantly reduced LUTS/BPH total IPSS and IPSS voiding but not IPSS storage versus the placebo (IPSS, −6.3 vs. −4.2, $p=0.001$; IPSS voiding subscore, −4.1 vs. −2.6, $p<0.001$; IPSS storage subscore, −2.2 vs. −1.6, $p=0.055$) [41]. In addition, tadalafil (5 mg) significantly improved erectile function compared with the placebo, while tamsulosin did not.

A fourth study was a double-blind, placebo-controlled, dose-finding randomized study comparing various doses of tadalafil (5 mg once daily) with a placebo for 12 weeks [72]. Tadalafil significantly reduced LUTS/BPH versus the placebo (IPSS, −6.1 vs. −3.8, $p<0.001$; IPSS voiding subscore, −3.6 vs. −2.2, $p=0.055$; IPSS storage subscore, −2.5 vs. −1.6, $p<0.001$) [72]. Tadalafil (5 mg) significantly improved erectile function compared with the placebo.

3. Tadalafil pooled-population analysis

1) Lower urinary tract symptoms/benign prostatic hyperplasia with or without erectile dysfunction

A pooled analysis population set from the 3 tadalafil studies that did not require men to have both ED and LUTS/BPH [70-72] provided a large dataset for analysis of tadalafil's effect on LUTS/BPH in men with and without ED [27]. A second pooled analysis population set from the four tadalafil studies [41,70-72] provided a large dataset of sexually active men with LUTS/BPH and co-existing ED for analysis [74].

Data from an integrated analysis of a pooled population from 3 randomized, double-blind, placebo-controlled, 12week studies in patients with LUTS/BPH [70-72] was recently assessed to determine the efficacy and safety of tadalafil in patients with and without ED [27]. A total of 338 (31%) patients reported no prior history of ED. Tadalafil (5 mg once daily) significantly reduced LUTS/BPH versus placebo in men without ED (IPSS, −5.4 vs. −3.3, $p<0.01$; IPSS voiding subscore, −3.5 vs. −2.0, $p<0.01$; IPSS stor-

age subscore, −1.9 vs. −1.3, $p<0.05$) and had similar degree reductions in men with ED [27]. Tadalafil also significantly improved QoL from baseline versus placebo in men without ED (IPSS-QoL, −1.0 vs. −0.7, $p<0.05$). Significant improvements in LUTS/BPH were similar between men with and without ED. Tadalafil was safe and well tolerated. Common treatment-emergent adverse events (TEAEs) reported by men with and without ED were also similar. Headache, dyspepsia, and nasopharyngitis were the most commonly reported TEAEs in men without ED treated with tadalafil; while headache, dyspepsia, and hypertension were the most commonly reported TEAEs in men with ED treated with tadalafil [27].

2) Lower urinary tract symptoms/benign prostatic hyperplasia with erectile dysfunction

An integrated analysis [74] of a pooled population from the three randomized, double-blind, placebo-controlled, 12-week studies in patients with LUTS/BPH [70-72] plus a randomized, double-blind, placebo-controlled, 12-week tadalafil study that required patients to have LUTS/BPH and co-existing ED [41] was recently assessed to determine the efficacy and safety of tadalafil in patients with co-existing ED at the time of randomization. Tadalafil (5 mg) significantly reduced LUTS/BPH versus the placebo in men with ED (IPSS, −6.0 vs. −3.6, $p<0.001$; IPSS voiding subscore, −3.7 vs. −2.1, $p<0.01$; IPSS storage subscore, −2.3 vs. −1.5, $p<0.05$) [74]. Improvements in IIEF-EF domain score (tadalafil, 6.3; placebo, 1.4) were also significant versus the placebo, as were the IPSS storage and voiding subscores, and IPSS-QoL (all $p<0.001$). Headache, back pain, and dyspepsia were the most commonly reported TEAEs in men with ED treated with tadalafil [74].

4. Tadalafil: global studies−summary

In the treatment of men with LUTS/BPH with or without ED, tadalafil (5 mg once daily) resulted in statistically significant and clinically meaningful improvements in LUTS/BPH compared to a placebo and also improved ED compared with the placebo. Tadalafil (5 mg) also provided durable effectiveness for LUTS/BPH without diminishing response over time and with a favorable risk-benefit profile. Tadalafil (5 mg) was well tolerated and no new safety issues were identified.

5. Tadalafil: Asian clinical studies

Efficacy of tadalafil in Asian men with LUTS/BPH was determined in 3 pivotal randomized, placebo-controlled clinical studies with long-term efficacy maintained during an OL extension study (Table 1) [75-77]. Results from one tadalafil study have yet to be published and are not discussed here.

The efficacy, safety, and dose response of tadalafil (2.5 mg and 5.0 mg once daily) were assessed in a prospective, multicenter, 12-week, double-blind, randomized, parallel-group, placebo-controlled study in Japanese men with LUTS/BPH [75]. A 42-week OL phase continued after the 12-week double-blind phase. The main inclusion criteria were patients who were Asian men 45 years and older, a >6-month history of LUTS/BPH, total IPSS ≥13, intermediate BOO per Qmax of 4 to 15 mL/s, and prostate volume >20 mL. The incidence of co-existing ED or other risk factors was not published. Numerical decreases in total IPSS for the change from baseline to the study endpoint observed for the 2.5 mg (−4.5, $p=0.201$) and 5.0 mg (−4.9, $p=0.062$) doses of tadalafil versus the placebo (−3.8) did not reach statistical significance. At week 12, a repeated-measures analysis identified a significant decrease in total IPSS for the 5 mg dose (−5.0, $p=0.035$) versus the placebo (−3.7). Significant decreases in IPSS voiding scores but not IPSS storage scores for only the 5.0 mg dose of tadalafil compared with the placebo were noted. There were no significant improvements in Qmax with tadalafil compared to the placebo. IPSS score changes seen in the double-blind phase were maintained over the OL extension phase. Nasopharyngitis, diarrhea, back pain, and headache were the most commonly reported TEAEs. Tadalafil was considered well tolerated, and no new safety concerns were identified [75].

The efficacy and safety of 2.5 mg and 5.0 mg once-daily doses of tadalafil were also assessed in a prospective, multicenter, 12-week, double-blind, randomized, parallel-group, placebo-controlled study, with tamsulosin as an active control, in Asian men with LUTS/BPH [76]. The main inclusion criteria were patients who were Asian men 45 years and older, a >6-month history of LUTS/BPH, total IPSS ≥13, intermediate BOO per Qmax of 4 to 15 mL/s,

and a prostate volume ≥20 mL. Of the 612 participants, 55.9% were Japanese, 29.4% were Korean, and 14.7% were Taiwanese. The incidence of co-existing ED or other risk factors was not published. Significant decreases in total IPSS for the change from baseline to the study endpoint were observed for the 2.5 mg (−4.8, p=0.003) and 5.0 mg (−4.7, p=0.004) doses of tadalafil versus the placebo (−3.0). Tamsulosin had numerically greater decreases in total IPSS, but statistical comparison with tadalafil was not conducted. Significant decreases in IPSS voiding scores but not IPSS storage scores were noted for both tadalafil groups compared with the placebo. There were no significant improvements in Qmax with tadalafil compared to the placebo [76].

Myalgia, headache, back pain, nasopharyngitis, and dizziness were the most commonly reported TEAEs. Tadalafil was considered well tolerated and no new safety concerns were identified [76].

6. Tadalafil: Asian studies—summary

The efficacy and safety results of tadalafil (5 mg once daily) observed in Asian men with LUTS/BPH were similar to the previously observed efficacy and safety in non-Asian men with LUTS/BPH.

CONCLUSIONS

The number of men diagnosed with LUTS/BPH in the general population has been increasing over the last decade. This may be due to better disease awareness and diagnosis, the increasing lifespan of men, and older men seeking medical help to increase their QoL by reducing LUTS. The prevalence and severity of LUTS/BPH is known to increase with increasing age [19]. Asian men may have a lower prevalence rate of LUTS/BPH and a lower risk for moderate or severe LUTS/BPH compared to Blacks, Hispanics, or Caucasians [14,18]. Co-existing ED and comorbidities such as hypertension, obesity, diabetes mellitus, and cardiovascular disease are present globally with similar incidence rates in Asian men [13,25]. Risk factors such as increasing age, sedentary lifestyle and lack of exercise, hypertension, cardiovascular disease, hyperlipidemia, type 2 diabetes mellitus, and obesity/waist circumference also are similarly present globally and in Asian men. Co-existing ED has underlying mechanisms, pathophysiology, and risk factors that are similar to LUTS/BPH [5]. LUTS/BPH and ED may occur independently of each other but often occur together, with ED tending to be noticed first. With a better understanding of the pathophysiology of LUTS/BPH, the mode of action of drug therapies, addition of the first-in-class PDE5i tadalafil, and new EAU treatment guidelines, physicians have more options for managing patients with LUTS/BPH with or without ED. It is increasingly being recognized that to best treat a patient, the patient must be assessed for BPE and BPO to determine whether a patient has LUTS storage or voiding problems or both. Storage LUTS and voiding LUTS are separate entities, with storage likely associated with the bladder, and voiding often associated with BPO. While storage and voiding LUTS are shared in LUTS/BPH, initial drug treatment guidelines may be based on a patient's initial LUTS/BPH assessment. One noticeable difference in LUTS/BPH treatment is that Asian men are more likely to be placed on drug treatment and then WW [47] than are global patients, who are more likely to be placed on WW and then drug treatment. Monotherapy or combination therapy can be tailored for each patient to best improve IPSS scores and QoL for the patient while minimizing potentially negating adverse side effects. With the link between LUTS/BPH and ED established, assessing patients for both LUTS/BPH and ED is prudent. Tadalafil (5 mg once daily) is a safe and efficacious drug that is approved for treating patients with LUTS/BPH and also patients with co-existing LUTS/BPH and ED.

Improvements in both storage and voiding urinary symptoms observed with tadalafil could be caused by the smooth muscle cell relaxation in the bladder neck, prostate, and urethra with increased blood perfusion in the LUT and reduced nonvoiding detrusor contractions with possible resulting modulation of the afferent nerve activity [5].

Treatment with tadalafil (5 mg) resulted in statistically significant and clinically meaningful improvements in LUTS/BPH compared to a placebo in Asian men, as demonstrated in two clinical trials [75,76]. Tadalafil (5 mg once daily) provided long-term effectiveness without diminishing the response.

Any treatments for BPH can modify sexual function, but tadalafil can improve co-existing LUTS/BPH and ED.

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