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SYSTEMATIC REVIEWS

Are phosphodiesterase type 5 inhibitors effective for the management of lower urinary symptoms suggestive of benign prostatic hyperplasia?

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Abstract

AIM: To review the efficacy of phosphodiesterase type 5 inhibitors (PDE5-Is) in lower urinary tract symptoms (LUTS) suggestive of 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. A meta-analytical technique was used for the analysis of integrated data from the included studies to evaluate the mean difference in the results.

RESULTS: Total IPSS score, IIEF and BII showed a significant improvement in trials in which LUTS/BPH with or without erectile dysfunction (ED) were 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 appear to improve IPSS storage, voiding and QoL subscore (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 significance 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 efficacy for improving LUTS in BPH patients with or without ED and could be considered to be the first line treatment for LUTS/BPH.

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 patients with lower urinary tract symptoms (LUTS) and benign prostate hyperplasia (BPH) has been evaluated and prescribed. Regardless of the significant improvement of total International Prostate Symptom Score and storage subscore, there are controversies about the urine flow rate. Also, we do not know the exact mechanism of how it works in the lower urinary tract. From the meta-analytical data, PDE5-I could be an alternative therapy for LUTS/BPH patients whether or not they have erectile dysfunction. Therefore, well designed large scale clinical trials 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 the transition zone of the prostate leading to nonmalignant enlargement of the prostate, which may result in lower urinary tract symptoms (LUTS), including storage and voiding symptoms[1-3]. BPH is a common disease of aging men. Moderate to severe LUTS secondary to BPH (LUTS/BPH) is predicted to 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 males will suffer from LUTS/BPH by the year 2018[4].

It is widely acceptable that BPH is not the exclusive source of LUTS[1-4]. Over the decades, LUTS/BPH treatment paradigms have shifted from surgical interventions to first-line pharmacotherapy for symptom 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 inhibitors or combined therapy[1-4]. Although they are proved to be efficacious, these therapies have potential 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 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 been clearly clarified, proposed contributors include inhibition of PDE5 iso-enzymes, present in the bladder, prostate, urethra and supporting vasculature, and consequently elevation in intracellular nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) concentration which functions to inhibit 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]. Understanding these complicated mechanisms shows 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 research has shown that PDE5-Is, either as monotherapy or combined with alpha blockers, also enhance LUTS/BPH, presumably *via* relaxation of smooth muscle in the bladder neck, urethra and prostate induced by the NO/cGMP signal pathway.

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

Epidemiological survey: two common conditions in 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 stromal-glandular hyperplasia rises, so does the prevalence of moderate to severe LUTS[30]. Correspondingly, the rate of ED also rises with aging. As such, it is not a surprise that many patients with LUTS will also suffer from ED and vice versa. 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, the epidemiology of which was summarized in a review[32]. It points out that the majority of well-designed longitudinal studies have been proposed to interpret the relationship between ED and LUTS, including varying NO levels, activated RhoA/Rho kinase and atherosclerosis in the pelvis.

A recent abstract from a larger cross-sectional and multinational assessment of LUTS and sexual function was conducted[33]. Logistic regression analysis showed that patients with severe LUTS were estimated to be twice 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 with severe LUTS were 6 fold as likely to complain of discomfort or pain on ejaculation. Another cross-sectional data analysis is from the multinational survey of the aging male (MSAM-7) in which patients aging 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 and it also showed that the link between LUTS and ejaculatory dysfunction still existed after controlling for age and other comorbidities.

Clinical studies of PDE5-Is: Are LUTS/BPH and ED independent?

It was speculated that enhancement in LUTS/BPH could be 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 whether the improvement of BPH symptoms is linked to improved ED symptoms[9,34]. In one study of dose-ranging tadalafil with 716 ED patients and 340 non-ED patients, alterations in LUTS/BPH after 3 mo of medication with distinct doses of tadalafil once daily and placebo was analogous in patients with or without comorbidity of ED, demonstrating that the enhancement in LUTS/BPH did not rely on ED alterations[35]. Another tadalafil study confirmed these finding[36]. As a consequence, they are independent of each other even although the mechanism by which PDE5-Is enhance LUTS/BPH could participate in analogous ways with PDE5-Is enhancing ED.

PDE5-I localization in the prostate

Much evidence from experimental research confirmed that the cGMP-degrading PDE5 as well as NO/cGMP signaling pathway are responsible for the regulation of the normal functions of the prostate, regulating proliferation of glandular epithelial cells and smooth muscle as well as stromal connective tissue[29,37]. As early as 1970, 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 PDE5 distribution in distinct histopathological portions of the prostate was disclosed by immunohistochemistry (IHC). It was demonstrated that cGMP PDE iso-enzyme localized in the glandular zone, the smooth musculature of stroma and blood vessels by utilization of antibodies[35]. It was also shown that PDE5 is detected in tight conjunction with other critical regulators of NO/cGMP pathway. The concentration of tadalafil in the prostate and plasma was 385.7 ± 83.8 and 305.8 ± 41.1 ng/mL, respectively. In addition, the ratio between tissue and plasma was 1.3[38]. Tadalafil and udenafil significantly enhanced the cGMP and cAMP levels in plasma and prostate tissue[38].

PDE5-Is mechanism of action

Briefly, the current postulated action mechanism in improvement of LUTS/BPH includes: (1) ascending NO synthase/NO activity in the prostate; (2) cGMP mediated protein kinase/endothelin inactivation; (3) decreased autonomic hyperactivity of the afferent nerve in the bladder and 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 in the present review met the following standards: (1) double blinded, clinical controlled trials; (2) LUTS/BPH was involved; and (3) control groups were given a placebo drug. Studies with PED5-Is monotherapy versus an alpha blocker or combination of both were excluded.

To assess the efficacy of PED5-Is, the outcomes of measurement contain at least one of: (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, IPSS obstructive (voiding) subscore and BPH impact index (BII).

Statistical analysis

The meta-analysis used the review manager (Version 5.3, the Cochrane Collaboration, Oxford, United Kingdom). The heterogeneity test was by χ^2 and I^2 ($I^2 \leqslant$ 50%, low heterogeneity; 50% < $I^2 \leqslant$ 75%, moderate heterogeneity; and I^2 > 75%, high heterogeneity). If the heterogeneity was less than 50%, the fixed-effects model was considered to estimate the integrated effect of the outcomes. For moderate or high heterogeneity, a random-effect was used. The continuous value was used as the mean difference with 95%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 LUTS/BPH therapy and 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 the studies are summarized in Table 1. The study designs were analogous, followed by up to 4 wk of washout periods in order to eliminate the medications prior to trials.

Efficacy of PDE5-Is of sildenafil, tadalafil and vardenafil

Sildenafil: In 2007, McVary *et al*[10] first 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) and IIEF-EF domain

Table 1 Characteristics and qualities of the studies included in the analysis of tadalafil, sildenafil and vardenafil

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]	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: Post-void residual volume.

score (sildenafil *vs* placebo: 9.17 *vs* 1.86, $P < 0.0001$) compared to the placebo group after 12 wk of daily treatment (50 mg for 2 wk, then increased to 100 mg). No significant difference of Qmax was 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 these 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 in LUTS/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 and IPSS QoL score were observed in the vardenafil group compared to the placebo group ($P < 0.0001$, respectively) (Table 2). Although Qmax was enhanced in vardenafil group, there was no significant 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, reported in 32 (29.6%) patients in the vardenafil group and 18 (15.9%) in the placebo group. None of the serious AEs was linked to the vardenafil medication. Nevertheless, it is too soon to consider the underlying role for vardenafil in LUTS/BPH therapy because further data clearly needed to ascertain the benefit-risk details relative to the existing treatment options were not provided.

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

Brock *et al*[39] (2013), investigating the efficacy of once daily tadalafil in the treatment of LUTS/BPH patients with or without ED, first 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 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, $P < 0.01$) and 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, a small

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

Ref.	Drug	Remarks	Total IPSS		IPSS voiding subscore		IPSS storage subscore		IPSS QoL subscore		BII		Qmax		IIEF	
	mg		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		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	-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	
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]	50		-6.3	-1.9					-0.9	-0.3	-2	-0.9	0.31	0.16	9.17	1.86
	100															
	Vardenafil															
Stief *et al*[40]	10		-5.8	-3.6									1.6	1		

IIEF: International index of erectile function; IPSS: International prostate symptom; Qmax: Maximum urinary flow rate; QoL: Quality of life; BII: Benign prostatic hyperplasia impact index; ED: Erectile dysfunction; T: Treatment; P: Placebo.

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 an 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 with LUTS/BPH patients treated once daily with 20 mg tadalafil for 12 wk, Dmochowski *et al*[13] (2010) pointed out that tadalafil significantly improved 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, $P = 0.006$) compared to the placebo group. Qmax from baseline to endpoints showed a small alteration with no significant difference (tadalafil *vs* placebo: -2.1 *vs* 0.1, $P = 0.33$). In addition, several points should be noted when considering these trials. A relatively high tadalafil dose was used without assessing rigorous intent to treat patients. Thus, the magnitude of improvement investigated in these trials in future clinical utilization should be treated with caution.

Donatucci *et al*[14] completed a double blind, placebo controlled, open-label 12 wk trial of tadalafil (2.5 mg, 5 mg, 10 mg or 20 mg once daily) extended to 1 year. The changes from baseline to endpoint in the total IPSS, IPSS voiding subscore, IPSS storage subscore, IPSS health-related 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 the 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] conducted a multinational phase 3 (12 wk) randomized, double blind and control-placebo trial to assess the efficacy of tadalafil 2.5 or 5 mg in the management of LUTS/BPH with ED patients. In this study, both doses of tadalafil significantly improved the IIEF-EF (tadalafil *vs* placebo: 6.5, 5.2 *vs* 1.8, both $P < 0.001$). 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 a significant difference (Table 2).

Kim *et al*[16] reported a 12 wk randomized, double-blind, controlled-placebo trial of 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 significantly improved compared with placebo (tadalafil *vs* placebo: IPSS, -5.6 *vs* -3.6, $P > 0.05$ and Qmax, 2.5 *vs* 2.3, $P > 0.05$).

In 2007, McVary *et al*[18] conducted a trial of 281 men allocated randomly to 5 mg tadalafil once daily for 6 wk with a dose escalation to 20 mg for another 6 wk. There was a 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 when comparing tadalafil to placebo (tadalafil *vs* placebo: 0.5 *vs* 0.9, $P > 0.05$).

Oelke *et al*[19] investigated the efficacy of 5 mg tadalafil once daily monotherapy through 12 wk 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 wk duration to evaluate the efficacy of LUTS/BPH and did not address longer term efficacy of tadalafil on disease progression. Maybe this kind of trial would trigger great interest in the future.

In a phase 2 to 3, multinational, randomized, double-blind, controlled-placebo study, Porst *et al*[21] (2009) randomly assigned patients to tadalafil 2.5 mg, 5 mg, 10 mg and 20 mg once daily for 12 wk. The least square mean difference of IIEF-EF compared to placebo (the value: 2) was significant for all four doses 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 significant 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 a parallel group without LUTS/BPH as a control reference and it could not summarize the minimum 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 study, Porst *et al*[36] 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, uroflowmetry parameters did not show a significant difference at the endpoint. The IIEF-EF in ED men was significantly improved at 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 5 mg tadalafil once daily for LUTS/BPH for 12 wk. The pooled data confirmed that tadalafil resulted

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 χ^2	Heterogeneity I^2 (%)	Overall *Z* value	*P* value
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	0.001
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	0.001
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)	24.7	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; QoL: Quality of life; BII: Benign prostatic hyperplasia impact index; ED: Erectile dysfunction.

in improvement in total IPSS score from baseline to endpoint (tadalafil *vs* placebo: -7.9 *vs* -5.1, $P < 0.001$), as well as IPSS QoL index and BII (both $P < 0.01$).

Roehrborn *et al*[22] conducted a 12 wk randomized, double-blind, placebo-controlled, dose-finding study in 10 countries. They randomly assigned the patient to tadalafil 2.5 mg, 5 mg, 10 mg and 20 mg once daily for 12 wk. The least square mean difference of IIEF-EF compared to placebo (the value: 2.2) was 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 significant 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 reached a significant difference ($P < 0.01$, 0.001, 0.05 and 0.05, respectively). However, Qmax failed to reach significance for the medication groups.

In the second study by Roehrborn *et al*[12] (2013), with 5 mg tadalafil for the LUTS/BPH for 12 wk, the effects on the Qmax with LUTS/BPH were investigated. Qmax changes were assessed compared to baseline Qmax. For baseline Qmax < 10 mL/s, increases were higher in tadalafil compared with the 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 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. Except for 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 integrated analysis. Heterogeneity was not observed (I^2 < 30%) and the fixed effect model was used.

For 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, showed an improvement of total IPSS, BII and IIEF domain (P < 0.0001 or P < 0.00001, Table 3). Changes in the storage, voiding and QoL were also reported (P < 0.00001, Table 3). 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].

COMMENTS

Background

Lower urinary tract symptoms suggestive of benign prostate hyperplasia (LUTS/BPH) are increasingly frequent in aging men. The majority coexist with erectile dysfunction (ED). Irrespective of coexisting ED, LUTS/BPH patients frequently suffer from a poorer quality of life (QoL).

Research frontiers

Until recently, surgical therapy was the cornerstone of management for male LUTS. As early as 1990s, medical therapy became a possible treatment option for voiding problems. Since then, the surgical option has dropped gradually and currently the first option for treatment of male LUTS is medical therapy. 5-alpha reductase inhibitors and α-blockers have dominated the management of LUTS for many years. Nowadays, new drugs have cast a light on the treatment of LUTS, including PDE5-Is and anticholinergics. In the traditional sense, LUTS occurring with aging has frequently been associated with outlet obstruction in the bladder resulting from BPH, whereas the complaint may be explained by the detrusor overactivity. More recently, increasing evidence has shown that phosphodiesterase type 5 inhibitor (PDE5-Is) could exert improvement in LUTS in aging men who frequently suffer from BPH.

Innovations and breakthroughs

PDE5-Is, including mainly tadalafil, sildenafil and vardenafil, were the first line medication 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 effects and the enthusiasm for PDE5-Is has decreased due to the lack of objective improvement. Furthermore, urodynamic parameters did not change. More important, coherently explaining the disconnection between objective and subjective changes is still pending. Therefore, it is necessary to determine whether PDE5-Is are effective in the treatment of LUTS/BPH on the basis of a systematic review and meta-analysis of published evidence. Meta-analysis has been increasingly utilized since it was introduced to assess clinical data in the urological community by Peter Boyle. In particular, it could give rise to invaluable insights for benefits. To a large extent, even although a large database was available, some predictive characteristics for responders and non-responders could still not be identified. However, all the convincing studies showed that LUTS was 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 be a useful treatment for this condition as 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 that PDE5-Is are a promising therapy for LUTS/BPH from other researchers, a couple of questions are still worthy of considering, including patient selection, durability and health economics, in the case of PDE5-Is for treatment of LUTS. In an ideal world, some situations could inevitably be avoided between doctors and patients while using PED5-Is for patients with any given condition. Firstly, the best candidates should be screened with male LUTS patients alone receiving any given treatment. Secondly, 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 includes the doctor's choice as well as the patient's.

Applications

PDE5-Is significantly improved total international prostate symptom score (IPSS) score, IPSS voiding score, IPSS storage score, IPSS QoL score and international index of erectile dysfunction score (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 was also demonstrated to be effective for LUTS/BPH. Therefore, well designed clinical studies of large scales are required to ascertain the efficacy and specific mechanisms of action of PDE5-Is for the management of LUTS/BPH.

Abbreviations

PDE5-I: Phosphodiesterase type 5 inhibitor; LUTS/BPH: Lower urinary tract symptoms suggestive of 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 PDE5-Is in lower urinary tract symptoms and benign prostate hyperplasia.

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