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BPH-RELATED VOIDING DYSFUNCTION (Y KOJIMA, SECTION EDITOR)

PDE5-Is for the Treatment of Concomitant ED and LUTS/BPH

M. Gacci · A. Sebastianelli · M. Salvi · L. Vignozzi · G. Corona · K. T. McVary · S. A. Kaplan · M. Oelke · M. Maggi · M. Carini

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Abstract Epidemiologic data in adult men exhibit a strong relationship between erectile dysfunction (ED) and lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH), indicating that men affected by ED should also be investigated for LUTS/BPH and those presenting with storage or voiding LUTS should be investigated for co-morbid ED. Common pathophysiolgical mechanisms underlying both LUTS/BPH and ED, including alteration of NO/cGMP or RhoA/Rho-kinase signaling and/or vascular or neurogenic dysfunction, are potential targets for proposed phosphodiesterase type 5 inhibitors (PDE5-Is). Several randomized controlled trials and only a few reviews including all commercially available PDE5-Is demonstrated the safety and efficacy of these drugs in the improvement of erectile function and urinary symptoms, in patients affected either by ED, LUTS, or both conditions.

Keywords Benign prostatic hyperplasia · Lower urinary tract symptoms · Erectile dysfunction · Prostate · PDE5 · PDE5-I · IPSS · IIEF · ED · LUTS · BPH

Introduction

Erectile dysfunction (ED) and lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) are common conditions in middle-aged or older men. Several reports indicated that patients with ED have a higher prevalence of LUTS strictly related to the urinary symptoms severity [1••]. Although the underlying mechanisms for the relationship between ED and LUTS/BPH men are not fully understood, it has been hypothesized that impaired NO/cGMP signaling could be the relevant underlying determinant for the pathophysiology of both ED and LUTS/BPH, suggesting that

M. Gacci (✉) · A. Sebastianelli · M. Salvi · M. Carini
Department of Urology, University of Florence, Careggi Hospital, Viale Pieraccini 18,
50139 Florence, Italy
e-mail: maurogacci@yahoo.it

A. Sebastianelli
e-mail: arcangelo.sebastianelli@gmail.com

M. Salvi
e-mail: m.salvi85@alice.it

M. Carini
e-mail: m.carini@unifi.it

L. Vignozzi · M. Maggi
Sexual Medicine & Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy

L. Vignozzi
e-mail: l.vignozzi@dfc.unifi.it

M. Maggi
e-mail: m.maggi@dfc.unifi.it

G. Corona
Endocrinology Unit, Maggiore-Bellaria Hospital, Bologna, Italy
e-mail: jocorona@libero.it

K. T. McVary
Department of Urology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA
e-mail: k-mcvary@northwestern.edu

S. A. Kaplan
Department of Urology, Weill Cornell Medical College, Cornell University, New York, NY, USA
e-mail: kaplans@med.cornell.edu

M. Oelke
Department of Urology, Hannover Medical School, Hannover, Germany
e-mail: Oelke.Matthias@mh-hannover.de

phosphodiesterase type 5 (PDE5) inhibitors (Is) are beneficial for the treatment of both conditions [2, 3••, 4–6].

PDE5 gene and protein expression has been described across the whole human lower urogenital tract, with different patterns of appearance [5, 7•]. The mechanism of action of PDE5-Is on LUTS/BPH includes several potential sites of actions such as the prostate and/or bladder [8, 9]. The remarkable improvement of urodynamic parameters during treatment with PDE5-Is, both in men with spinal cord injury [10] or during continence recovery after radical prostatectomy for prostate cancer [11], underline the importance of the bladder as a target of PDE5-Is in LUTS. In addition, pelvic ischemia due to the pelvic artery insufficiency, caused by metabolic syndrome (MetS), can induce functional and morphological changes of the bladder and prostate, that can be restored by the use of PDE5-Is [12, 13].

At the present time, several clinical trials on the use of PDE5-Is - either alone or in combination with other drugs (such as α-blockers) in men with LUTS/BPH and comorbid ED - have been reported in literature [3••]. All commercially available PDE5-Is have been tested in men with LUTS/BPH, with or without ED, by analyzing both urinary and sexual symptoms.

The aim of the present review is to summarize the current literature concerning the use of PDE5-Is for the treatment of LUTS/BPH and concomitant ED by analyzing epidemiological data, common pathophysiological pathways and efficacy as well as safety outcomes of clinical trials on PDE5-Is for ED and LUTS/BPH.

Epidemiology Data Concerning Comorbidity of ED and LUTS/BPH

Several national or cross-national studies, based on an unselected population of LUTS/BPH or ED patients, demonstrated a tight correlation between LUTS/BPH and ED. We analyzed the results of the most important single center and cross sectional trials.

Single Center Trials

LUTS and ED are highly prevalent in men with BPH (see Table 1) [14–26]. Despite well-known risk factors of ED, such as age, diabetes, drugs, coronary artery disease or behavior, several studies have shown that the increasing prevalence of ED is related to the increasing severity of LUTS.

The Cologne Male Survey, a community-based study in 4477 men aged 30–80 years, demonstrated that the overall prevalence of LUTS was significantly higher in men with ED than in those without ED (72 % vs. 38 %) [15]. Similarly, in another study from UK enrolling 11,327 men, with median age of 60 years at the diagnosis of ED, with any recorded LUTS/ED, the odds ratios (OR) for ED in men with LUTS compared to those without LUTS were: storage LUTS 3.0, voiding LUTS 2.6 and both storage and voiding LUTS 4.0. Moreover, LUTS diagnosis preceded ED in 63.1 % of patients by a mean of 4.8 years [17].

More recently, several authors have looked for the correlation between LUTS and ED in a population screened for prostate cancer. In particular, in a Brazilian study on 1008 consecutive patients enrolled in a prostate cancer screening program, with a mean age of 61.2 years (range 45–87), only 5.4 % of the patients without ED had severe LUTS, compared to 27.1 % of patients with severe ED ($P<0.001$) [19].

Multicenter Trials

Several cross-sectional multicenter trials investigating the epidemiological association between LUTS and ED have been published in the last 10 years (see Table 1).

The National Health and Social Life Survey, a community-based involving 1410 men aged 18–59 years demographically representative of US adults, demonstrated that LUTS are significant risk factors for ED, with an OR of 3.13 [14].

Later on in 2003, three different cross-national studies were published. In a study carried out in Brazil, Italy, Japan and Malaysia on 2412 men aged 40–70 years, Nicolosi et al. [20] evaluated the prevalence of ED and associated factors among men without concomitant diseases. Among 1335 healthy men, the prevalence of ED was 16.1 %. In this population, age, cigarettes smoking and LUTS were all associated with an increased risk of ED. The UrEpik study group, including 4800 men aged 40–79 years, from Auxerre, Birmingham, Boxmeer and Seoul [21], demonstrated that both the presence of BPH and LUTS severity were associated with an increased risk of ED, similar to that observed in subjects with diabetes and hypertension. In addition, the results of the Multinational Survey of the Aging Male (MSAM-7), a survey in 12,815 men aged 50–80 years conducted in the United States and six European countries to investigate the relationship between LUTS and ED in older men, clearly demonstrated that erection problems significantly increased with both age and LUTS severity [22]. In this study, ED was reported by 30 %, 51 %, and 76 % of study participants aged 50–59 years, 60–69 years, and 70–80 years, respectively ($p<0.001$) and in 43 %, 66 %, and 83 % of men with mild, moderate, and severe LUTS, respectively ($p<0.001$).

The Tampere Aging Male Urological Study, a prospective population-based postal survey in Finland in 1683 men aged 50–70 years followed for 5 years, reported an association between the severity of ED at baseline and the incidence of LUTS or bother during follow-up [16]. In line with these data, the European Male Aging Study, a multicenter

Table 1 Association between lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) and erectile dysfunction (ED) in single- and multicenter trials

Authors/ Country	Name of study	Sample and assessment	Prevalence	
			LUTS	ED
Single center trials				
Laumann et al. [14] (USA)	National Health and Social Life Survey	1410 men (aged 18–59) Self-report of LUTS, 1 question on ED	-	10 %
Braun et al. [15] (Germany)	Cologne Male Survey	4477 men (aged 30–80) IPSS, 18 questions KEED	44 %	19 %
Shiri et al. [16] (Finland)	Tampere Aging Male Urological Study	1126 men (aged 50–70) DAN-PSS, 2 ED questions	-	70 %
Morant et al. [17] (UK)	Health Improvement Network database in 333 general practices in UK	11,327 men with LUTS and ED, aged >18 years questionnaire assessing voiding and storage LUTS	-	1.7 % in2000 4.9 % in2007
McVary et al. [18] (USA)	Retrospective US claims data analysis (1999–2004)	81,659 men with ED (mean age 57 years) IPSS	-	at baseline: 1.5 % after 2 years:7.6 %
Antunes et al. [19] (Brazil)	Prostate cancer screening program in San Paulo (Brazil)	1008 men screened for PCa (mean age 61 years) IPSS, IIEF	81.4 %	mild 52 %, moderate30% severe 17 %.
Multicenter trials				
Nicolosi et al. [20] (international)	ED Epidemiology Cross National Study (Brazil, Italy, Japan, Malaysia)	2412 men (aged 40–70) IPSS, 1 question on ED	-	16 % in healthy men (32 % in other men)
Boyle et al. [21] (international)	UrEpik Study Group. (UK, Netherlands, France, Korea)	4800 men (aged 40–79) IPSS, O'Leary's Sexual Function Inventory	-	21 %
Rosen et al. [22] (international)	Multinational survey of the aging male (MSAM-7) USA/Europe	12,815 men (aged 50–80) IPSS, DAN-PSSsex, IIEF	90 %	49 %
Holden et al. [23] (Australia)	Men in Australia Telephone Survey (MATeS)	5990 men (aged ≥40) IPSS, 1 question on ED	16 %	21 % ED/LUTS + prostate disease + androgen deficiency: 34 %
Wein et al. [24] (international)	Epidemiology of LUTS (EpiLUTS) study USA, UK, Sweden	11,834 men (mean age 56.1) SF-12, IPSS, IIEF, Male Sexual Health Questionnaire,	-	26 %
Frankel et al. [25] (international)	12 countries: Community population and Urology clinic	423 (aged 40) community 1271 (aged>55) with LUTS/BPH ICSmale and ICSsex questionnaires	-	In Clinic men: 60 %
Li et al. [26] (international)	Asian multinational registry (Hong Kong, Malaysia, Philippines, Singapore, Thai)	994 men (aged 40–88 years) with BPH IPSS, DAN-PSS, IIEF-5	90 %	82 %

DAN-PSS = Danish Prostate Symptom Score; IPSS = International Prostate Symptom Score; ED = erectile dysfunction; LUTS = lower urinary tract symptoms; BPH = benign prostatic hyperplasia; SF = sexual function; QoL = quality of life; ICS = International Continence Society; KEED = Cologne Erectile Inventory; IIEF = International Index of Erectile Function

population-based survey, performed on more than 3400 subjects across eight European centers, found that LUTS severity was significantly associated with ED and lower quality of life independent of other associated morbidities [27]. In 2008, McVary et al. published the retrospective US claims data analysis of 81,659 men with a mean age of 57 years. The authors analyzed men with a new diagnosis or medication for ED, and showed a baseline LUTS/BPH prevalence of 1.5 %, and demonstrated a total prevalence of 7.6 % after two years follow-up [18].

Evidence linking disorders of the prostate and bladder with LUTS and ED is irrefutable, but the contribution of metabolic, cardiovascular, and endocrine factors cannot be discounted. In 2010, the Men in Australia Telephone Survey (MATeS) study, including 5990 men aged ≥40 years, evaluated lifestyle and biomedical associations as possible causes of ED, prostate disease, LUTS and perceived symptoms of androgen deficiency in a representative population of middle-aged and older men. They demonstrated that diabetes mellitus and cardiovascular diseases were both

associated with ED, and hypertension was strongly associated with LUTS and perceived symptoms of androgen deficiency, while cigarettes smoking and depressive symptoms were the only variables independently associated with prostate diseases [23]. This was a first clue of the potential relationship between metabolic syndrome (including BMI and waist circumference), LUTS and ED.

Pathophysiology and Mechanisms of Action of PDE5-Is on both ED and LUTS

There is an increasing body of evidence that all theories currently proposed for a common causality for both ED and LUTS are interconnected and that treatment options may overlap allowing prevention and/or treatment of both conditions simultaneously. These pathophysiolgoical pathways, which are also possible targets for the treatment of both ED and LUTS/BPH with PDE5-Is, are: a) modification of the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway; b) improvement of the RhoA/Rho-kinase (ROCK) pathway; c) hyperactivity of autonomic nervous system; d) atherosclerosis of pelvic vessels (see Fig. 1).

The NO/cGMP pathway in the regulation of erection has been well clarified [28]; currently, there is a body of evidence for a role of NO in the regulation of smooth muscle tone of bladder, prostate and urethra [29]. In particular, calcium-dependent NOS, including endothelial (eNOS) and neuronal (nNOS) have been described in several lower urinary tract (LUT) tissues. The nNOS isoform was identified in nerve terminals of the prostate, specifically in the peripheral and

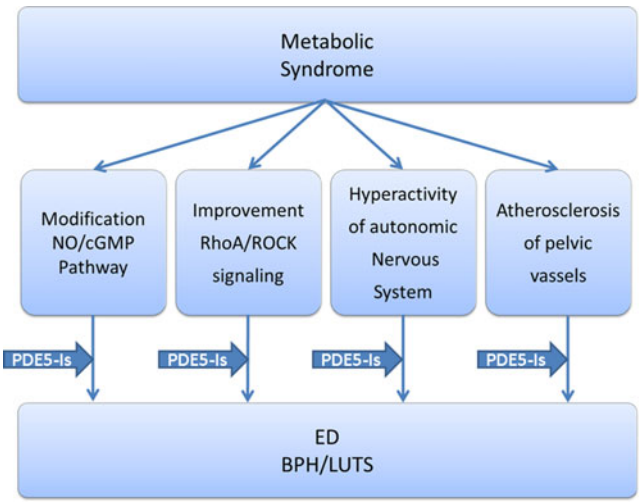

Fig. 1 Schematic presentation of common pathophysiological mechanisms linking erectile dysfunction (ED) to lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). All components are potential targets for phosphodiesterase type 5 inhibitors (PDE5-Is). *NO* nitric oxide; *cGMP* cyclic guanosine monophosphate; *ROCK* Rho-kinase; *BPH* benign prostatic hyperplasia; *LUTS* lower urinary tract symptoms; *ED* erectile dysfunction; *PDE5-Is* phosphodiesterase type 5 inhibitors

transitional zones [30]. NOS activity has also been described in the urothelium, smooth muscles, blood vessels, and nerves of the bladder [31]. A potential role for the NO pathway in LUTS/BPH is suggested by the proof of antiproliferative and pro-apoptotic effects of NO donors on culture of bladder, prostate and urethra smooth muscle cells [32].

An overactivity of the contractile RhoA/ROCK pathway has further been indicated as a common pathological mechanism underlying both ED and LUTS. Pathological conditions that alter relaxant/contractile mechanisms balance, such as those associated with reduced function of NO production and/or overactivity of RhoA/ROCK contractile signaling (i.e., aging, hypertension, smoking, diabetes and MetS), cause impaired smooth muscle relaxation in both penile and LUT tissue function, leading to ED and uncontrolled detrusor contractility [8, 33, 34]. Up-regulated RhoA/ROCK signaling has been demonstrated in corpora cavernosa [35] and bladder [36] of spontaneously hypertensive rats (SHR), a rat strain predisposed to erectile dysfunction, BPH and overactive bladder. Similarly, hyperactivation of RhoA/ROCK signaling has been demonstrated in penis and bladder tissue in an animal model of MetS [37, 38]. The inhibition of ROCK can limit bladder hyperactivity, reduce contractions in bladder strips from SHR and improves erection [35]. Interestingly, PDE5 inhibition with vardenafil reversed RhoA/ROCK hyperactivation in SHR; thus, preventing deterioration of urodynamic parameters [9]. Another important mechanism linking ED to LUTS is the autonomic hyperactivity with an increased sympathetic tone [39]. Various subtypes of α_1-adrenergic receptors have been identified in the bladder, prostate and penile tissue, mediating the tone of smooth muscle vasculature [40, 41]. In particular, α_{1A}- and α_{1D}- receptors have been recognized as the predominant α-adrenoceptor subtypes in the penis. α_{1A}-adrenoceptors identified in bladder neck and prostate are involved in voiding symptoms while α_{1D}-adrenoceptors, concentrated in hypertrophied detrusor muscle, are involved in storage symptoms [42]. Correlation between autonomic hyperactivity and LUTS/ED has been further suggested by preclinical studies using SHRs, which were shown to develop increased autonomic activity, BPH, LUTS, and ED [43, 44].

Atherosclerosis of the penis and lower urinary tract is indicated as a further potential mechanism which ties all the previously described pathways, since pelvic atherosclerosis reduces NO signaling, up-regulates RhoA-ROCK, and is a component of the metabolic syndrome/autonomic hyperactivity. Traditional risks factors for ED and atherosclerosis, such as diabetes mellitus and hypertension, can also affect LUTS/BPH [45, 46]. Several pre-clinical and clinical trials have demonstrated that bladder ischemia/hypoxia can be strongly associated with alteration of erectile and LUT tissues [47, 48]. A positive immunostaining for the hypoxia-inducible factor 1α (HIF-1α), a protein not present in normal cells but induced under hypoxic conditions, has been

identified in prostatic tissue from patients with BPH, while no HIF-1α immunostaining was detected in tissue from healthy controls [49]. Finasteride, a 5α-reductase inhibitor, reduces prostate size through reducing HIF-1α and other hypoxia-related growth factors, which can contribute to the growth of prostate [50]. In animal models of chronic ischemia of the lower urinary tract [12] and penis [51–54], administration of PDE5-Is restored normal oxygenation, thereby preventing tissue fibrosis and functional modifications.

In conclusion, PDE5-Is may exert beneficial effects on smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion at both the lower urinary tract and penile level, thus affecting major mechanisms contributing to ED and LUTS, including reduced NO/cGMP/PKG signaling, increased RhoA kinase pathway activity, autonomic overactivity, and tissue ischemia [55, 56, 57•, 58–64]. Together, these effects on the mechanisms overlapping ED and LUTS pathophysiology may explain the positive effects of PDE5 inhibition on both conditions reported to date.

Evidence Syntesis on PDE5-Is and LUTS/BPH

In 2002, Sairam et al. first suggested that PDE-Is can ameliorate LUTS in men attending the andrology outpatient clinic for ED [65]. In 2006, Mulhall confirmed this observation in a population of men with co-morbid ED and mild to moderate LUTS [66]. During the following years, in a study of men with LUTS/BPH with or without ED, McVary et al. conclusively established the emerging role of PDE5-Is as an effective and well tolerated treatment for LUTS [67]. After these studies, several clinical trials have investigated the use of PDE5-Is in LUTS/BPH men. Until November 2012, only three systematic reviews [3••, 68, 69] on the use of PDE5-Is alone or in combination with α-blockers in LUTS/BPH men have been published, of which only one [3••] included a meta-analysis.

Sildenafil

McVary et al. [70] evaluated for the very first time in literature the role of sildenafil for LUTS/BPH in a double-blind, placebo controlled study in men aged 45 years or older who scored ≤25 on the IIEF-erectile function domain and ≥12 on the IPSS questionnaire. The authors reported a significant improvement in IEEF with sildenafil compared to placebo (9.17 vs. 1.86, $p<0.0001$). Moreover, they described significant improvements of both IPSS and BPH Impact Index (BII) with sildenafil compared to placebo (IPSS −6.32 vs. –1.93, $p<0.0001$; BII −2.0 vs. –0.9, $p<0.0001$, respectively). No differences of maximum urinary flow rate (Q_{max}) were observed between the groups ($p=0.08$).

Kaplan et al. [71] evaluated 62 men aged 50–76 years with previously untreated ED and LUTS/BPH randomized to alfuzosin (n=20), sildenafil (n=21), or the combination of both (n=21) for 12 weeks. Sexual function (IIEF-score) was not statistically improved with alfuzosin alone (+16.7 %, $p=0.11$), whereas it was improved with either sildenafil alone (+49.7 %, $p=0.01$) and the combination of alfuzosin and sildenafil (+58.6 %, $p=0.002$). LUTS (IPSS) were significantly ameliorated with alfuzosin (−15.6 %, $p=0.01$) and sildenafil alone (−16.9 %, $p=0.03$) and even more with combination therapy (−24.1 %, $p=0.002$). There was a significant improvement in Q_{max} with alfuzosin alone (11.7 %, $p=0.03$) or in combination with sildenafil (21.1 %, $p=0.02$) but not with sildenafil monotherapy.

Tuncel et al. [72] screened 60 men with LUTS/BPH who were randomized to receive sildenafil only (n=20), tamsulosin only (n=20) or the combination of sildenafil and tamsulosin (n=20) for 8 weeks. Sildenafil monotherapy was compared with combination treatment regarding erectile function and, in particular, the improvements of questions 3 (frequency of sexual intercourse) and 4 (maintenance of erections) of the IIEF-questionnaire; improvements were 83.3 % vs. 75.0 % ($p=0.438$) and 73.3 % vs. 89.1 % ($p=0.083$), respectively. The improvements of IPSS after 8 weeks were 40.1 % for combination therapy vs. 36.2 % for tamsulosin monotherapy ($p=0.206$) and 28.1 % for sildenafil monotherapy ($p<0.001$). The mean improvement of Q_{max} for sildenafil or tamsulosin monotherapy was 26.9 % and 26.2 % ($p=0.870$), respectively while improvement for combination therapy was 42.0 % ($p<0.001$).

Sildenafil was well tolerated when used for LUTS/BPH, with an overall incidence of adverse events (AEs) of 31 % (50/160) of all patients treated with sildenafil in monotherapy vs. 7.7 % (12/155) of patients treated with placebo and in 15 % (3/19) of all patients treated with sildenafil alone vs. 11 % (2/18) of men treated with combination therapy [3••].

Tadalafil

Tadalafil has been more extensively and systematically investigated for the use in LUTS/BPH than any other PDE5-I. All tadalafil trials were randomized, double-blind, placebo-controlled trials in men with LUTS/BPH >6 months, aged ≥45 years, IPSS ≥13 at start of placebo lead-in period, and Q_{max} between 4 and 15 ml/s. All trial participants had a 4-week washout and a 4-week placebo lead-in phase. Trial duration was usually 12 weeks and only the open-label trial lasted 52 weeks. Common efficacy parameters in all trials were IPSS (including IPSS storage and voiding sub-scores), BII, and IIEF in sexually active men with ED, with special focus on the erectile function (EF) domain of the questionnaire. Safety parameters included treatment-emergent adverse events (TEAEs), post-void residual urine, and Q_{max}.

In 2007, McVary et al. [67] investigated 281 men randomly allocated to 5 mg tadalafil once daily for 6 weeks, followed by dose escalation to 20 mg once daily for another 6 weeks, or placebo for 12 weeks. The improvement of sexual function was significant for tadalafil vs. placebo (IIEF: +8.4 vs. +1.6, p<0.001). Moreover, LUTS improvement was greater with tadalafil vs. placebo at week 6 (mean improvement of IPSS: 49.3 % vs. 36.4 %, p=0.03) and week 12 (60.9 % vs. 42.7 %, p<0.01), while Q_{max} was not significantly changed in both treatment groups throughout the study.

Roehrborn et al. [73] evaluated 1058 men with LUTS/BPH with or without ED. Patients were randomly allocated to receive tadalafil 2.5 mg, 5 mg, 10 mg, 20 mg or placebo once daily for 12 weeks. IIEF-EF significantly improved after 12 weeks of treatment: +5.59 for tadalafil 2.5 mg, +6.97 for tadalafil 5 mg, +7.98 for tadalafil 10 mg, and +8.34 for tadalafil 20 mg; the differences compared to placebo (+2.2) were significant for all tadalafil doses (p<0.001). Regarding LUTS, mean changes of IPSS from baseline to study end were also significantly different for all tadalafil doses: -3.9 for tadalafil 2.5 mg (p=0.015), -4.9 for tadalafil 5 mg (p<0.001), -5.2 for tadalafil 10 mg (p<0.001), and −5.2 for tadalafil 20 mg (p<0.001) as compared to placebo (−2.3) while Q_{max}, although increased with increasing tadalafil dose, was insignificant for all treatment groups.

Porst et al. [74] investigated 581 LUTS/BPH men with ED treated with placebo or tadalafil 2.5 mg, 5 mg, 10 mg, or 20 mg once daily for 12 weeks. The overall improvement of sexual function with tadalafil was significant for all tadalafil treated patients. With once-daily tadalafil, normal erectile function (IIEF-EF domain score >26) was attained at end point in 21.2 % (24/113 men) with 2.5 mg, 34.2 % (40/117 men) with 5 mg, 42.5 % (51/120 men) with 10 mg and 40.0 % (46/115 men) with 20 mg of tadalafil vs. 14 % with placebo. Moreover, tadalafil significantly ameliorated LUTS/BPH compared to placebo treated men: mean changes in IPSS were −2.1 with placebo, -3.6 with tadalafil 2.5 mg (p=0.043), -4.2 with tadalafil 5 mg (p=0.004), -4.7 with tadalafil 10 mg (p<0.001), and −4.7 with tadalafil 20 mg (p<0.001). In contrast, Q_{max} was not significantly different for any tadalafil group vs. placebo.

In a second study of Porst et al. [75], the authors randomized 325 men who were treated with either tadalafil 5 mg (n=161) or placebo (n=164). IIEF-EF score in sexually active men with ED improved after 12 weeks of tadalafil vs. placebo (6.7 vs. 2.0; p<0.001). Tadalafil also significantly improved IPSS from baseline to endpoint as compared to placebo (−5.6 vs. -3.6; p=0.004), while uroflowmetry parameters did not significantly change at study end.

Recently, Oelke et al. [76] designed a randomized, double-blind, placebo-controlled, parallel-group study in men with LUTS/BPH. In total, 511 patients were randomized to placebo (n=172), tadalafil 5 mg (n=171), or tamsulosin 0.4 mg (n=168) once daily and were treated for 12 weeks. However, the study was not powered to directly compare both active compounds. Compared to placebo, sexual function significantly improved with tadalafil but not with tamsulosin in sexually active men with ED (IIEF-EF score +4.0, p<0.001 and −0.4, p=0.699, respectively). Moreover, LUTS/BPH significantly decreased with tadalafil and tamsulosin as compared to placebo as early as one week after start of treatment. Significant LUTS/BPH improvement was documented throughout the study period; at study end, IPSS decreased by −2.1 with tadalafil 5 mg (p=0.001) and −1.5 with tamsulosin 0.4 mg (p=0.023) relative to placebo. Finally, Oelke et al. first reported about a significant increase of Q_{max} with both tadalafil and tamsulosin, as compared to placebo: Q_{max} +2.4 ml/s for tadalafil (p=0.009) and +2.2 ml/s for tamsulosin (p=0.014). This data was corroborated by similar improvements of average urinary flow rate with both tadalafil (+1.6 ml/s, p=0.002) and tamsulosin (+1.3 ml/s, p=0.023).

Donatucci et al. conducted a 1-year, open-label extension study reporting the long-term safety and maintenance of efficacy for the once daily use of tadalafil 5 mg in men with LUTS/BPH. The study population consisted of 427 men who completed the 12-week, double-blind, placebo-controlled period [73]. In total, 299 patients (69.9 %) completed the 1-year, open-label extension period. TEAEs were reported by 57.6 % of patients, with most TEAEs being mild (44 %) or moderate (45 %) in severity; the most common TEAEs (≥2 %) were dyspepsia, gastro-oesophageal reflux disease, back pain, headache, sinusitis, hypertension and cough. Twenty-two patients (5.2 %) discontinued the study as a result of TEAEs. Changes in IPSS, IPSS irritative and obstructive sub-scores, IPSS health-related quality of life, BII, and IIEF–EF domain in sexually-active patients with ED were maintained after one year [77].

Regarding combination therapy of tadalafil and α-blockers, two trials were analyzed. Bechara et al. [78] randomized 30 men aged >50 years with LUTS/BPH into two groups to receive once daily tamsulosin vs. tamsulosin plus tadalafil 20 mg for 45 days and then switched to the other treatment mode for another 45 days. IIEF-EF significantly improved with tamsulosin plus tadalafil (p<0.001) but not with tamsulosin alone. Improvements of IPSS were statistically significant with both treatments but greater with combination therapy. Both regimens similarly improved Q_{max} (p<0.001) with no significant differences between tamsulosin monotherapy vs. combination treatment (p>0.05). In the other study, Liguori et al. [79] randomized 66 men with LUTS/BPH and co-morbid ED and allocated these patients into three treatment arms: alfuzosin 10 mg once daily (22 men),

tadalafil 20 mg every second day (21 men), or a combination of both drugs (23 men). ED, as measured by the IIEF-EF domain score, improved with alfuzosin alone (+15 %) but much more with tadalafil alone (+36.3 %) or combination therapy (+37.6 %). LUTS/BPH, as measured by IPSS, significantly improved with alfuzosin (27.2 %) and combination therapy (41.6 %), but not with tadalafil alone (8.4 %). Increase in Q_{max} was more pronounced with combination therapy (29.6 %) than with alfuzosin (21.7 %) or tadalafil monotherapy (9.5 %).

Overall [3••], TEAEs in men treated with tadalafil vs. placebo were documented in 12.6 % (171/1360) vs. 5.3 % (30/568) of patients while TEAEs in patients treated with tadalafil vs. tadalafil plus α-blockers were 7.7 % (1/13) vs. 7.2 % (1/14).

Vardenafil

Stief et al. [80] published the first randomized, double-blind, placebo-controlled study with vardenafil. In this 8-week multicenter trial, the authors included 221 men who were equally distributed to vardenafil 10 mg (n=108) or placebo (n=113) twice daily. Sexual function was significantly improved by vardenafil as compared to placebo (IIEF-EF +7.5 vs. +1.5; p=0.0001). At the same time, there was a significant improvement of LUTS/BPH with vardenafil vs. placebo (IPSS −5.9 vs. -3.6; p=0.0013). Although Q_{max} was more improved with vardenafil, the difference compared to placebo was not statistically significant (+1.6 ml/s vs. +1.0 ml/s; p=0.5614).

Table 2 Characteristics of the studies included in the present analysis. Weighted differences (with 95 % confidence interval [CI]) of International Prostate Symptom Score (IPSS), and International Index of Erectile Function (IIEF) score for the studies on phosphodiesterase type 5 inhibitors (PDE5-Is) versus placebo; PDE5-Is plus α-blocker versus α-blocker alone (*)

Study characteristics		Baseline data			IIEF-EF Mean relative differences			IPSS Mean relative differences		
Reference	Jadad Score	Age [years]	IIEF-EF	IPSS	Diff in means	LL, 95%CI	UL, 95%CI	Diff in means	LL, 95%CI	UL, 95%CI
Sildenafil										
McVary KT, J Urol. 2007 [67]	**4**	60	14.6	-	7.6	6.2	9.0	−3.9	−5.4	−2.4
*Kaplan SA, Eur Urol 2007 [71]	**3**	63.4	14.3	15.9	5.4	2.3	8.5	−1.1	−3.5	1.3
*Tuncel A, Word J Urol 2010 [72]	**2**	58.8	-	15.4	-	-	-	0	−1.8	1.8
Tadalafil										
McVary KT, J Urol 2007 [67]	**3**	61.5	14	17.9	6.8	4.3	9.3	−2.5	−3.9	−1.1
Roehrborn CG, J Urol 2008 [73]	**3**	62.0	-	17	7.9	-		−2.2 (20 mg)	−4.6	0.2
Porst H, Eur Urol 2009 [74]	**3**	61.9	16 (20 mg arm)	16.1	5.2 (20 mg)	2.9	7.5	−4.7	-	-
Porst H, Eur Urol 2011 [75]	**3**	64.8	-	16.8	4.7	2.5	6.9	−1.4	−3.9	1.1
*Bechara A, J Sex Med 2008 [78]	**3**	63.7	15	19.4	6.3	0.9	11.7	−2.5	−5.7	0.7
*Liguori G, J Sex Med 2009 [79]	**3**	6.,3	14.4	15	3.9	1.1	6.6	−1.5	−3.7	0.7
Oelke M, Eur Urol 2012 [76]	**3**	63.6	-	17.3	4.0	-	-	−2.1	-	-
DonatucciF, BJU Int. 2011 [77]	**3**	60.7	-	-	5.9 Week 0 to endpoint	-	-	−5.0 Week 0 to endpoint	-	-
Vardenafil										
Stief CG, Eur Urol 2008 [80]	**3**	55.9	-	15.9	6.0	3.5	8.5	−2.2	−5.2	0.8
*Gacci M, J Sex Med 2012 [81]	**3**	68.0	16.3	19.6	3.5	2.9	4.0	−3.8	−4.3	−3.3

The Jadad score assesses the quality of published clinical trials based methods relevant to random assignment, double blinding, and the flow of patients. There are seven items in total; the last two attract a negative score, which means that the range of possible scores is 0 (bad) to 5 (good). LL = lower limit; UL = upper limit

Gacci et al. [81] compared the safety and efficacy of once-daily tamsulosin plus placebo vs. tamsulosin plus vardenafil 10 mg in 60 patients with LUTS/BPH in a randomized, double blind trial with a 12-week follow-up. Erectile function and LUTS were significantly improved with combination therapy as compared to tamsulosin alone (IIEF-EF combination +2.61 vs. tamsulosin alone +0.06, p=0.030; IPSS combination −3.11 vs. -1.67, p=0.039). Furthermore, vardenafil plus tamsulosin achieved an additional improvement of Q_{max} compared to tamsulosin alone (+2.56 vs. + 0.07, p=0.034) Table 2.

Regarding the tolerability of vardenafil, the authors of a systematic review found TEAEs in 38 % (40/105 men) vs. 3.6 % (4/110 men) in participants treated with vardenafil or placebo while there were TEAEs in 10 % (3/30 men) with vardenafil monotherapy compared to 6.9 % (2/29 men) with vardenafil and α-blocker combination therapy [3••].

Conclusions

Epidemiological data underlines the strong association between ED and LUTS, either in the general population or in urological patients. Moreover, ED and LUTS share several common pathways which can be a potential target for PDE5-Is, including NO/cGMP and RhoA/Rho-kinase pathways such as pelvic atherosclerosis and autonomic hyperactivity.

PDE5-Is are well tolerated and effective for the treatment of both ED and LUTS/BPH. Flushing, gastro-esophageal reflux, headache and dyspepsia are the most frequently reported adverse events. PDE5-Is significantly improve erectile function, as measured with the IIEF-questionnaire, and LUTS/BPH, as measured with the IPSS questionnaire, with an overall improvement of quality of life.

PDE5-Is can be considered as the first choice of treatment in men with both ED and LUTS/BPH but treatment of either ED or LUTS/BPH with PDE5-Is is also feasible. Nevertheless, further studies are needed to evaluate the long-term safety, efficacy, influence on disease progression, and cost-effectiveness of PDE5-Is.

Conflict of Interest Mauro Gacci declares that he has no conflict of interest.

Arcangelo Sebastianelli declares that he has no conflict of interest.

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Marci Carini declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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3. •• Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol. 2012;61:994–1003. *A systematic review and meta-analysis of available prospective and cross-sectional studies on the use of PDE5-Is for BPH related LUTS.*
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