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Review – Benign Prostatic Hyperplasia

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

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Abstract

Context: Several randomized controlled trials (RCTs) on phosphodiesterase type 5 inhibitors (PDE5-Is) have showed significant improvements in both lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) in men affected by one or both conditions, without a significant increase in adverse events. However, the results are inconsistent.
Objective: Perform a systematic review and meta-analysis of available prospective and cross-sectional studies on the use of PDE5-Is alone or in combination with α1-adrenergic blockers in patients with LUTS/benign prostatic hyperplasia (BPH).
Evidence acquisition: A systematic search was performed using the Medline, Embase, and Cochrane Library databases through September 2011 including the combination of the following terms: *LUTS, BPH, PDE5-Is, sildenafil, tadalafil, vardenafil, udenafil, α-blockers*, and *α1-adrenergic blocker*. The meta-analysis was conducted according to the guidelines for observational studies in epidemiology.
Evidence synthesis: Of 107 retrieved articles, 12 were included in the present meta-analysis: 7 on PDE5-Is versus placebo, with 3214 men, and 5 on the combination of PDE5-Is with α1-adrenergic blockers versus α1-adrenergic blockers alone, with 216 men. Median follow-up of all RCTs was 12 wk.

Combining the results of those trials, the use of PDE5-Is alone was associated with a significant improvement of the International Index of Erectile Function (IIEF) score (+5.5; $p < 0.0001$) and International Prostate Symptom Score (IPSS) (−2.8; $p < 0.0001$) but not the maximum flow rate (Q_{max}) (−0.00; p = not significant) at the end of the study as compared with placebo. The association of PDE5-Is and α1-adrenergic blockers improved the IIEF score (+3.6; $p < 0.0001$), IPSS score (−1.8; $p = 0.05$), and Q_{max} (+1.5; $p < 0.0001$) at the end of the study as compared with α-blockers alone.
Conclusions: The meta-analysis of the available cross-sectional data suggests that PDE5-Is can significantly improve LUTS and erectile function in men with BPH. PDE5-Is seem to be a promising treatment option for patients with LUTS secondary to BPH with or without ED.

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1. Introduction

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are common conditions in middle-age or older men. LUTS range from mild to severe, depending on their occurrence, and include frequency, urgency, nocturia, incomplete emptying, and weak stream that can strongly worsen the quality of life (QoL). For several years, surgery has represented the gold standard of care for this condition, allowing the relief of urinary symptoms and the consequent improvement in QoL [1].

However, since the 1990s, there has been a substantial shift in BPH management from surgical to medical therapy. The current standard of care for LUTS/BPH includes α-adrenergic blockers, 5α-reductase inhibitors, and phytotherapies, used alone or in combination. These therapies are associated with bothering sexual side effects, however, differing in rate and characteristics between different classes of medications, different medications within the same classes, and different combinations of drugs.

Sexual dysfunction is a highly prevalent comorbidity in aging men with LUTS associated with BPH [2]. Although the underlying mechanisms for the relationship between LUTS and erectile dysfunction (ED) in BPH men are not fully elucidated, common links such as the nitric oxide–cyclic guanosine monophosphate (NO/cGMP) pathway, RhoA/Rho-kinase signaling, pelvic atherosclerosis, and autonomic adrenergic hyperactivity can be potential targets for phosphodiesterase type 5 inhibitors (PDE5-Is) [3].

The pathophysiology of male LUTS is highly complex, multifactorial, and far from being completely understood [3] including an impaired NO/cGMP signaling, an increased RhoA/Rho-kinase pathway activation, pelvic ischemia, autonomic overactivity, and increased bladder/prostate afferent activity. As reported in a recent review [3], all these major mechanisms of BPH LUTS could be counteracted by PDE5Is. The mechanism of action of PDE5-Is on LUTS includes several potential targets such as prostate, urethra, bladder, and LUTS vasculature [4–7]. A recent comparative study evaluating PDE5 tissue distribution and activity in the human prostatic urethra, prostate, and bladder from the same patient indicate that in human LUTS, PDE5 is mostly expressed and biologically active in the muscular compartment with the following rank order of activity: bladder neck more than prostatic urethra more than prostate [8]. This selective distribution and activity of PDE5 in LUTS [8], along with inhibition of the RhoA/Rho-kinase contractile mechanism induced by PDE5-I in the bladder [7], could be the mechanistic rationale for the use of PDE5-I treatment to ameliorate the dynamic component (bladder dysfunction and urethral contractions) of male LUTS. The importance of the bladder as a target of PDE5-Is in LUTS is further underlined by the significant improvement of urodynamic parameters in spinal cord injury patients after PDE5-Is administration [1] and the efficacy of PDE5-Is on continence recovery after radical prostatectomy for prostate cancer [9] and therefore in men without the prostate gland. PDE5 is also highly expressed in the LUTS vasculature [10]. Chronic ischemia due to pelvic artery insufficiency, caused by the metabolic syndrome (MetS) or hypertension, can induce functional and morphologic changes in the bladder and prostate that can be restored by the use of PDE5-Is [10,11]. In addition, a modulation of autonomic nervous system overactivity and bladder/prostate afferent nerve activity by PDE5-Is has also been suggested [12–14].

Finally, although the exact mechanism of action remains to be clarified, inhibition of PDE5 has been demonstrated to have an effect on several pathogenetic pathways contributing to LUTS.

In 2002, Sairam et al. suggested for the first time that PDE-Is could improve urinary symptom scores in men attending an andrology outpatient clinic for ED [14]. In 2006, Mulhall and colleagues confirmed this evidence in a population of men with comorbid ED and mild to moderate LUTS [15]. The following year, with a randomized double-blind placebo-controlled study on BPH men (with or without ED), McVary et al. conclusively established the emerging role of PDE5-Is as an effective and well-tolerated treatment for LUTS [16]. After this research, several clinical trials investigated the use of PDE5-Is in LUTS/BPH men. At the present time, only 17 reviews on the use of PDE5-IS in LUTS/BPH men are available on PubMed (September 2011), with only 2 systematic reviews published in 2011, without meta-analysis, including data from 5 and 4 randomized controlled trials (RCTs), respectively [17,18].

The aim of the present systematic review is to summarize and meta-analyze the current literature concerning the use of PDE5-Is in LUTS due to BPH, to determine the relative efficacy and safety of PDE5-Is alone or in combination with α-blockers, and to define the best candidates for this treatment based on clinical features and LUTS severity.

2. Evidence acquisition

2.1. Systematic search strategy

An extensive PubMed, Embase, and Cochrane Library search was performed including the following terms: *phosphodiesterase type 5, phosphodiesterase type 5 inhibitors, PDE5, PDE5-I, sildenafil, tadalafil, vardenafil, udenafil, lower urinary tract symptoms, LUTS, benign prostatic hyperplasia, and BPH*. Reference lists of relevant articles were hand-searched to identify additional articles, and the "related articles" function in PubMed was used. No "language," "publication year," or other limits were used.

Completed but still unpublished trials were obtained through a formal request to the authors. If more than one paper of one RCT was found, only data from the most complete manuscript were assessed. The last search was in September 2011.

The identification of relevant abstracts, the selection of studies based on the criteria just described, and the subsequent data extraction were performed independently by two of the authors and conflicts resolved by a third investigator.

The quality of included RCTs was assessed using the current available consolidated standards of reporting

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trials [19] and some selected parameters (randomization, blinding, and withdrawn/dropout description) among those proposed by Jadad et al. [20].

2.2. Study selection

Trials included in this review were selected using the following inclusion criteria: (1) They were RCTs, (2) the subject of the study was PDE5-Is for LUTS/BPH, (3) control groups received placebo for PDE5-Is alone or α-blockers for combined PDE5-Is plus α-blockers, (4) the primary outcomes are International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF), and maximum flow rate (Q_{max}) at uroflowmetry.

Heterogeneity was assessed using the I^2 test for IPSS in studies comparing PDE5-I versus placebo. Considering that heterogeneity could not be excluded (I^2 = 46.4%), standardized mean differences in IPSS between subjects treated with placebo or PDE5-I were calculated using a random effect model. In studies comparing α-blocker alone versus the combination with PDE5-Is, the lack of homogeneity (I^2 = 92.89%) suggested the use of a random effect model to calculate the standardized difference in IPSS and other parameters.

Adverse events (AEs) were recorded from all the RCTs. AEs reported at least in two papers comparing the effect of PDE5i alone versus placebo were included in a meta-analysis.

All analyses were performed using Comprehensive Meta-Analysis v.2, Biostat (Englewood, NJ, USA) and SPSS 17.0. All tests were two sided. The p values <0.05 were considered statistically significant. All of the statistical analysis was monitored by a professional statistician.

3. Evidence synthesis

3.1. Study characteristics

Of 508 retrieved studies, 497 articles were excluded for different reasons; one unpublished trial was added. Figure 1 summarizes the total flowchart, and Table 1 lists the characteristics of the trials included in the meta-analysis. Among the 12 published studies included, 7 compared the effect of PDE5-Is versus placebo [16,21–26], and 5 evaluated the effect of α-blockers versus the combination of PDE5-Is and α-blockers [27–31] (see also Fig. 1 and Table 1).

More than 6000 men were screened for the 12 studies included in our meta-analysis (Fig. 1). RCTs comparing PDE5-Is versus placebo randomized 3214 patients (with 2749 patients completing the studies), and RCTs comparing PDE5-I plus α-blocker versus α-blocker alone randomized 278 patients (with 260 patients completing the studies, including 58 patients treated with PDE5-Is alone). Different PDE5-Is and different doses were administered (Table 1). The Begg adjusted rank correlation test, calculated on the basis of IPSS score at the end of the study, suggested no major publication bias (Kendall τ = 0.21; p = 0.34).

3.2. Results

3.2.1. Efficacy

Studies comparing the effect of PDE5-I alone versus placebo included 2250 patients (1879 completing the study) and 964 (870 completing the study), respectively. Combining the results of those trials, PDE5-Is significantly ameliorate

Table 1 – Characteristics of the studies included in the meta-analysis

Study	Baseline characteristics			Treatment				Population characteristic			
	Age, yr	Body mass index	IPSS	Drug	Dosage, mg	Pills per week	Run-in, wk	No. of patients active, completed	No. of patients control, completed	Study duration, wk	Jadad score
PDE5-Is alone											
McVary et al. [21]	60	–	–	Sildenafil	50 (2 wk); 100	7	4	168	155	12	4
McVary et al. [16]	61.5	–	17.9	Tadalafil	20 (2 wk); 100	7	4	125	126	12	3
Stief et al. [22]	55.9	27.3	16.8	Vardenafil	10	14	4	105	110	8	3
Roehrborn et al. [23]	62.0	28.5	17.2	Tadalafil	2.5; 5; 10; 20	7	4	701	185	12	3
Porst et al. [24]	61.9	28.3	16.1	Tadalafil	2.5; 5; 10; 20	7	4	386	105	12	3
Tamimi et al. [25]	60.9	26.9	19.0	UK-369003	10;25; 50; 100	7	2	246	37	12	3
Porst et al. [26]	64.8	27.8	16.8	Tadalafil	5	7	4	148	152	12	4
PDE5-Is plus α-blockers											
Kaplan et al. [27]	63.4	25.4	17.3	Sildenafil plus alfuzosin	25	7	–	19*	18†	12	3
Bechara et al. [28]	63.7	–	19.4	Tadalafil plus tamsulosin	20	7	2	13*	14†	12	3
Liguori et al. [29]	61.3	–	15	Tadalafil plus alfuzosin	20	7	–	21*	18†	12	3
Tuncel et al. [30]	58.8	–	15.4	Sildenafil plus tamsulosin	25	4	–	20*	20†	8	2
Gacci et al. [31]	68.0	25.7	19.6	Vardenafil plus tamsulosin	10	7	2	30*	29†	12	3

PDE5-Is = phosphodiesterase type 5 inhibitors.
* With α-blockers.
† α-Blockers alone.

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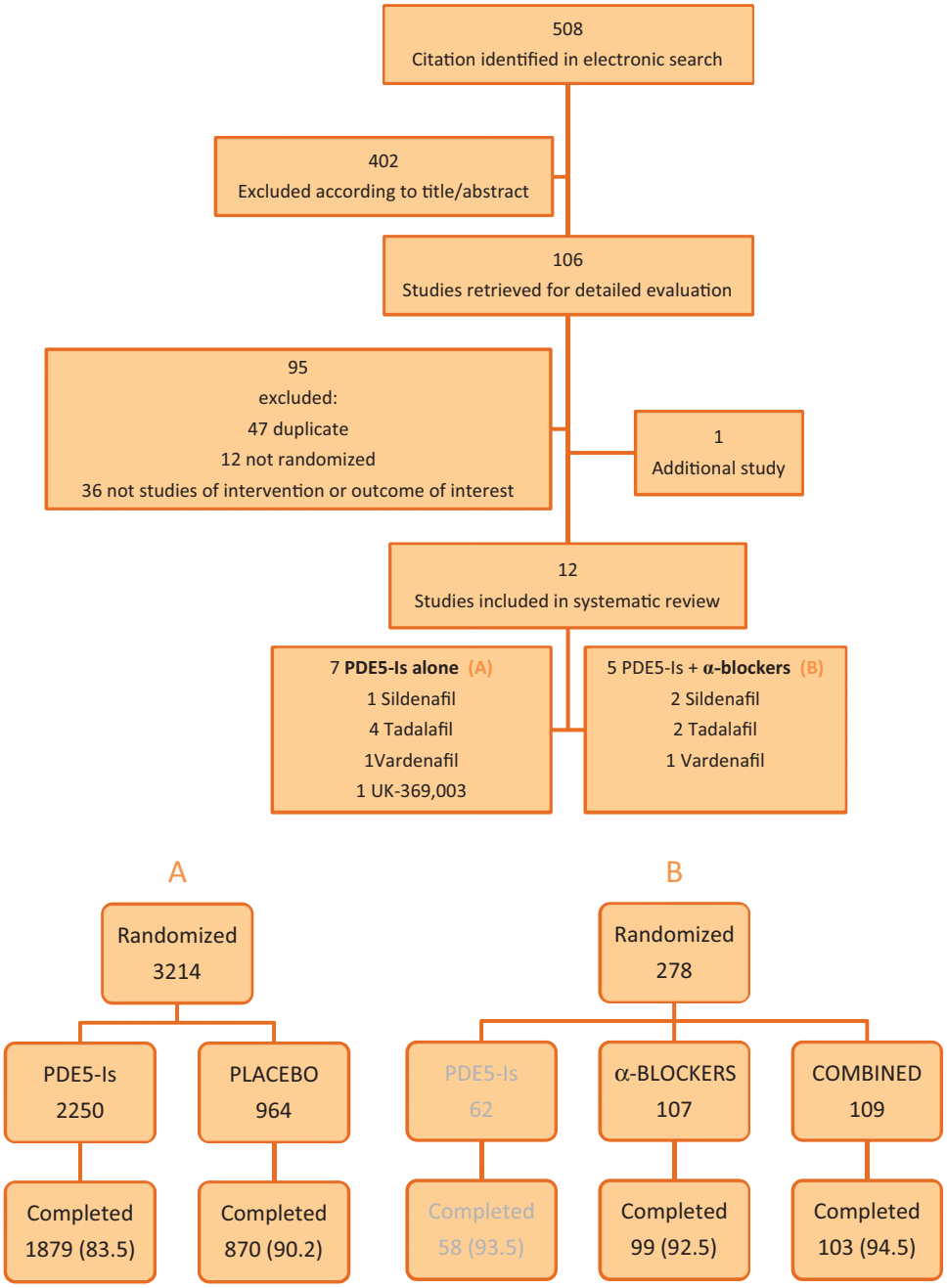

Fig. 1 – Upper section: flowchart of literature searches and results. Lower section: number of patients randomized and completing the protocol in studies on phosphodiesterase type 5 inhibitors (PDE5-Is) versus (A) placebo and (B) PDE5-Is plus α-blocker versus α-blocker alone.

IPSS (−2.8 [−3.6 to −2.1]; $p < 0.0001$) and IIEF score (+5.5 [+4.1 to +6.9]; $p < 0.0001$) but not Q_{max} (−0.0 ml/s [−0.6 to 0.6]; p = not significant) when compared with placebo (Fig. 2, panel A–C). Meta-regression analysis showed that differences in IPSS score were significantly lower in older and obese patients (Fig. 3, panel A and B). Not unexpected, the effect of PDE-5 Is on IPSS significantly increased as a function of higher IPSS at baseline, which likely reflects the well known relationship between higher baseline scores and greater numerical improvements, but similar percentage score improvements (Fig. 3, panel C). No further meta-regression analyses on other outcomes were performed due to insufficient available data.

Studies comparing the effect of α-blockers alone versus the combination of α-blockers and PDE5-I included 107 patients (99 completing the study) and 109 (103 completing the study), respectively. The combination of the two medications significantly improved IPSS (−1.8 [−3.7 to 0.0]; $p = 0.05$) and IIEF score (+3.6 [+3.1 to +4.1]; $p < 0.0001$) as well as Q_{max} (+1.5 ml/s [+0.9 to +2.2]; $p < 0.0001$) when compared with the use of α-blockers alone (Fig. 2, panel D–F).

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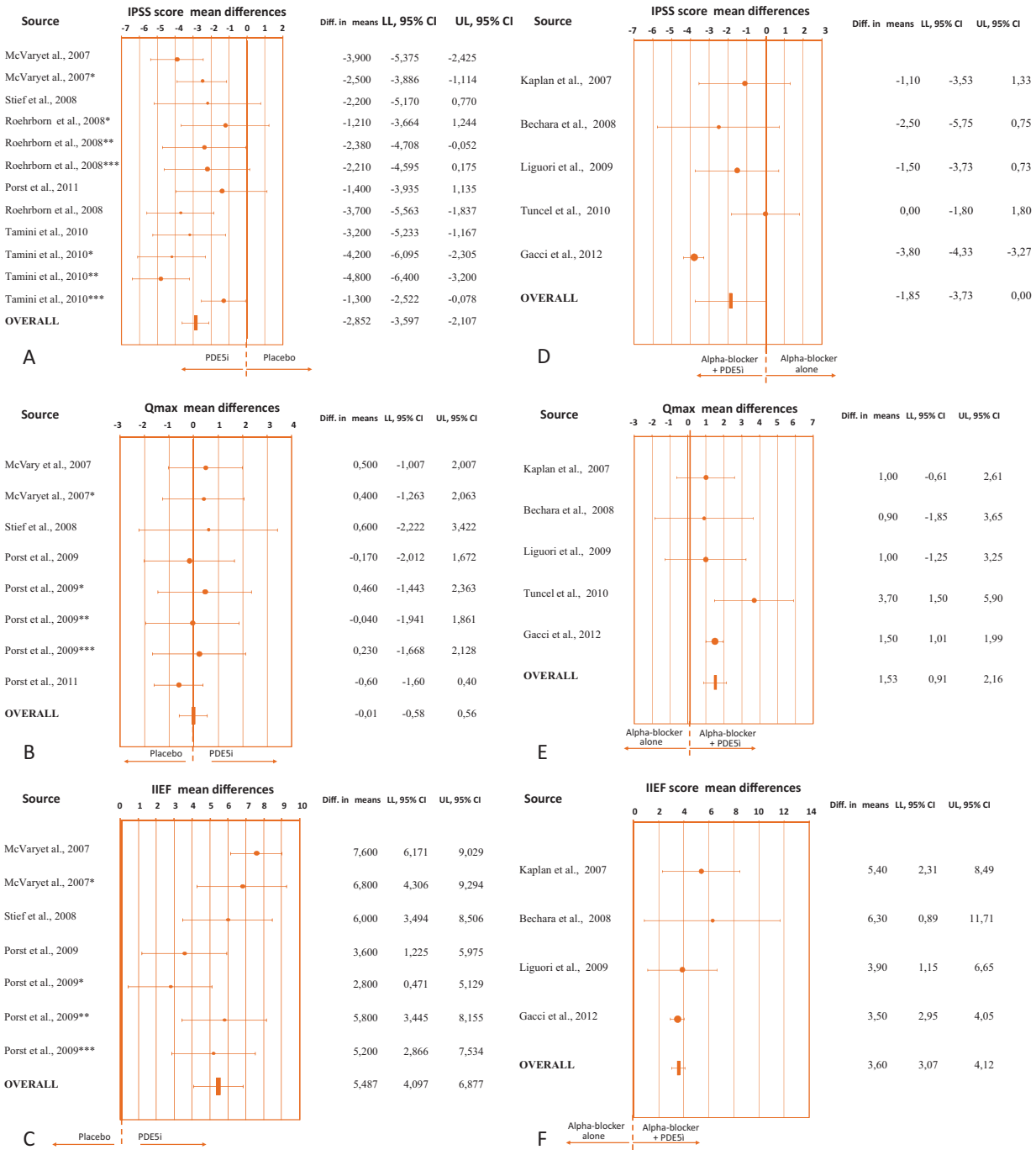

Fig. 2 – Weighted differences (with 95% confidence interval [CI]) of International Prostate Symptom Score (IPSS), maximum flow rate (Q_{max}), and International Index of Erectile Function (IIEF) score for the studies on phosphodiesterase type 5 inhibitors (PDE5-Is) versus placebo (A, B, and C, respectively) and PDE5-Is plus α-blocker versus α-blocker alone (D, E, and F, respectively).
LL = lower limit; UL = upper limit.

3.2.2. *Safety*

Table 2 lists all the AEs reported in papers selected for the review. In studies comparing the effect of PDE5-Is versus placebo, 301 of 1879 AEs (16.0%) were reported in men treated with PDE5-Is versus 52 of 870 AEs (6.0%) in men treated with placebo. In studies comparing the effect of combination therapy of PDE5-Is plus α-blocker versus α-blocker alone, 7 of 103 AEs (6.8%) were reported in men treated with combined therapy and 5 of 99 AEs (5.1%) in men treated with α-blocker alone. The meta-analysis of AEs demonstrated that flushing, gastroesophageal reflux, headache, and dyspepsia have a higher risk of occurrence after PDE5-I administration (see Table 3).

3.3. *Discussion*

This is the first systematic review and meta-analysis regarding the efficacy and safety of PDE5 inhibitors alone

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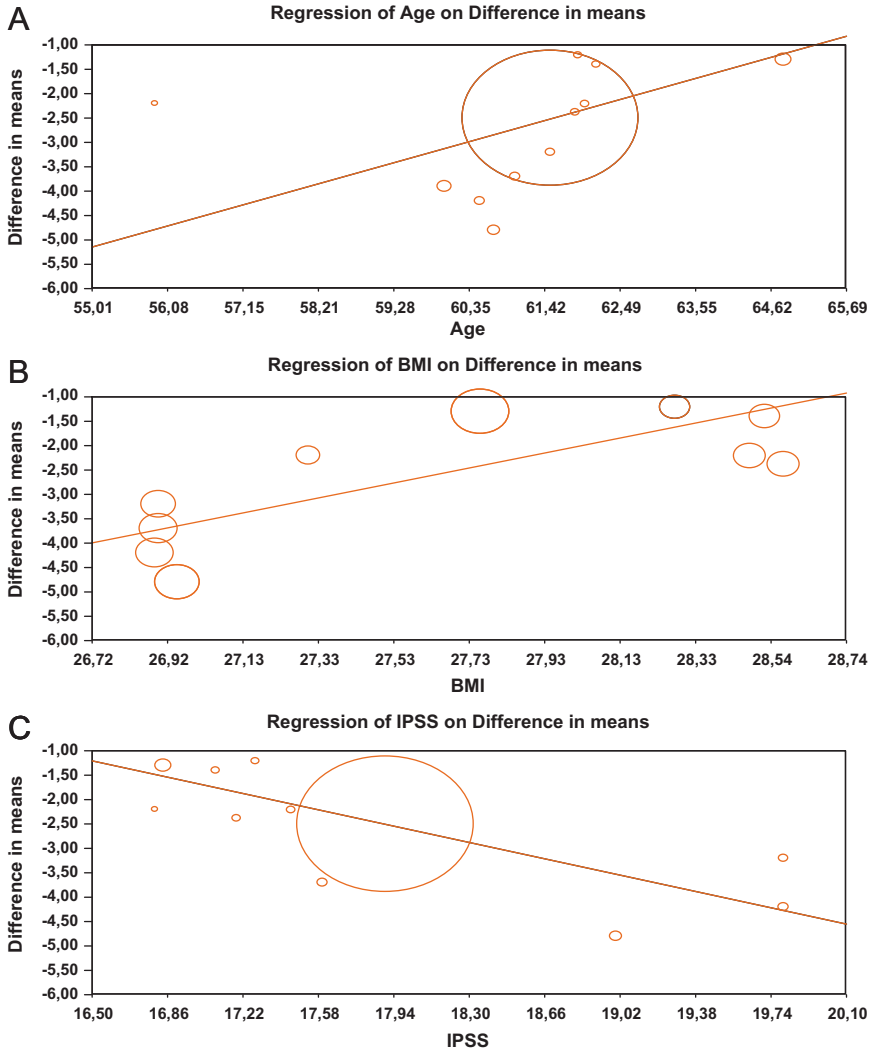

Fig. 3 – Influence of (A) age, (B) body mass index (BMI), and (C) baseline International Prostate Symptom Score (IPSS) on IPSS improvement in men treated with phosphodiesterase type 5 inhibitors.

or in combination with α-adrenergic blockers in LUTS/BPH. In January 2011, Liu et al. published for the first time a review and meta-analysis of five RCTs assessing the use of PDE5-Is alone versus placebo in LUTS/BPH men. He concluded that PDE5-Is are effective and safe, and should be used as first-line treatment for men with comorbid LUTS/ED [17]. Three months later, Laydner and colleagues in a systematic review without meta-analysis, including four trials on PDE5-Is alone in men with LUTS/BPH, reported a significant improvement of both urinary and erectile function, without a change in urinary flow rate [18]. Finally, in October 2011, Martinez-Salamanca et al, in a nonsystematic descriptive review, tried to analyze the role of combined therapy of PDE5-Is and α-blockers, reporting a significant improvement of urinary symptoms with no evidence of the effect on urodynamic parameters [32].

One of the most remarkable outcome of our meta-analysis on 12 RCTs is that the combination of PDE5-Is and α-adrenergic blockers can significantly improve maximum urinary flow rate as compared with α-adrenergic blockers alone, whereas PDE5-Is alone cannot increase Q_{max} as compared with placebo (see Fig. 2, panel B vs E). In particular, a small clinically insignificant increase in maximum flow rate was seen after PDE5-Is alone in any of the treatment arms (see Fig. 2, panel E), even if associated with an improvement in total IPSS, suggesting that PDE5-Is alone can exert their clinical activity differently than α-blockers, which are acting mainly to relieve a prostatic obstruction but with a direct relaxation of the bladder smooth muscle tone [8]. The relaxation of the prostate and bladder neck after PDE5-Is treatment could theoretically improve urinary flow rate; however, the concomitant relaxation of the detrusor muscle counteracts this effect, with no final improvement in the Q_{max} [33]. Conversely, a further improvement of maximum flow rate above 1 ml/s in combined therapy, as compared with α-blockers alone, was reported by all authors (see Fig. 2, panel E). Baseline urinary flow rate seems determinant for the final improvement after combined therapy. Tuncel

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Table 2 – Most common reported treatment-related adverse events stratified according to trials (column) and treatment arms*

	Arm	McVary et al. [16]	McVary et al. [21]	Stief et al. [22]	Roehrborn et al. [23]				Porst et al. [24]				Tamimi et al. [25]				Porst et al. [26]	Overall	Arm	Kaplan et al. [27]	Bechara et al. [28]	Liguori et al. [29]	Tuncel et al. [30]	Gacci et al. [31]	Overall
		Sildenafil	Tadalafil	Vardenafil	Tadalafil				Tadalafil				UK-369003				Tadalafil			Sild	Tadalafil	Tadalafil	Sildenafil	Vardenafil	
		100 mg	100 mg	10 mg	2.5 mg	5 mg	10 mg	20 mg	2.5 mg	5 mg	10 mg	20 mg	10 mg	25 mg	50 mg	100 mg	5 mg			25 mg	20 mg	20 mg	25 mg	10 mg	
Headache	D	21 (11.0)	4 (2.9)	14 (13.0)	0	0	6 (7.1)	4 (5.6)	4 (3.5)	4 (3.4)	6 (5.0)	2 (1.7)	5 (9.0)	2 (4.0)	4 (8.0)	5 (6.0)	6 (3.7)	87(4.6)	C		1			2	3 (2.9)
	P	6 (3.0)	1 (0.7)	2 (1.8)	3 (3.3)				4 (3.5)				1(3.0)				1 (0.6)	18 (2.1)	α		1			1	2 (2.0)
Dyspepsia	D	12 (6.0)	6 (4.3)	8 (7.4)	3 (3.1)	4 (4.8)	3 (3.5)	3 (4.2)	1 (0.9)	5 (4.3)	2 (1.7)	3 (2.6)	1 (2.0)	1 (2.0)	4 (8.0)	3 (3.0)		59 (3.1)	C	2				1	3 (2.9)
	P	2 (1.0)	0	0	4 (4.3)				0	0	0	0	1 (3.0)					7 (0.8)	α					1	1 (1.0)
Back pain	D		5 (3.6)	3 (2.8)	5 (5.2)	2 (2.4)	3 (3.5)	2 (2.8)	2 (1.8)	1 (0.9)	5 (4.2)	6 (5.2)	0	2 (4.0)	2 (4.0)	4 (4.0)	5 (3.1)	47 (2.5)	C						0
	P		2 (1.4)	0	4 (4.3)				1 (0.9)				2 (5.0)				4 (2.4)	13 (1.5)	α						0
Flushing	D	9 (5.0)		7 (6.5)									1 (2.0)	0	1 (2.0)	2 (2.0)		20 (1.2)	C						0
	P	1 (1.0)		1 (0.9)									0	0	0	0		2 (0.2)	α						0
Gastroesophageal reflux	D			3 (2.8)	4 (4.2)	2 (2.4)	5 (5.9)	4 (5.6)										18 (1.0)	C						0
	P			0	2 (2.2)													2 (0.2)	α						0
Sinusitis	D				2 (2.1)	2 (2.4)	5 (5.9)	3 (4.2)					0	0	1 (2.0)	1 (1.0)		14 (0.7)	C						0
	P				0	0	0	0					2 (5)					2 (0.2)	α						0
Rhinitis	D	8 (4.0)	3 (2.2)															11 (0.6)	C						0
	P	3 (2.0)	0															3 (0.3)	α						0
Hypertension	D				3 (3.1)	3 (3.6)	3 (3.5)	2 (2.8)										11 (0.6)	C						0
	P				0	0	0	0										0	α						0
Myalgia	D								1 (0.9)	5 (4.3)	2 (1.7)	3 (2.6)						11 (0.6)	C						0
	P								0	0	0	0						0	α						0
Cough	D				3 (3.1)	1 (1.2)	2 (2.4)	2 (2.8)										8 (0.4)	C						0
	P				1 (1.1)													1 (0.1)	α						0
Diarrhoea	D			5 (4.6)														5 (0.3)	C						0
	P			1 (0.9)														1 (0.1)	α						0
UTI	D		3 (2.2)															3 (0.2)	C						0
	P		1 (0.7)															1 (0.1)	α						0
Priapism	D		7 (5.1)															7 (0.4)	C						0
	P		2 (1.4)															2 (0.2)	α						0
Extremity pain	D																	0	C						0
	P																	0	α						0
Dizziness	D																	0	C	1					1 (0.97)
	P																	0	α	2					2 (2.0)
Hypotension	D																	0	C						0
	P																	0	α						0
Overall	D	50 (29.8)	28 (22.2)	40 (38.1)	20 (11.0)	14 (7.7)	27 (15.4)	20 (12.3)	7 (6.2)	15 (12.8)	15 (12.5)	14 (12.1)	8 (15.4)	5 (8.9)	12 (23.5)	15 (17.2)	11 (7.4)	301 (16.0)	C	3 (15.8)	1 (7.1)	.	.	3 (10.0)	7 (6.8)
	P	12 (7.7)	6 (4.8)	4 (3.6)	14 (7.6)				5 (4.3)				6 (16.2)				5 (3.3)	52 (6.0)	α	2 (11.1)	1 (7.7)	.	.	2 (6.9)	5 (5.1)

D = drugs (ie, phosphodiesterase type 5 inhibitors [PDE5-Is]); P = placebo; C = combined therapy (ie, PDE5-Is plus α-blocker); α = α-blocker alone.

* Data are reported as number of events and percentage (%).

Table 3 – Odds ratio, lower limits, upper limits, and *p* value of the meta-regression of adverse events reported at least in two papers comparing the effect of phosphodiesterase type 5 inhibitor alone versus placebo

Side effect	OR	LL	UL	*p* value
Flushing	4.888	1.546	15.459	0.007
Gastroesophageal reflux	2.214	0.556	5.123	0.063
Headache	1.876	1.181	2.980	0.008
Dyspepsia	1.850	1.064	3.216	0.029
Back pain	1.177	0.731	1.897	0.503
Sinusitis	1.376	0.428	4.426	0.552

OR = odds ratio; LL = lower limit; UL = upper limit.

reported the most remarkable outcome in Q_{max} (+3.7 ml/s) in men with a minimal baseline obstruction (Q_{max} at baseline: 14 ml/s), and all the remaining authors reported an improvement of 1–1.5 ml/s in men with a true obstruction (Q_{max} at baseline: 9.5–10 ml/s) [30]. In a RCT there were no differences from baseline men randomized to placebo versus tadalafil 20 mg daily for 12 wk in either noninvasive or invasive urodynamics [34]. This study was conducted to demonstrate the safety of tadalafil daily in terms of negative impact on bladder contractility and found no such effect. It did, however, also not suggest a positive effect on contractility or outlet condition.

The utility of PDE5-I for LUTS was not endorsed in the recent American Urological Association (AUA) clinical guidelines because the AUA guidelines panel only evaluates therapies that are approved [35]. The European Association of Urology guidelines reported the use of PDE5-Is as "new emerging drugs" but state that these drugs have not yet been officially registered for the treatment of male LUTS [36].

From this meta-analysis it is clear that substantial work has been performed to address the relationship between ED and LUTS. More than 3000 patients have been studied in RCTs comparing PDE5-Is against a placebo. Taken together, IPSS was significantly improved for all treatment groups compared with placebo with a mean difference of almost 3 points on the IPSS. This is an improvement that is clinically relevant for symptomatic men and perceived by patients, as reported in the current clinical guidelines [35]. The efficacy seems to be quite similar across the different classes of PDE5-Is and the different dosages. Variations in urinary outcomes may be explained by inclusion criteria such as patient age and additional risk factors for LUTS. This level of improvement is comparable with that seen in well-controlled α-blocker studies.

As shown in other analyses for α-blockers alone in the treatment of LUTS, the degree of improvement in the IPSS partially depends on the baseline IPSS [37,38]. Patient improvement with any treatment depends on the scoring of baseline IPSS; the higher the score, the better the result. Most interesting is the observation that improvement in IPSS after PDE5-Is depends on age (younger) and body mass index (BMI; less obese) (see Fig. 3). This has potential implications for the understanding of the mechanisms of action of PDE5-Is and delineates young men with low BMI and severe urinary symptoms as the best candidates for treatment with PDE5-Is. One possible explanation is the finding in an animal model of an androgen dependency of PDE5 expression within the bladder [7]. It is well known that both obesity and aging are associated with a testosterone decline, which, in turn, can decrease the main target (PDE5) of PDE5-Is [39,40]. There are negligible data on the progression of LUTS when treated with PDE5-Is. There is little to suggest that PDE5-Is would have any impact on prostate volume, prostate-specific antigen value, acute urinary retention, or the need for surgery. Therefore a model of a risk-stratified approach based on progression parameters such as those reported here is currently not available.

Although not as robust as the data for PDE5-I alone, the RCTs comparing PDE5-Is plus α-blocker versus α-blocker alone include <300 patients. There is greater variation in the treatment effect related to the smaller number of participants, different doses of various medications, and, of course, lack of uniformity of patient cohorts. Adding PDE5-Is to the α-blockers results in only modest effects on efficacy. There is an absence of three armed controlled studies comparing PDE5-Is versus α-blocker versus placebo. Such a study design, although cumbersome, would be useful in determining the relative value of PDE5-I in treating LUTS.

According to previously published reports [17,18,32], the effect of PDE5-Is on erectile function (EF), as measured by the IIEF, is impressive with a mean difference of 5.5. In contrast, α-blockers have little power to improve EF. In our review, there is a consistent superiority of PDE5-Is plus α-blockers over α-blockers alone in treating EF alterations. This finding corroborates the use of combined therapy for men with comorbid LUTS and ED.

In the present systematic review, the overall incidence of adverse events (16%; see Table 3) was more remarkable after the use of PDE5-Is as compared with placebo. However, most cases of treatment-related AEs were of mild to moderate grade, and the overall safety profile of these drugs was good. Only a few cases of discontinuation due to AEs were reported in >2000 men included in this review. In RCTs comparing α-blocker alone with combined therapy, AEs were recorded and analyzed only by Kaplan et al. [27], Bechara et al. [28], and Gacci et al. [31], with a similar incidence of AEs across the two treatment arms, suggesting that the addition of PDE5-Is to α-blockers was well tolerated and accepted by men with LUTS.

The overall value of the present systematic review and meta-analysis is lessened by several limitations of the studies included: small size populations (in particular for the group with combined therapy), short duration (12 wk), and inconsistent/unavailable recording of safety data. However, in the only longer term study, an open-label 1-yr-long extension study, the patients converted after 12 wk from placebo to 5 mg tadalafil experienced an additional improvement of 2.2 points for a total of 4.1 points, those converted from 2.5 mg tadalafil to 5 mg tadalafil an additional improvement of 2.5 points, whereas those maintained on 5 mg or converted from 10 and 20 mg, respectively, to 5 mg tadalafil experienced no additional improvements but also no deterioration [41]. These data suggest the maintenance of efficacy over 12 mo and that the 5-mg dose is in fact the most

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effective and safest dosage. Long-term efficacy end points such as acute urinary retention rates and/or urinary flow rate should be addressed by additional prospective studies on long-term treatments.

In our review there are no data about ejaculation or global sexuality improvement, which would be useful in the context of LUTS/BPH men with or without sexual (including ejaculatory) dysfunction.

No RCTs directly comparing different classes of PDE5-Is are still available. Studies regarding the efficacy (risk of acute urinary retention/surgery) and the side-effect profile (sexual outcomes) of combination therapy of PDE5-Is and 5α-reductase inhibitors are not published. Finally, the important issue of the cost effectiveness of daily treatment with PDE5-Is has not been raised, and unfortunately none of the RCTs included in this review had performed cost analyses. An accurate cost analysis should take into account the drug costs, the long safety and efficacy profile, and the overall QoL of men treated with PDE5-Is alone or in combination with other drugs in continuous or intermittent administration. Therefore, further high-quality RCTs are strongly desirable to address these data.

The MetS has become a major public health challenge globally [42]. Treatment for sexual dysfunction and LUTS associated with the MetS can target the sexual symptoms and LUTS resulting from the MetS as well as different components of the MetS (eg, central obesity, hypertension, insulin resistance, etc.). Currently, no direct pharmacologic treatment for the MetS exists; rather, lifestyle modifications in the form of changes in diet and physical exercise represent the foundation of therapy. These same strategies including consumption of alcohol and caffeine can improve LUTS. Lifestyle modifications have been shown to improve endothelial function, decrease inflammatory marker levels, and prevent diabetes. Primary treatment of ED includes the use of PDE5 inhibitors. However, data from several studies have now demonstrated their secondary impact on male LUTS. Effective and comprehensive treatment of urinary symptoms and ED must therefore take into consideration treatment of any underlying elements of the MetS [43].

4. Conclusions

PDE5-Is are effective and well tolerated either alone or in combination with α-blockers in men with LUTS/BPH in the first 12 wk of treatment. PDE5-Is with α-blockers induce a small improvement in flow rate, whereas PDE5-Is alone fail to do it.

Younger men with lower BMI and severe urinary symptoms seem to be the best candidates for PDE5-Is in terms of improvement of their urinary function. Headache, dyspepsia, and back pain are the most frequently reported AEs after PDE5-Is in men with LUTS/BPH.

Further studies are needed to evaluate the long-term safety and efficacy outcomes and the overall cost-effectiveness analysis of this treatment.

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Study concept and design: Gacci.
Acquisition of data: Salvi, Vignozzi.
Analysis and interpretation of data: Corona.
Drafting of the manuscript: Gacci, Maggi, McVary, Kaplan.
Critical revision of the manuscript for important intellectual content: Mirone, Roehrborn, Serni, Carini.
Statistical analysis: Corona.
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