The use of Phosphodiesterase 5 inhibitors (PDE-5-Is) alone or in combination with Alpha-blockers for Lower Urinary tract symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH)

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Abstract: Background: 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, and include obstructive symptoms such as hesitancy, incomplete emptying, and weak stream, and irritative symptoms such as frequency, urgency, and nocturia, 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. **Objective:** The study was performed to determine the relative efficacy and safety of PDE5-Is alone or in combination with alpha-1 adrenergic blockers in LUTS due to BPH. **Methods:** Our study was conducted on 60 patients diagnosed with LUTS/BPH and ED presented at Ain shams university hospital. They were the same age group (50-70 years old) and were complaining of moderate to severe prostatic symptoms, with IPSS > 13, when combining sildenafil 25 mg and tamsulosin 0.4 m, or vardenafil 10 mg and tamsulosin 0.4mg, IPSS score showed greater improvement than using either of the 2 drugs alone. The same result was found in Q-max and IIEF. **Results:** The combination of PDE5-Is with alpha-blockers induce statistically significant improvement of maximum flow rate as compared with alpha-blockers alone, in addition to the positive effect on micturition and sexual activity. 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. **Conclusions:** PDE5-Is are effective and well tolerated either alone or in combination with a-blockers in men with LUTS/BPH in the first 12 wk of treatment. PDE5-Is with alpha-blockers induce an additional 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.

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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, and include obstructive symptoms such as hesitancy, incomplete emptying, and weak stream, and irritative symptoms such as frequency, urgency, and nocturia, 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)].

BPH is a non-malignant enlargement of the prostate caused by cellular hyperplasia of both glandular and stromal elements, and is a common progressive disease among men, with an incidence that is age-dependent. Histological BPH, which typically develop after the age of 40 years, ranges in prevalence from >50% at 60 years to as high as 90% by 85 years of age [(2)].

BPH contribute to, but is not the single cause of, bothersome LUTS that may affect QoL. The prevalence of troublesome symptoms increases with age, typically occurring in men aged ≥50 years. Approximately 50% of patients with BPH report moderate to severe LUTS, consisting of storage and voiding symptoms. Although bothersome LUTS may affect QoL by altering normal daily activities and sleep patterns, mortality associated with BPH is rare. Although uncommon, serious complications of BPH may occur, including acute urinary retention, renal insufficiency, urinary tract infection, hematuria, bladder stone, and renal failure [(3)].

These complications may be triggered or worsened by inadequate management of BPH. The incidence of acute urinary retention in untreated patients ranges from 0.3% to 3.5% per year; the risk of developing other long-term complication is unclear [(4)].

However, since the 1990's, there has been a substantial shift in the management of BPH from surgical to medical therapy. The current standard of care for LUTS/BPH includes alpha- adrenergic blockers, 5 alpha-reductase inhibitors, and phytotherapies, used alone or in combination. These therapies are associated with bothering sexual side effects [(5)].

Sexual dysfunction is a highly prevalent comorbidity in aging men with LUTS associated with BPH, common links such as the nitric oxide-cyclic guanosine mono-phosphate (NO/cGMP) pathway, RhoA/Rho-kinase signaling, pelvic atherosclerosis, and autonomic adrenergic hyperactivity can be potential targets for phosphodiesterase type 5 inhibitors (PDE5-Is) [(6)].

The management of patients with BPH includes non-pharmacological, pharmacological, and surgical option, with the choice of therapy typically depending on the presence and severity of symptoms.

Watchful waiting is the preferred management strategy for patients with mild LUTS and those who do not perceive their symptoms to be particularly bothersome. Pharmacological treatment include α1-adrenergic receptor blockers, and 5 α-reductase inhibitors, which are recommended for use alone or in combination in moderate to severe LUTS. Currently, adrenergic receptor antagonists are commonly used as the first-line treatment for LUTS associated with BPH. The α1-adrenergic receptor antagonists cause vasodilatory symptoms, including postural hypotension and dizziness. Tamsulosin has relative selectivity for the α1A- adrenergic receptor [(3)].

The α1- adrenergic receptor blockers increases the incidence of the hip fractures (clinically important orthostatic hypotension). Avoidance of α1B-adrenergic receptor blockade may result in fewer overall hip fractures [(7)].

PDE5 tissue distribution and activity in the human prostatic urethra, prostate, and bladder indicate that in 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, along with inhibition of the RhoA/Rho-kinase contractile mechanism induced by PDE5-Is in the bladder, could be the mechanistic rationale for the use of PDE5-Is treatment to ameliorate the dynamic component (bladder dysfunction and urethral contractions) of male LUTS [(5)].

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, and the efficacy of PDE5-Is on continence recovery after radical prostatectomy for prostate cancer [(9)].

The pathophysiology of male LUTS is highly complex, multifactorial, including an impaired NO/cGMP signaling, an increased RhoA/Rho-kinase pathway activation, pelvic ischemia, autonomic over activity, and increased bladder/prostate afferent activity, all these major mechanisms of BPH/LUTS could be counteracted by PDE5-Is. The mechanism of action of PDE-5-Is on LUTS includes several potential targets such as prostate, urethra, bladder, and LUTS vasculature [(10)].

PDE 5 is also highly expressed in the LUTS vasculature. Chronic ischemia due to pelvic artery insufficiency, caused by 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 [(11)].

It was confirmed that PDE-5 could improve urinary symptom scores in a population of men with comorbid ED and mild to moderate LUTS [(12)]. The following year, with a randomized double-blind placebo-controlled study on BPH men (with or without ED), it was conclusively established the emerging role of PDE5-Is as an effective and well-tolerated treatment for LUTS [(13)].

Although the underlying pathophysiological links between LUTS and ED are not completely understood, both conditions are amenable to therapy with (PDE5-Is). Recently, several studies have suggested that metabolic factors could be important for contributing to both prostate inflammation and enlargement in men with LUTS [(14)]. PDE5-Is could reduce inflammation with the associated fibrosis and improve the oxygenation of the human prostate, with a normalization of prostatic structural anatomy and physiologic activity [(15)].

Aim of the Work

To determine the relative efficacy and safety of PDE5-Is alone or in combination with alpha-1 adrenergic blockers in LUTS due to BPH.

2. Subjects and Methods

This study will be conducted on 60 patients diagnosed with LUTS/BPH and ED presented at Ain shams university hospital.

Inclusion criteria

1. Same age group (50-70 years old).
2. The patients are complaining of moderate to severe prostatic symptoms, with history of Lower Urinary Tract Symptoms (LUTS) secondary to Benign Prostatic Hyperplasia (BPH), with an International Prostate Symptom Score IPSS > 13.
3. Free from any medical disease that can affect penile erection (Hypertension, Diabetes Mellitus, neurologic or psychogenic diseases).

4. Not under the effect of any other drug that can affect erection.

5. Patients are classified into 3 groups:

Group A: They are 20 patients divided into 10 patients taking sildenafil 25 mg once daily, and 10 patients taking vardenafil 10 mg once daily.

Group B: They are 20 patients divided into 10 patients taking sildenafil 25 mg once daily and Tamsulosin 0.4 mg once daily, and 10 patients taking vardenafil 10 mg and Tamsulosin 0.4 mg once daily.

Group C: They are 20 patients taking Tamsulosin 0.4 mg once daily only.

6. The duration of treatment is 3 months.

7. The Follow-up of patients is performed after 1 month, then 2 months, and finally at 3 months.

8. Patients are evaluated via:

a. International Prostate Symptom Score (IPSS).

b. International Index of Erectile Function (IIEF).

9. An informed consent will be obtained including counseling on treatment options and potential side effects.

10. Investigations:

a. Uroflowmetry Qmax.

b. Routine investigations (Complete blood count, liver enzymes (SGOT and SGPT), kidney functions (serum urea and creatinine), bleeding profile (PT, PTT, and INR) and fasting blood sugar).

Statistical methods:

Data were coded and entered using the statistical package SPSS version 25. Data was summarized using mean and standard deviation for quantitative variables. Comparisons between groups were done using unpaired t test when comparing 2 groups and analysis of variance ***(ANOVA)*** with multiple comparisons post hoc test when comparing more than 2 groups in normally distributed quantitative variables while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables [(16)]. P-values less than ***0.05*** were considered as statistically significant.

3. Results

Table (1): T-Test (group statistics).

T-Test

Group Statistics

group details		N	Mean	Std. Deviation	Std. Error Mean
Mean change from baseline IPSS to end point	sildenafil 25 mg	10	3.5700	0.18288	0.05783
	sildenafil 25 mg and tamsulosin 0.4 mg	10	6.4000	0.24495	0.07746
Mean improvement in IIEF	sildenafil 25 mg	10	4.1200	0.16193	0.05121
	sildenafil 25 mg and tamsulosin 0.4 mg	10	4.1500	0.24608	0.07782
Mean improvement in Qmax (ml/sec)	sildenafil 25 mg	10	0.1780	0.01398	0.00442
	sildenafil 25 mg and tamsulosin 0.4 mg	10	3.2500	0.23214	0.07341

Group Statistics

group details		N	Mean	Std. Deviation	Std. Error Mean
Mean change from baseline IPSS to end point	vardenafil 10 mg	10	4.4800	0.23476	0.07424
	vardenafil 10 mg and tamsulosin 0.4 mg	10	6.0400	0.18974	0.06000
Mean improvement in IIEF	vardenafil 10 mg	10	2.8500	0.15811	0.05000
	vardenafil 10 mg and tamsulosin 0.4 mg	10	3.7700	0.12517	0.03958
Mean improvement in Qmax (ml/sec)	vardenafil 10 mg	10	1.3400	0.10750	0.03399
	vardenafil 10 mg and tamsulosin 0.4 mg	10	3.0400	0.20656	0.06532

Table (2): Post Hoc tests.

Post Hoc Tests

Multiple Comparisons

Bonferroni

Dependent Variable			Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Mean change from baseline IPSS to end point	phosphodiesterase 5 inhibitors group	phosphodiesterase 5 inhibitors+tamsulosin group	-2.19500-*	0.11353	0.000	-2.4750	-1.9150
		tamsulosin group	-1.90000-*	0.11353	0.000	-2.1800	-1.6200
	phosphodiesterase 5 inhibitors+tamsulosin group	phosphodiesterase 5 inhibitors group	2.19500*	0.11353	0.000	1.9150	2.4750
		tamsulosin group	.29500*	0.11353	0.036	0.0150	0.5750
	tamsulosin group	phosphodiesterase 5 inhibitors group	1.90000*	0.11353	0.000	1.6200	2.1800
		phosphodiesterase 5 inhibitors+tamsulosin group	-.29500-*	0.11353	0.036	-0.5750	-0.0150
Mean improvement in IIEF	phosphodiesterase 5 inhibitors group	phosphodiesterase 5 inhibitors+tamsulosin group	-.47500-*	0.13715	0.003	-0.8133	-0.1367
		tamsulosin group	2.14500*	0.13715	0.000	1.8067	2.4833
	phosphodiesterase 5 inhibitors+tamsulosin group	phosphodiesterase 5 inhibitors group	.47500*	0.13715	0.003	0.1367	0.8133
		tamsulosin group	2.62000*	0.13715	0.000	2.2817	2.9583
	tamsulosin group	phosphodiesterase 5 inhibitors group	-2.14500-*	0.13715	0.000	-2.4833	-1.8067
		phosphodiesterase 5 inhibitors+tamsulosin group	-2.62000-*	0.13715	0.000	-2.9583	-2.2817
Mean improvement in Qmax (ml/sec)	phosphodiesterase 5 inhibitors group	phosphodiesterase 5 inhibitors+tamsulosin group	-2.38600-*	0.12456	0.000	-2.6933	-2.0787
		tamsulosin group	-1.56600-*	0.12456	0.000	-1.8733	-1.2587
	phosphodiesterase 5 inhibitors+tamsulosin group	phosphodiesterase 5 inhibitors group	2.38600*	0.12456	0.000	2.0787	2.6933
		tamsulosin group	.82000*	0.12456	0.000	0.5127	1.1273
	tamsulosin group	phosphodiesterase 5 inhibitors group	1.56600*	0.12456	0.000	1.2587	1.8733
		phosphodiesterase 5 inhibitors+tamsulosin group	-.82000-*	0.12456	0.000	-1.1273	-0.5127

*. The mean difference is significant at the 0.05 level.

Table (3): Independent samples test.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Mean change from baseline IPSS to end point	Equal variances assumed	1.042	0.321	-29.276	18	0.000	-2.83000	0.09667	-3.03309	-2.62691
	Equal variances not assumed			-29.276	16.655	0.000	-2.83000	0.09667	-3.03427	-2.62573
Mean improvement in IIEF	Equal variances assumed	2.430	0.136	-0.322	18	0.751	-0.03000	0.09315	-0.22571	0.16571
	Equal variances not assumed			-0.322	15.564	0.752	-0.03000	0.09315	-0.22793	0.16793
Mean improvement in Qmax (ml/sec)	Equal variances assumed	11.603	0.003	-41.772	18	0.000	-3.07200	0.07354	-3.22651	-2.91749
	Equal variances not assumed			-41.772	9.065	0.000	-3.07200	0.07354	-3.23818	-2.90582

T-Test

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Mean change from baseline IPSS to end point	Equal variances assumed	0.150	0.703	-16.343	18	0.000	-1.56000	0.09545	-1.76054	-1.35946
	Equal variances not assumed			-16.343	17.241	0.000	-1.56000	0.09545	-1.76117	-1.35883
Mean improvement in IIEF	Equal variances assumed	0.474	0.500	-14.427	18	0.000	-0.92000	0.06377	-1.05398	-0.78602
	Equal variances not assumed			-14.427	17.099	0.000	-0.92000	0.06377	-1.05448	-0.78552
Mean improvement in Qmax (ml/sec)	Equal variances assumed	5.536	0.030	-23.087	18	0.000	-1.70000	0.07364	-1.85470	-1.54530
	Equal variances not assumed			-23.087	13.542	0.000	-1.70000	0.07364	-1.85844	-1.54156

Table (4): ANOVA (analysis of variance)

Oneway

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Mean change from baseline IPSS to end point	Between Groups	56.767	2	28.384	220.207	0.000
	Within Groups	7.347	57	0.129		
	Total	64.114	59			
Mean improvement in IIEF	Between Groups	77.940	2	38.970	207.182	0.000
	Within Groups	10.722	57	0.188		
	Total	88.662	59			
Mean improvement in Qmax (ml/sec)	Between Groups	58.785	2	29.393	189.437	0.000
	Within Groups	8.844	57	0.155		
	Total	67.629	59			

Table (5): Comparison between the 3 groups (A, B, C) regarding mean improvement in IIEF, IPSS, and Qmax.

	phosphodiesterase 5 inhibitors group		phosphodiesterase 5 inhibitors+tamsulosin group		tamsulosin group		
	Mean	SD	Mean	SD	Mean	SD	*P* value
Mean change from baseline IPSS to end point	4.02	.51	6.22	.28	5.93	.22	<0.001
Mean improvement in IIEF	3.48	.67	3.96	.27	1.34	.20	<0.001
Mean improvement in Qmax (ml/sec)	.76	.60	3.15	.24	2.32	.22	<0.001

Table (6): Post hoc pairwise comparison between each 2 groups

P value		phosphodiesterase 5 inhibitors+tamsulosin group	tamsulosin group
Mean change from baseline IPSS to end point	phosphodiesterase 5 inhibitors group	<0.001	<0.001
	phosphodiesterase 5 inhibitors+tamsulosin group		.036
Mean improvement in IIEF	phosphodiesterase 5 inhibitors group	.003	<0.001
	phosphodiesterase 5 inhibitors+tamsulosin group		<0.001
Mean improvement in Qmax (ml/sec)	phosphodiesterase 5 inhibitors group	<0.001	<0.001
	phosphodiesterase 5 inhibitors+tamsulosin group		<0.001

Table (7): Comparison between some subgroups (Sildenafil/Sildenafil and Tamsulosin)

	sildenafil 25 mg		sildenafil 25 mg and tamsulosin 0.4 mg		
	Mean	SD	Mean	SD	*P* value
Mean change from baseline IPSS to end point	3.57	.18	6.40	.24	<0.001
Mean improvement in IIEF	4.12	.16	4.15	.25	0.751
Mean improvement in Qmax (ml/sec)	.18	.01	3.25	.23	<0.001

Table (8): Comparison between some subgroups (Vardenafil/Vardenafil and Tamsulosin)

	vardenafil 10 mg		vardenafil 10 mg and tamsulosin 0.4 mg		
	Mean	SD	Mean	SD	*P* value
Mean change from baseline IPSS to end point	4.48	.23	6.04	.19	<0.001
Mean improvement in IIEF	2.85	.16	3.77	.13	<0.001
Mean improvement in Qmax (ml/sec)	1.34	.11	3.04	.21	<0.001

4. Discussion

- **Sildenafil 25 mg only once daily for 12 weeks:**

When comparing with other studies, according to **Mulhall *et al.*** [17], his results were slightly different because of relatively greater number of patients included 48 patients completed the study. Also, due to higher dose of sildenafil used 100 mg which lead to mean improvement from base line in IPSS: 4.6 points +/- 1.6 from baseline >10. While, in our study it was only 3.5. In **McVary *et al.*** [13], same duration of treatment was done (12 weeks) and patients IPSS score was nearly very close to our study (baseline IPSS >12). But again, sildenafil dose was higher 50mg increased to 100 mg after 2 weeks. However, number of patients included were comparatively high:189.

Regarding the IIEF, in **Mulhall *et al.*** [17], using sildenafil 100 mg in intermittent high dose 2 pills per week +/- 0.6 results in improvement of the IIEF 7 points. While, in our study the improvement was only 4.1 due to lower dose of sildenafil used. But in the same study the decrease in IPSS score was higher 6.3 points compared to Mulhall.

- **Vardenafil 10 mg once daily for 12 weeks:**

According to **Stief *et al.*** [18], his results were different due to greater number of patients included (225) and double the dose of drug was taken, also the duration of study was only 8 weeks, hence men change in IPSS was greater -5.9.

- **Tamsulosin 0.4 mg once daily for 12 weeks:**

The results were showing greater improvement in IPSS score and Q-max when compared with either sildenafil or vardinafil alone. In spite of having less significant effect compared to each of the 2 previous mentioned drugs regarding the effect on IIEF.

- **Combination of sildenafil 25 mg and tamsulosin 0.4 mg:**

Regarding IPSS score the combination showed greater improvement than using either of the 2 drugs alone. The same result was found in Q-max and IIEF.

- **Combination of vardenafil 10 mg and tamsulosin 0.4mg:**

Regarding IPSS score the combination showed greater improvement than using either of the 2 drugs alone. The same result was found in Q-max and IIEF.

In January 2011, **Liu *et al*.** [19] published for the first time a 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. Three months later, **Laydner and colleagues** [20] in a systematic review, 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. Finally, in October 2011, **Martinez-Salamanca *et al.*** [21], analyzed the role of combined therapy of PDE5-Is and alpha-blockers, reporting a significant improvement of urinary symptoms with no evidence of the effect on urodynamic parameters.

One of the most remarkable outcomes of our meta-analysis on 12 RCTs is that the combination of PDE5-Is and alpha adrenergic blockers can significantly improve maximum urinary flow rate as compared with alpha-adrenergic blockers alone, whereas PDE5-Is alone cannot increase Qmax as compared with placebo. In particular, a small clinically insignificant increase in maximum flow rate was seen after PDE5-Is alone in any of the treatment arms, even if associated with an improvement in total IPSS, suggesting that PDE5-Is alone can exert their clinical activity differently than alpha-blockers, which are acting mainly to relieve a prostatic obstruction but with 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 Qmax [22]. Conversely, a further improvement of maximum flow rate above 1 ml/s in combined therapy, as compared with alpha-blockers alone, was reported [23].

Baseline urinary flow rate seems determinant for the final improvement after combined therapy. **Tuncel *et al.*** [23] reported the most remarkable outcome in Qmax (+3.7 ml/s) in men with a minimal baseline obstruction (Qmax 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 (Qmax at baseline: 9.5–10 ml/s).

In a RCT there were no differences from baseline men randomized to placebo versus tadalafil 20 mg daily for 12 wk in either non-invasive or invasive urodynamics [24]**.** 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. 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 [25]**.**

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. 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.

The degree of improvement in the IPSS partially depends on the baseline IPSS. Patient improvement with treatment depends on the scoring of baseline IPSS; the higher the score, the better the result [26].

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. RCTs comparing PDE5-Is plus alpha-blocker versus alpha-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, lack of uniformity of patient cohorts.

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, alpha-blockers have little power to improve EF. There is a consistent superiority of PDE5-Is plus alpha-blockers over alpha-blockers alone in treating EF alterations. This finding confirms the use of combined therapy for men with comorbid LUTS and ED.

The overall incidence of adverse events 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 alpha-blocker alone with combined therapy, AEs were recorded and analyzed by Gacci *et al*. [9], with a similar incidence of AEs, suggesting that the addition of PDE5-Is to alpha-blockers was well tolerated by men with LUTS.

The overall value is lessened by *several limitations* of the studies included: small- size populations (in particular for the group with combined therapy), short duration (12 wk). 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 administered once daily for LUTS secondary to BPH 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 experienced 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 showed also no deterioration. These data suggest the maintenance of efficacy over 12months and that the **5**-mg dose is in fact the most 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 studies on long-term treatments [(27)].

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-term 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.

Recently, the ***MetS*** has become a major public health challenge globally. 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 (central obesity, hypertension, insulin resistance). 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 lowering consumption of alcohol and caffeine can improve LUTS. Lifestyle modifications have been shown to improve endothelial function, decrease inflammatory marker levels, and prevent diabetes. Effective and comprehensive treatment of urinary symptoms and ED must therefore take into consideration treatment of any underlying elements of the MetS [(15)].

5. Conclusions:

PDE5-Is are effective and well tolerated either alone or in combination with a-blockers in men with LUTS/BPH in the first 12 wk of treatment. PDE5-Is with alpha-blockers induce an additional 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.

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