ORIGINAL PAPER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Editor's Choice

Comparison of efficacy for erectile function and lower urinary tract symptoms of tadalafil 20 mg on-demand and 5 mg once daily in patients with erectile dysfunction

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SUMMARY

Aim: To compare the improvement in erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) as well as safety of tadalafil dosed at 20 mg on-demand and 5 mg once daily among ED patients. **Materials and methods:** A total of 194 ED patients visited between March 2010 and June 2011 were recruited. Out of 194 individuals, 168 (86.6%) met inclusion criteria after completing the two-week screening period (V0). The Patients were randomly allocated into two groups: (i) 20 mg of tadalafil as needed (Group 1: $n = 84$, 50.0%) and (ii) 5 mg of tadalafil once daily (Group 2: $n = 84$, 50.0%). Blood pressure (BP), heart rate (HR) and the five-item version of the International Index of Erectile Function (IIEF-5) were assessed immediately before initiation of treatment (V1) and after four (V2) and twelve weeks of treatment (V3). In men with an IPSS of ≥ 8 at V1, IPSS, maximal flow rate (Qmax) and post-void residual volume (PVR) were also assessed. **Results:** Of the 168 patients, 134 (79.8%; Group 1: $n = 68$, 81.0%; Group 2: $n = 66$, 78.6%) patients completed the trial. IIEF-5 improved in both groups, and the mean change was larger in Group 2 at V3 (4.9 ± 4.2 vs. 6.5 ± 4.5; $p = 0.032$) Similarly, though IPSS (with ≥ 8, $n = 88$, 65.7%; Group 1: $n = 44$, 64.7%; Group 2: $n = 44$, 66.7%) improved in both groups, the mean change was larger in Group 2 at V3 (-2.8 ± 4.3 vs. -4.8 ± 4.1; $p = 0.026$). Qmax and PVR did not differ significantly in either group. **Conclusions:** Once daily tadalafil was more efficacious in treating both ED and LUTS than on-demand dosing. However, no differences were observed between the two dosing schedules with regard to the improvement in LUTS when stratified by improvement in ED. The side effects were insignificant for both dosing schedules.

What's known

Low-dose once daily phosphodiesterase type-5 inhibitor intake allows the user to partake in sexual intercourse at any time, eliminating the need to dose prior to intercourse. In addition to the general improvement in sexual function, tadalafil also improves voiding symptoms in individuals with lower urinary tract symptoms. However, no data exist comparing the improvement in lower urinary tract symptoms between on-demand and once daily tadalafil dosing.

What's new

Both dosing schedules of tadalafil effectively enhance sexual function and improve lower urinary tract symptoms. When compared to on-demand dosing, once daily dosing was more efficacious in treating both erectile dysfunction and lower urinary tract symptoms. No differences were observed between the two dosing schedules with regard to the improvement in lower urinary tract symptoms when stratified by improvement in erectile dysfunction.

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Disclosures
The authors declare that they have no conflicts of interest to disclose.

Introduction

While sildenafil citrate (Viagra®, Pfizer Inc, New York, NY) was the first phosphodiesterase type-5 inhibitor (PDE5i) developed in 1998, additional agents such as vardenafil HCL (Levitra®, Bayer-GSK, Bayer/GSK, Raritan, NJ) and tadalafil (Cialis®, Lilly-ICOS, Indianapolis, IN) have been subsequently released. PDE5i are now the first-line treatment for erectile dysfunction (ED) because of their well-established safety, efficacy, and general ease of use. These three drugs – all of which have been approved for use by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) – induce an increase in arterial blood flow, which leads to smooth muscle relaxation, vasodilatation, and ultimately penile erection (1).

Compared with other PDE5i agents, tadalafil has the longest *in vivo* half-life at 17.5 h, with drug efficacy potentially lasting up to 36 h (2). PDE5i therapy allows for two types of dosing: 'on-demand' before sexual intercourse and 'low-dose once daily' intake (3). Low-dose once daily PDE5i intake allows the user to partake in sexual intercourse at any time, eliminating the need to dose prior to intercourse. In addition to the general improvement in sexual function, the results from several studies indicate that tadalafil also improves voiding symptoms in individuals with lower urinary tract symptoms (LUTS) (4,5). However, no data exist comparing the improvement in LUTS between on-demand and once daily tadalafil dosing. In the present study, both the efficacy and safety of erectile function and the improvement of LUTS were compared between

20 mg on-demand and 5 mg once daily tadalafil dosing in patients with ED.

Material and methods

Patients and study design

In total, 194 patients who visited the five Impotence Centers between March 2010 and May 2011 were recruited for the present study. Institutional review board approval was obtained prior to the clinical study. Subjects were stratified by the five-item version of the International Index of Erectile Function (IIEF-5) score as follows: scores more than 18 were classified as not having ED, scores between 14 and 17 as mild ED, scores between 10 and 13 as moderate ED, and scores less than 10 as severe ED. This stratification methodology was based on a study by Ahn et al. (6) that established cut-off values for the diagnosis of ED and validated the Korean version of the IIEF-5. Inclusion criteria for subjects included: (i) age of 20 years and above, (ii) an IIEF-5 score < 18 on screening, and (iii) interest and ability to participate in this clinical study. Exclusion criteria were as follows: (i) a history of hypersensitivity reaction to PDE5i, (ii) current use of medications that affect erectile function (e.g. 5-alpha-reductase inhibitor use within the previous month), (iii) any previous surgery for the treatment of ED, and (iv) current use of nitrate preparations and NO providers.

All subjects visited a clinical center four times. During the two-week screening visit (V0), physical examinations were conducted to evaluate current alcohol and tobacco use and obtain past medical history. At this time blood pressure (BP), heart rate (HR), a 12-lead electrocardiogram (ECG), a complete blood count, a blood chemistry panel, a routine urinalysis, and IIEF-5 score were also obtained. Out of 194 individuals, 168 met inclusion criteria after completing V0.The Patients were randomly allocated into two groups using computer random number generator: (i) patients dosed with 20 mg of tadalafil as needed (Group 1: $n = 84$, 50.0%) and (ii) patients dosed with 5 mg of tadalafil once daily (Group 2: $n = 84$, 50.0%). Prior to the initial drug dosing (V1), the following parameters were assessed: IIEF-5, the Sexual Encounter Profile Questions 2 and 3 (SEP2 and SEP3), International Prostate Symptoms Score (IPSS), BP, and HR. Maximum flow rate (Qmax) and post-void residual volume (PVR) were evaluated in addition to IIEF-5 in individuals with an IPSS of 8 or greater and who had been given α-blockers (tamsulosin or alfuzosin) to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia (LUTS/BPH) for more than 3 months before the study. Erectile function, voiding symptoms, BP, and HR were all re-obtained four (V2) and twelve weeks (V3) after study initiation. Any side effects related to the medication were also recorded at this time. During the study period, individuals assigned to Group 1 were instructed to take 20 mg of tadalafil orally up to two times a week as needed, while subjects assigned to Group 2 were instructed to take 5 mg of tadalafil orally every morning before breakfast. Subjects concurrently taking α-blockers for LUTS/BPH were also instructed to allow for a six hour interval between medication administration. Regardless of group, participants with compliance rates below 70% were excluded. The primary outcome was improvement of erectile function at V3. And the secondary outcome was effectiveness of voiding symptoms.

Efficacy and safety measures

The efficacy of tadalafil in treating ED was evaluated via IIEF-5, SEP2 ('Were you able to insert your penis into your partner's vagina?'), SEP3 ('Did your erection last long enough for you to have successful intercourse?') and the Global Assessment Questionnaire ('Do you note improvements in your erectile function after oral intake of 20 mg of tadalafil on-demand or 5 mg once daily?', GAQ). Specifically, the IIEF-5 is a self-administered questionnaire, in which five domains evaluate erectile function and intercourse satisfaction, with higher scores in each domain representing better sexual function. The impact of tadalafil on LUTS was evaluated in patients who scored 8 or higher on the IPSS at the screening visit and who had been given α-blockers to treat LUTS/BPH for more than 3 months before the study. In these groups of patients, Qmax and PVR were also measured, as well as IIEF-5 at V1. And IPSS, Qmax and PVR were also reevaluated at V2 and V3. In addition, subjects who scored 8 or higher on the IPSS at the screening visit were divided into subgroups by the degree of improvement in ED symptoms between V1 and V3 (Group A: IIEF-5 ≥ 5; Group B: IIEF-5 < 5), and IPSS, Qmax and PVR were reevaluated after stratification. Patient satisfaction was scored using Likert scale: very satisfied, somewhat satisfied, somewhat dissatisfied, and very dissatisfied. Patient's statement of satisfaction was regarded as either 'very satisfied' or 'somewhat satisfied.' All attempts were made to ensure subject safety, including BP, HR, history taking, physical exams, side effect monitoring, and 12-lead ECG to evaluate subjects' risk of heart disease.

Statistical analysis

Characteristics of baseline were evaluated by intent-to-treat analysis. Change of erectile function and voiding symptom were evaluated by per protocol analysis. All continuous variables were analysed by

paired *t*-test (or Wilcoxon signed rank test), while efficacy and stability were compared between the two groups using an independent *t*-test (or Mann–Whitney *U* test). Chi-square tests were used for categorical variences. All data analysis and statistical processing were performed using SPSS v.18.0 was used for statistical analysis. In all cases, p values less than 0.05 were defined as statistically significant.

Results

Patient population and demographics

Out of a total of 168 individuals, 134 patients (79.8%; Group 1: $n = 68$, 81.0%; Group 2, $n = 66$, 78.6%) completed the full course of the twelve-week clinical study. At V0, no statistically significant differences were identified in demographics or other baseline characteristics (Table 1). At V2, 20 men (11.9%; Group 1: $n = 9$, 10.7%); Group 2: $n = 11$, 13.1%) dropped out of the study, while an additional 14 men (8.3%; Group 1: $n = 7$, 8.3%, Group 2: $n = 7$, 8.3%) dropped out after V3, with Figure 1 listing the reasons for dropout.

Efficacy: Sexual function & satisfaction

Among the subjects in Group 1, the mean domain score for IIEF-5 improved significantly: 9.2 ± 4.8 at V1, 11.2 ± 5.4 at V2, and 14.1 ± 6.2 at V3 ($p < 0.001$ for V1–V2 and V1–V3). A similar statistically significant improvement was also observed among subjects in Group 2: 9.4 ± 4.9 at V1, 11.9 ± 6.8 at V2, and 15.9 ± 6.2 at V3 ($p < 0.001$ for V1–V2 and V1–V3). When compared at V3, Group 2 showed significantly more improvement than Group 1 (4.9 ± 4.2 vs. 6.5 ± 4.5; $p = 0.032$) (Table 2). At V1, SEP2 for Groups 1 and 2 were 27.9% and 25.8%, respectively ($p = 0.776$). SEP2 were 57.4% for Group 1 and 68.2% for Group 2 at V2 (in both cases $p < 0.001$ vs. baseline; $p = 0.195$ for Group 1 vs. Group 2) and 64.7% and 81.8% at V3 (in both cases $p < 0.001$ vs. baseline; $p = 0.025$ for Group 1 vs. Group 2) (Figure 2). At V1, SEP3 for Group 1 and Group 2 were 20.6% and 21.2%, respectively ($p = 0.929$). SEP3 were 52.9% for Group 1 and 65.2% for Group 2 at V2 (in both cases $p < 0.001$ vs. baseline; $p = 0.151$ for Group 1 vs. Group 2), and 60.3% and 77.3% at V3 (in both cases $p < 0.001$ vs. baseline; $p = 0.034$ for Group 1 vs. Group 2) (Figure 3). At V2, 43 patients from both Group 1 (63.2%) and Group 2 (65.2%) answered 'yes' to the GAQ questionnaire ($p = 0.817$). At V3, 50 subjects from Group 1 (76.5%) and 54 subjects from Group 2 (81.8%) answered yes. No statistically significant differences in the GAQ questionnaire results were observed between the two groups at V3 ($p = 0.250$). On analysis of the patient satisfaction results, 67 individuals (50.0%; Group 1: $n = 32$, 47.1%; Group 2: $n = 35$, 53.0%) reported being very satisfied, 33 (24.6%; Group 1: $n = 17$, 25.0%; Group 2: $n = 16$, 24.3%) being somewhat satisfied, 23 (17.2%; Group 1: $n = 14$, 20.6%; Group 2: $n = 9$, 13.6%) being somewhat dissatisfied and 11 (8.2%; Group 1: $n = 5$, 7.3%; Group 2: $n = 6$, 9.1%) being very dissatisfied ($p = 0.726$). In total, 100 patients (74.6%; Group 1: $n = 49$, 72.1%; Group 2: $n = 51$, 77.3%) reported being 'satisfied'.

Table 1 Patient characteristics at baseline

Characteristics	Group 1	Group 2	p value
No. of patients	84	84	
Age (years)	55.8 ± 8.9	55.4 ± 9.1	0.784
BMI (kg/m^2)	25.6 ± 2.3	25.8 ± 2.4	0.671
Duration of erectile dysfunction (months)	7.9 ± 4.8	7.1 ± 4.2	0.256
Severity			
Mild (%)	20 (23.8)	20 (23.8)	0.983
Moderate (%)	22 (26.2)	21 (25.0)	
Severe (%)	42 (50.0)	43 (51.2)	
Etiology of erectile dysfunction			
Psycogenic (%)	10 (11.9)	11 (13.1)	0.965
Organic (%)	33 (39.3)	30 (35.7)	
Mixed (%)	23 (27.4)	25 (29.8)	
Unknown (%)	18 (21.4)	18 (21.4)	
Underlying disease			
BPH (%)	34 (40.5)	32 (38.1)	
DM (%)	31 (36.9)	34 (40.5)	
Hypertension or cardiovascular disease (%)	27 (32.1)	26 (31.0)	
Pulmonary disease (%)	7 (8.3)	4 (4.8)	
Neurologic disease (%)	5 (6.0)	5 (6.0)	

BMI, body mass index; BPH, benign prostatic hyperplasia

Efficacy: voiding symptoms

At V1, 44 patients in both Group 1 (64.7%) and Group 2 (66.7%) had an IPSS ≥ 8. Over the course of the study, IPSS significantly decreased in both groups. Among individuals in Group 1 IPSS scores decreased by 13.6 ± 6.1 at V1, 12.2 ± 6.8 at V2, and 10.8 ± 6.8 at V3 ($p = 0.008$ for V1–V2; $p < 0.001$ for V1–V3). Among individuals in Group 2 IPSS scores decreased by 13.9 ± 6.1 at V1, 11.2 ± 6.2 at V2, and 9.1 ± 6.4 at V3 ($p < 0.001$ for V1–V2 and V1–V3).When compared at V3, the mean decrease in IPSS was greater among individuals in Group 2 (−2.8 ± 4.3 vs. −4.8 ± 4.1; $p = 0.026$) (Table 2). At V1, 24 patients in Group 1 (35.3%) and 21 patients in Group 2 (31.8%) had been given α-blockers to

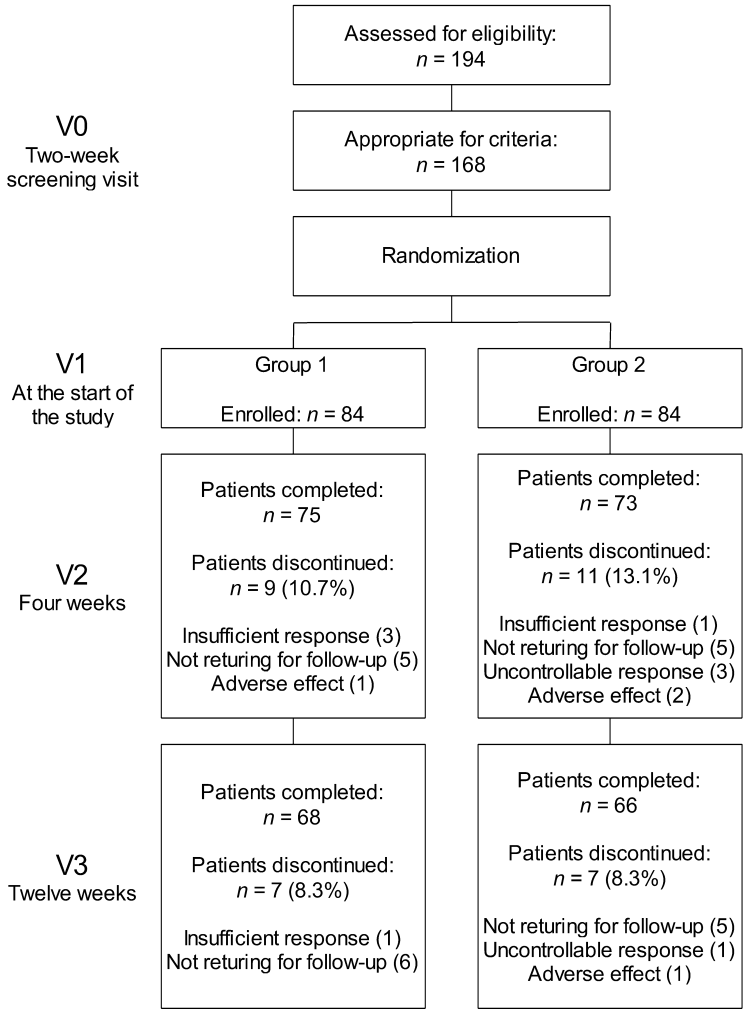

Figure 1 The reasons for dropout

treat LUTS/BPH for more than 3 months before the study. Over the course of the study, IPSS significantly decreased in both groups. Among individuals in Group 1, IPSS scores decreased by 14.3 ± 8.2 at V1, 13.5 ± 8.6 at V2, and 12.3 ± 8.2 at V3 ($p = 0.003$ for V1–V2; $p < 0.001$ for V1–V3). Among individuals in Group 2, IPSS scores decreased by 15.3 ± 7.9 at V1, 12.2 ± 8.1 at V2, and 10.2 ± 8.1 at V3 ($p < 0.001$ for V1–V2 and V1–V3). When compared at V3, the mean decrease in IPSS was greater among individuals in Group 2 (−2.1 ± 4.1 vs. −5.1 ± 4.7; $p = 0.030$). No significant differences in IPSS with regard to ED improvement was observed in either subgroup, as determined by the degree of improvement in ED symptoms (Group 1; Group A: $n = 22$, 50.0%, Group B: $n = 22$, 50.0%; Group 2; Group A: $n = 24$, 54.5%, Group B: $n = 20$, 45.5%) (Table 3). Neither Qmax nor PVR differed significantly in Group 1 or 2 (Table 2). Likewise, no significant differences in Qmax and PVR with regard to ED improvement were observed in either subgroup, as determined by the degree of improvement in ED (Table 3).

Safety

Among those assigned to Group 1, adverse effects occurred in three men (4.4%) at V2 and four men (5.9%) at V3. In Group 2, three men (4.5%) experienced adverse effects at V2 and three men (4.5%)at V3. Facial flushing was the most common adverse effect [$n = 8$, 6.0%; Group 1: $n = 4$, 5.9%, V2/V3: 2 (2.9%)/2 (2.9%); Group 2: $n = 4$, 6.1%, V2/V3: 2 (3.0%)/2 (3.0%)], followed by headache [$n = 4$, 3.0%; Group 1: $n = 2$, 2.9%, V2/V3: 1 (1.5%)/1 (1.5%); Group 2: $n = 2$, 2.9%, V2/V3: 1 (1.5%)/1 (1.5%)], and dizziness [$n = 1$, 0.7%; Group 1: V3: 1 (1.4%)]. A total of four men dropped out of the study because of adverse effects (facial flushing in three; Group 2: V2/V3: 2/1; headache in one; Group 1: V2: 1). Notably, no statistically significant differ-

Table 2 Comparison of IIEF-5, IPSS, Qmax and PVR of patients in V1*, V2† and V3‡ between two groups

	Group 1					Group 2						
				p value					p value			
	V1	V2	V3	V1 vs. V2	V1 vs. V3	V1	V2	V3	V1 vs. V2	V1 vs. V3	p value§	p value¶
IIEF-5	9.2 ± 4.8	11.2 ± 5.4	14.1 ± 6.2	< 0.001	< 0.001	9.4 ± 4.9	11.9 ± 6.8	15.9 ± 6.2	< 0.001	< 0.001	0.838	0.032
IPSS	13.6 ± 6.1	12.2 ± 6.8	10.8 ± 6.8	0.008	< 0.001	13.9 ± 6.1	11.2 ± 6.2	9.1 ± 6.4	< 0.001	< 0.001	0.793	0.026
Qmax (ml/s)	14.3 ± 7.8	14.7 ± 7.0	14.4 ± 7.2	0.400	0.797	14.4 ± 8.2	14.8 ± 6.8	14.5 ± 7.5	0.921	0.659	0.789	0.609
PVR (ml)	38.6 ± 44.9	37.4 ± 36.3	37.7 ± 36.2	0.623	0.795	38.8 ± 38.5	37.3 ± 42.8	35.1 ± 34.1	0.692	0.296	0.990	0.579

*At the start of the study. †4 weeks. ‡12 weeks. §p value of baseline (Group 1 vs. Group 2). ¶p value of difference between V1 and V3 (Group 1 vs. Groups 2). IIEF-5, International Index of Erectile Function-5; IPSS, International Prostate Symptom Score; Qmax, maximal flow rate; PVR, post-void residual volume

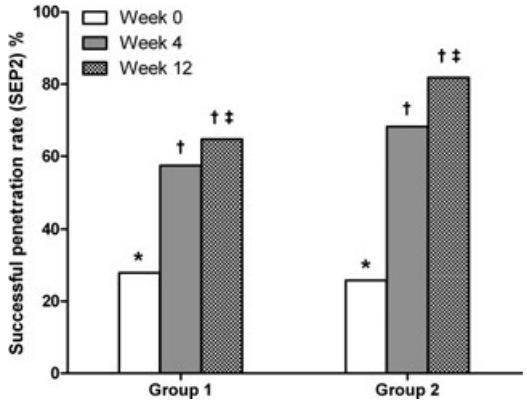

Figure 2 Successful penetration rate (SEP2) of Group 1 and Group 2. *p value of baseline (0.776; Group 1 vs. Group 2). †p value of each group (< 0.001; V1 vs. V2 and V1 vs. V3). ‡p value at V3 (0.025; Group 1 vs. Group 2)

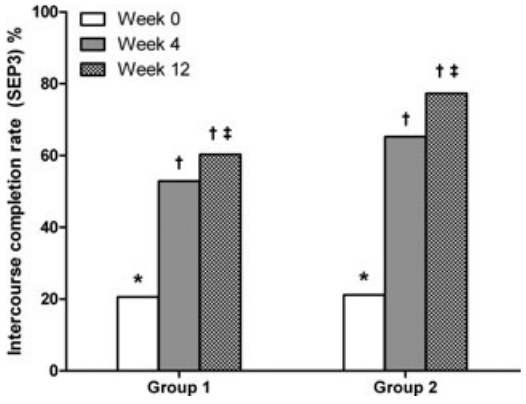

Figure 3 Intercourse completion rate (SEP3) of Group 1 and Group 2. *p value of baseline (0.929; Group 1 vs. Group 2). †p value of each group (< 0.001; V1 vs. V2 and V1 vs. V3). ‡p value at V3 (0.034; Group 1 vs. Group 2)

ences in either of the variables relating to the cardiovascular system (BP and HR) occurred (Table 4).

Discussion

To date, several studies have examined the efficacy of on-demand tadalafil dosing in the treatment of ED (7–9), all of which have reported improvements in sexual function, satisfaction and quality of life for both subjects and their partners. Compared with on-demand dosing, once daily tadalafil dosing has the advantage of helping users manage voluntary sexual activities. Eardley et al. (10), reported most individuals intending to have sexual intercourse initiate sexual activity 30 min prior. Moreover, according to the FEMALES study from Fisher et al. (11), 30% and 34% of men and women do not set a specific time for sex. These two studies confirm that sexual activity is often not scheduled and does not happen at a specific time. Accordingly, once daily tadalafil dosing was proposed, and has since been evaluated by several studies. Specifically, Althof et al. demonstrated that men taking once daily 5 mg doses of tadalafil reported better sexual function and increased sexual satisfaction vs. placebo (12). In another study from McVary et al. (13), once daily dosing of tadalafil at 5 mg resulted in significantly higher IIEF EF domain scores after 6 and 12 weeks of treatment when compared with placebo.

Several studies have also compared the safety and efficacy of the two dosing forms among ED patients. In one study from McMahon et al. (14), 145 men were divided into two groups. One group received 20 mg of tadalafil on-demand and the other group was treated daily with 10 mg of tadalafil. At study completion, the individuals receiving once daily dosing exhibited better results in terms of IIEF, SEP2, SEP3 and GAQ when compared with the 'on-demand' group. In another study, Ricardi et al. (15) conducted once daily tadalafil dosing at 5 mg with 20 mg of tadalafil on-demand among prostate cancer patients treated with radiotherapy, with

Table 3 Comparison of IPSS, Qmax and PVR according to erectile function response at V1* and V3†

	Group 1					Group 2					
				p value					p value		
	V1	V3	difference	V1 vs. V3	Group A vs. B‡	V1	V3	difference	V1 vs. V3	Group A vs. B‡	p value§
IPSS											
Group A¶	13.3 ± 6.4	11.3 ± 7.8	−2.0 ± 4.2	0.016	0.216	14.5 ± 5.8	9.7 ± 5.9	−4.8 ± 4.5	< 0.001	0.878	0.521
Group B††	13.8 ± 5.8	10.3 ± 5.8	−3.5 ± 4.4	0.002		13.2 ± 6.4	8.5 ± 7.2	−4.7 ± 3.8	< 0.001		
Qmax (ml/s)											
Group A	14.2 ± 7.4	14.7 ± 7.1	0.5 ± 3.0	0.333	0.159	16.4 ± 8.8	15.5 ± 8.8	−1.0 ± 4.7	0.243	0.251	0.656
Group B	14.4 ± 8.2	14.1 ± 7.4	−0.3 ± 2.8	0.640		12.8 ± 7.0	13.3 ± 5.7	0.5 ± 4.0	0.642		
PVR (ml)											
Group A	41.1 ± 39.9	41.4 ± 36.4	0.2 ± 17.5	0.668	0.584	30.2 ± 30.5	23.8 ± 21.8	−6.5 ± 21.1	0.163	0.484	0.674
Group B	36.1 ± 50.2	34.1 ± 36.4	−2.1 ± 28.0	0.875		49.0 ± 44.9	48.8 ± 41.2	−0.3 ± 24.8	0.716		

*At the start of the study. †12 weeks. ‡p value of difference between V1 and V3. §p value of difference between V1 and V3 of Group A vs. Groups B (total patients, $n = 88$; Group A, $n = 46$; Group B, $n = 42$). ¶Those with difference of IIEF-5 ≥ 5 between V1 and V3 ($n = 46$; Group 1, $n = 22$; Group 2, $n = 24$). ††Those with difference of IIEF-5 < 5 between V1 and V3 ($n = 42$; Group 1, $n = 22$; Group 2, $n = 20$). IIEF-5, International Index of Erectile Function-5; IPSS, International Prostate Symptom Score; Qmax, maximal flow rate; PVR, postvoid residual volume

Table 4 Comparison of hemodynamic parameters of patients in V1*, V2† and V3‡ between 2 groups

	Group 1					Group 2						
				p value					p value			
	V1	V2	V3	V1 vs. V2	V1 vs. V3	V1	V2	V3	V1 vs. V2	V1 vs. V3	p value§	p value¶
Systolic BP†† (mmHg)	127.2 ± 9.8	125.1 ± 11.1	125.5 ± 12.0	0.153	0.069	126.9 ± 12.2	126.2 ± 11.5	124.8 ± 14.3	0.709	0.160	0.852	0.761
Diastolic BP†† (mmHg)	80.9 ± 9.9	80.0 ± 7.3	80.5 ± 10.2	0.511	0.383	80.3 ± 10.4	80.1 ± 7.7	80.5 ± 9.6	0.878	0.792	0.762	0.542
Systolic BP‡‡ (mmHg)	124.5 ± 11.1	124.3 ± 10.1	124.0 ± 11.1	0.907	0.594	125.7 ± 11.7	124.9 ± 12.4	124.9 ± 12.5	0.606	0.509	0.535	0.825
Diastolic BP‡‡ (mmHg)	79.5 ± 9.3	79.2 ± 7.9	78.8 ± 10.3	0.762	0.055	81.4 ± 9.7	79.4 ± 8.6	79.6 ± 9.4	0.102	0.084	0.246	0.370
Heart rate (beats per min)	70.8 ± 9.0	71.4 ± 6.9	71.1 ± 9.3	0.600	0.546	72.0 ± 9.0	71.9 ± 7.5	72.9 ± 9.8	0.894	0.430	0.449	0.577

*At the start of the study. †4 weeks. ‡12 weeks. §p value of baseline (Group 1 vs. Group 2). ¶p value of difference between V1 and V3 (Group 1 vs. Groups 2). ††BP in the standing position. ‡‡BP in the sitting position. BP, blood pressure

significant improvements in sexual function occurring in both groups. Moreover, while both dosing schedules were well tolerated, the once daily 5 mg dosing group showed higher compliance and marginally fewer side effects. The results from the current study were not significantly different from any of the previous reports, as tadalafil produced excellent effects on all parameters, such as IIEF-5, SEP2 and SEP3. When compared, the once daily group had an increase in IIEF-5 of 6.5 ± 4.5 from baseline, an increase larger than the 4.9 ± 4.2 observed in the on-demand group. The once daily group also exhibited better results in SEP2 and SEP3. Though not entirely clear, the mechanism for the better results seen in the once daily group likely relates to an enhancement in endothelial function (16). In the case of chronic treatment with PDE5i, functional tissue modification occurs, involving the upregulation of transduction mechanisms that activate muscarinic receptors and induce endothelial nitric oxide synthesis (17).

Alternatively, these results may be explained by the plasma concentration of tadalafil, even though no direct correlation between plasma concentration and efficacy has ever been verified. In one *in vitro* study (18), a total tadalafil plasma concentration of 55 ng/ml resulted in approximately 90% enzyme inhibition, thus producing a reasonable pharmacodynamic target. Furthermore, once daily 5 mg tadalafil dosing maintained a plasma concentration of 55 ng/ml longer than did 20 mg of tadalafil dosed every 2.65 days, with such results providing a pharmacologic rationale for low-dose once daily therapy.

In the present study, the two different tadalafil dosing schedules were also compared with regard to improvements in voiding function. Previously, epidemiologic data has correlated ED with LUTS/BPH. And, though no detailed mechanism for this correlation has ever been proven, both are thought to share a common pathophysiology (19), with four different hypotheses proposed to explain this relationship: (i) NOS/NO levels are decreased or altered in prostate and penile smooth muscle; (ii) autonomic hyperactivity and metabolic syndrome may affect LUTS, prostate growth and ED; (iii) an alternate pathway involving Rho-kinase activation/endothelin activity; (iv) pelvic atherosclerosis as a underlying etiology for LUTS and ED (20). Though a treatment agent for ED, PDE5i agents also relieve LUTS, as PDE5i partially reverses prostatic tissue contraction. Additionally, these agents have been shown to increase cGMP, ultimately producing an antiproliferative effect on cultured human prostatic smooth muscle cells (21). In one study, McVary et al. (13) evaluated the safety and efficacy of once daily tadalafil dosing for the treatment of LUTS/BPH, showing that tadalafil was associated with significant decreases in IPSS from baseline. In another randomised, parallel-group, double-blind, placebo-controlled study by Roehrborn et al. (22), 1058 men with LUTS/BPH were randomly allocated to either receive once daily treatment with placebo or tadalafil (2.5, 5, 10 or 20 mg) for 12 weeks, with all tadalafil groups exhibiting a significant improvement in IPSS between baseline and study termination. In this study, the effects of once daily and on-demand tadalafil dosing on LUTS were evaluated and compared. In both dosing schedules, IPSS improved, though there was no effect on Qmax and PVR in either group. When compared head-to-head, both IPSS and erectile function improved more in the once daily group than in the on-demand group. We contend that these results can be explained by the similarities in pathophysiology between ED and LUTS/BPH, with the improvements in LUTS because of the two mechanisms explained above (enhanced endothelial function and maintained plasma concentration level). Nonetheless, this relationship has never been proven, and there have been no studies on chronic treatment of PDE5i for LUTS.

Recently, PED5i/α-blockers combination therapy is stealing the spotlight in the treatment of LUTS/BPH because of the similarities in pathophysiology between ED and LUTS/BPH. And, the efficacy and safety of tadalafil/α-blockers combination therapy for LUTS/BPH patients already had been improved by several studies (23,24). In the present study, we also evaluated the impact of tadalafil on LUTS in patients who had been given α-blockers to treat LUTS/BPH for more than 3 months before the study. IPSS significantly improved in both groups, but the mean change was larger in Group 2 at V3 similar to the whole group.

IPSS, Qmax and PVR were also examined before and after treatment among the subgroups of patients who reported LUTS, with these individuals grouped according to the degree of improvement in IIEF-5. We assessed both ED and LUTS based on the assumption that they have a similar pathophysiology. Notably, significant differences in parameters were not observed in either group, though this may be because of the smaller sample sizes of the subgroups. In addition, there is a limitation in evaluating correlation because the severity of ED was not taken into consideration before treatments.

The major known side effects of tadalafil include headache, dyspepsia, back pain, dizziness and flushing (25). In the current study, the major side effects reported were facial flushing, headache and dizziness, with the severity intermediate and duration transient in all cases. The number of subject dropouts was also negligible, and no significant changes in hemody-

namic parameters were observed in either group. Under normal treatment circumstances, both tadalafil dosing schedules are considered safe, and no differences in safety were observed between groups.

One notable limitation of the current study is the lack of a placebo group. Given the different dosing schedules of the two groups, incorporating a placebo group was challenging. Other limitations include the lack of evaluation of partner satisfaction. Yet, despite these limitations, this study is significant as it is the first prospective randomised study that evaluates the effects of on-demand and once daily tadalafil dosing on both erectile function and LUTS in the practical clinical environment. Further studies with larger sample sizes over longer periods of time are clearly needed to better elucidate differences between the two dosing schedules.

Conclusions

Both dosing schedules of tadalafil (5 mg once daily and 20 mg on-demand) effectively treat ED, enhance sexual function, and improve patient satisfaction. Additionally, both dosing schedules also have been shown to produce improvements in LUTS. When compared with on-demand dosing, once daily tadalafil was more efficacious in treating both ED and LUTS. Notably, no differences were observed between the two dosing schedules with regard to the improvement in LUTS when stratified by improvement in ED. The side effects were negligible for both dosing schedules.

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Paper received February 2012, accepted March 2012